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Tolerable upper intake level for dietary sugars

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Abstract

Following a request from five European Nordic countries, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was tasked to provide scientific advice on a tolerable upper intake level (UL) or a safe level of intake for dietary (total/added/free) sugars based on available data on chronic metabolic diseases, pregnancy-related endpoints and dental caries. Specific sugar types (fructose) and sources of sugars were also addressed. The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. Based on a systematic review of the literature, prospective cohort studies do not support a positive relationship between the intake of dietary sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases or pregnancy-related endpoints assessed. Based on randomised control trials on surrogate disease endpoints, there is evidence for a positive and causal relationship between the intake of added/free sugars and risk of some chronic metabolic diseases: The level of certainty is moderate for obesity and dyslipidaemia (> 50–75% probability), low for non-alcoholic fatty liver disease and type 2 diabetes (> 15–50% probability) and very low for hypertension (0–15% probability). Health effects of added vs. free sugars could not be compared. A level of sugars intake at which the risk of dental caries/chronic metabolic diseases is not increased could not be identified over the range of observed intakes, and thus, a UL or a safe level of intake could not be set. Based on available data and related uncertainties, the intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. Decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent. This opinion can assist EU Member States in setting national goals/recommendations.

Keywords: added sugars, free sugars, chronic metabolic diseases, pregnancy-related endpoints, dental caries, Tolerable upper intake level, safe level of intake

Requestor: European Commission

Question number: EFSA-Q-2016-00414

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Amendment: An editorial error in relation to the conclusions on fruit juices was corrected. Information describing the process of the public consultation on the draft opinion was added. An editorial correction was carried out that does not materially affect the contents or outcome of this scientific output. To avoid confusion, the original version of the output has been removed from the EFSA Journal, but is available on request.

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Summary

Following a request from the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden), the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver a Scientific Opinion on the tolerable upper intake level (UL) for dietary sugars on the basis of available data on chronic metabolic diseases, pregnancy-related endpoints and dental caries.

The UL is the maximum level of chronic daily intake of (total/added/free) sugars from all dietary sources judged to be unlikely to pose a risk of adverse health effects to humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. The UL is not a recommended level of intake. The underlying assumption of the UL concept is that a threshold can be identified below which no risk from consumption of dietary sugars is expected for the general population, and above which the risk of adverse health effects, including risk of disease, increases.

If there are no, or insufficient, data on which to base a UL, then assessing a safe level of intake could be considered. This requires the identification of a level of sugars intake up to which no adverse health effects are observed. Advice on quantitative intakes of a particular type of sugar (e.g. fructose, glucose, sucrose), and/or on one or more sources of sugars, could also be provided to assist EU Member States when developing food-based dietary guidelines (FBDGs).

The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose). Among these, glucose and fructose as monosaccharides, and sucrose and lactose as disaccharides, are the most abundant sugars in mixed diets. Added sugars are defined as mono- and disaccharides added to foods as ingredients during processing or preparation at home, and sugars eaten separately or added to foods at the table. Free sugars are defined as added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.

This assessment follows the principles and processes illustrated in the EFSA PROMETHEUS project. A draft protocol was developed, opened for public consultation and amended in view of the comments received. According to EFSA's principles for deriving UL for nutrients, a four-step approach was applied: hazard identification, hazard characterisation, intake assessment and risk characterisation. Systematic reviews of the literature on dietary sugars and their sources and chronic metabolic diseases (obesity, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension (HTN), cardiovascular diseases (CVDs) and gout), pregnancy-related endpoints (gestational diabetes mellitus, birthweight-related endpoints) and dental caries were conducted to inform the hazard identification and hazard characterisation. The Office of Health Assessment and Translation (OHAT) of the US National Toxicology Program Approach for Systematic Review and Evidence Integration was used as reference and modified to appraise the internal validity of eligible studies and to formulate conclusions on hazard identification, accounting for the uncertainties identified in the eligible body of evidence (BoE). Dose-response analyses were conducted where data allowed. Background information on digestion, absorption and metabolism of sugars from different sources in humans and the mode(s) of action underlying the potential adverse effects were addressed through a narrative review. Intakes of dietary sugars in European populations were calculated by developing food composition databases for total, added and free sugars using harmonised food composition data (EFSA Nutrient Composition Database), linked to data from the EFSA Comprehensive Food Consumption Database.

Body of evidence

Eligible studies were randomised controlled trials (RCTs) and non-randomised comparative studies of interventions, and prospective (cohort and case-cohort) studies (PCs) in humans on the exposures and endpoints of interest.

Dental caries

One publication reporting on an intervention study and 11 publications reporting on seven PCs met the inclusion criteria. Five PCs report on total sugars (of which two also report on sugar-sweetened beverages (SSBs) and one on fruit juices (FJs)) and two PCs report on sucrose. Cohorts were very heterogeneous regarding the outcome of interest consistent with the demographic characteristics of their participants, which included children, adolescents, adults and older adults.

Chronic metabolic diseases including pregnancy-related endpoints

A total of 49 RCTs reported in 61 publications were included. These allowed investigating the effect of the amount of added sugars, free sugars and SSBs when consumed ad libitum and in isocaloric exchange with other macronutrients (mostly starch), as well as the effect of fructose compared to glucose.

A total of 104 publications reporting on 66 different cohorts were included. PCs assessed total sugars, added sugars, sucrose, free sugars, fructose, SSBs and FJs. Dietary sugars (total, added and free sugars; glucose and fructose) were investigated mostly keeping total energy intake (TEI) constant in the analysis (i.e. in isocaloric exchange with other macronutrients). In contrast, most PCs on SSBs and FJs have explored whether these could be associated with the endpoint not keeping TEI constant in the analysis when the exposure was analysed as a categorical variable (e.g. for dichotomous disease endpoints).

Dietary sugars

Studies investigating added sugars, sucrose (as a proxy for added sugars) and free sugars were combined to draw conclusions in relation to the endpoints of interest, owing to the low number of studies available per each exposure and endpoint and the fact that intakes of added and free sugars widely overlap. Therefore, the health effects of added vs. free sugars could not be compared.

The relationship between the intake of dietary sugars and the development of dental caries in humans is well established. Positive linear dose-response relationships have been observed between the intake of total sugars and risk of dental caries in permanent dentition and between the intake of sucrose and risk of dental caries in primary dentition in individual PCs across a wide range of total sugars and sucrose intakes. Dose-response relationships could not be explored across the BoE owing to the high heterogeneity of the exposures and endpoints assessed. Therefore, the available data do not allow conclusions on the shape of the relationship between the intake of dietary sugars and risk of dental caries for any age group, or to identify a level of sugar intake at which the risk of dental caries is not increased.

The mechanisms by which the intake of dietary sugars increases the risk of developing dental caries are well established. Dietary sugars are metabolised by plaque microorganisms to organic acids which demineralise enamel and dentine, subsequently causing caries. Sucrose is also known to contribute to the formation of dental plaque.

There is evidence for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be moderate for obesity and dyslipidaemia (> 50–75% probability), low for NAFLD/NASH and T2DM (> 15–50% probability) and very low for hypertension (0–15% probability), based on data from RCTs which investigated the effect of 'high' vs. 'low' sugar intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and systolic blood pressure. The data available, however, did not allow identifying a level of added/free sugars intake at which the risk of chronic metabolic disease is not increased over the range of observed intakes. The Panel notes that the relationship between the intake of added and free sugars and risk of chronic metabolic diseases could not be adequately explored at levels of intake < 10 E% owing to the low number of RCTs available, and that the uncertainty about the shape and direction of the relationship at these levels of intake is higher than at intakes ≥ 10 E%.

The available BoE from PCs does not support a positive relationship between the intake of dietary (total/added/free) sugars and any of the chronic metabolic diseases or pregnancy-related endpoints considered in this assessment. Dietary sugars were mostly assessed keeping TEI constant (i.e. in isocaloric exchange with other macronutrients).

Excess energy intake leading to positive energy balance and body weight gain appears to be the main mechanism by which the intake of dietary sugars may contribute to the development of chronic metabolic diseases in free living conditions. Mechanisms which are specific to sugars as found in mixed diets (i.e. de novo lipogenesis leading to ectopic fat deposition, increased hepatic insulin resistance and impaired glucose tolerance in the long term; increase in uric acid levels) may also play a role, particularly in positive energy balance.

The Panel concludes that the available data do not allow the setting of a UL or a safe level of intake for either total, added or free sugars.

Based on the available BoE and related uncertainties, the Panel considers that the intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. The

Panel notes that decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent.

Food groups contributing the most to the intake of added and free sugars in European countries were 'sugars and confectionery' (i.e. table sugar, honey, syrups, confectionery and water-based sweet desserts), followed by beverages (SSBs, FJs) and fine bakery wares, with high variability across countries. The main difference between the intake of added and free sugars was accounted for by FJs. In infants, children and adolescents, sweetened 'milk and dairy' products were also major contributors to mean intakes of added and free sugars.

The information provided in this opinion can assist EU Member States in setting goals for populations and/or recommendations for individuals in their country, taking into account the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed. The Panel notes that the lowest amount of added/free sugars that is compatible with a nutritionally adequate diet in Europe may vary across population groups and countries.

Sugar types

Fructose

There is evidence for a positive and causal relationship between the intake of fructose (as monosaccharide and bound to glucose in sucrose) and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability), based on data from PCs. However, the external validity of the findings for European populations is unclear. In the eligible RCTs, the effects of free fructose and free glucose (as monosaccharides) on body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure did not appear to be different, whereas free fructose appeared to increase hepatic insulin resistance and uric acid levels more than equivalent amounts of free glucose.

Fructose is a component of added and free sugars in mixed diets, i.e. containing comparable amounts of fructose and glucose. The Panel considers that the conclusions for added and free sugars also apply to fructose in that context. The Panel notes that limiting the intake of added and free sugars in mixed diets would also limit the intake of fructose. This may not be the case if pure fructose or isoglucose with high fructose content (> 55%) is used to replace sucrose in foods and beverages.

Sources of dietary sugars

Sugar-sweetened beverages

There is evidence for a positive and causal relationship between the intake of SSBs and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability), based on data from RCTs and PCs. When dose-response relationships between the intake of these beverages and incidence of disease (T2DM, HTN and CVDs) could be investigated using data from PCs, these were positive and linear. It is unclear, however, whether the risk of HTN and CVDs associated with the consumption of these beverages could be attributed to their sugar content because the relationship between the consumption of artificially sweetened (sugar-free) beverages and incidence of HTN and CVDs was similar to, or stronger than, for SSBs in these studies. In addition, the external validity of the findings in relation to the risk of gout for European populations is unclear.

Based on data from PCs, there is low certainty (> 15–50% probability) that habitual consumption of SSBs by women of child-bearing age could increase the risk of gestational diabetes mellitus (GDM), and very low certainty (0–15% probability) that consumption of SSBs during pregnancy by women not developing GDM increases the risk of having infants small for gestational age.

In PCs, SSBs were mostly assessed not keeping TEI constant in the analysis, thus allowing for the contribution of energy to the associations.

The proportion of consumers of SSBs (sugar-sweetened soft drinks and sugar-sweetened fruit drinks) in Europe varied widely across population groups and countries, ranging from 0% to 97% of the dietary survey's sample. In consumers, the contribution of added and free sugars in SSBs to total energy intake ranged from 1 to 8 E%, depending on the survey. With few exceptions, the contribution of SSBs to the intake of added and free sugars ranged from 15% to about 50%.

Fruit juices

There is evidence for a positive and causal relationship between the intake of FJs and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be moderate for T2DM and gout (> 50–75% probability) and very low for obesity (0–15% probability), based on data from PCs. The dose-response relationship between the intake of FJs and incidence of T2DM was positive and linear. Fruit juices were mostly assessed not keeping TEI constant in the analysis, thus allowing for the contribution of energy to the associations. As for SSBs, the external validity of the findings in relation to the risk of gout for European populations is unclear.

The proportion of consumers of fruit juices in Europe varied widely across population groups and countries, ranging from 15% to 96% of the sample. In consumers, the mean contribution of free sugars in fruit juices to total energy intake ranged from 1 to 11 E% depending on the survey. With few exceptions, the contribution of fruit juices to the intake of free sugars ranged from 15% to about 50%.

Other sources of dietary sugars

Data from PCs on other sources of dietary sugars were not extracted because: (a) reliable estimates of sugars intake from these sources were not feasible, (b) foods for which sugar intakes could have been calculated were either small contributors to the intake of sugars or were investigated in relation to metabolic disease endpoints for other reasons than their sugar content and/or (c) the few studies quantifying sugars intake from other sources were heterogeneous regarding the exposure of interest and the endpoint assessed, so that only one study was available for each specific exposure–endpoint relationship. However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDGs.

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Background as provided by the requestor

In June 2016, the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden) sent a request to the European Food Safety Authority (EFSA) in order to provide a dietary reference value (DRV) for sugars, with particular attention to added sugars, on the basis of most recent scientific evidence. After discussing the mandate at its plenary meeting on 22–23 September 2016, the NDA Panel asked for some clarifications to the requestors, particularly regarding the type of DRV to be established, the exposure of interest, the target population and the health endpoints to be considered. In February 2017, the requestors clarified that they were interested in a science-based cut-off value for a daily exposure to added sugars from all sources (i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing) which is not associated with adverse health effects. The target population for the assessment was defined as the general healthy population, including children, adolescents, adults and elderly. The requestors also clarified that the request relates to an update of the EFSA's Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010a) in relation to the effects of added sugars on nutrient density, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

In the EFSA NDA Panel (2010a) opinion, the term 'added sugars' referred to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing.

With regard to the effects of added sugars intake, the NDA Panel reached the following conclusions on the endpoints assessed:

- Micronutrient density of the diet: observed negative associations between added sugars intake and micronutrient density of the diet are mainly related to patterns of intake of the foods from which added sugars in the diet are derived rather than to the intake of added sugars per se. The available data are not sufficient to set an upper limit for (added) sugars intake.
- Glucose and insulin response: there are limited, and mainly short-term, data on the effects of high intakes of sugars on glucose and insulin response. Most studies do not find any adverse effects at intakes of predominantly added sugars up to 20–25% of total energy (E%), provided that body weight is maintained.
- Serum lipids: although there is some evidence that high intakes (> 20 E%) of sugars may increase serum triglycerides and cholesterol concentrations, the available data are not sufficient to set an upper limit for (added) sugars intake.
- Body weight: the evidence relating high intake of sugars (mainly as added sugars), compared to high intakes of starch, to weight gain is inconsistent for solid foods. However, there is some evidence that high intakes of sugars in the form of sugar-sweetened beverages (SSBs) might contribute to weight gain. The available evidence is insufficient to set an upper limit for sugars based on their effects on body weight.
- Type 2 diabetes: controversial findings on the association between total sugars and/or specific types of sugars and diabetes risk were reported in large prospective cohort studies. However positive associations were found between SSBs and increased type 2 diabetes risk. The available evidence was found insufficient to set a Tolerable Upper Level of Intake (UL) for sugars based on their effects on type 2 diabetes risk.
- Dental caries: available data do not allow the setting of a UL for (added) sugars on the basis of a risk reduction for dental caries, as caries development related to consumption of sucrose and other cariogenic carbohydrates does not depend only on the amount of sugars consumed, but it is also influenced by oral hygiene, exposure to fluoride, frequency of consumption and various other factors.

The NDA Panel concluded that the available data did not allow the setting of a UL for total or added sugars, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However, evidence on the relationship between patterns of consumption of sugar-containing foods and dental caries, weight gain and micronutrient intake should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDGs).

Terms of Reference as provided by the requestor

The request is for scientific assistance in line with Regulation (EC) No 178/2002 in assessing a DRV for added sugars, which would benefit risk managers and substantially support their work with dietary guidelines and nutrient recommendations if they could base their advices on an up-to-date assessment by EFSA. To this end, EFSA has been requested to update its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre published in 2010 (EFSA NDA Panel, 2010a), on the basis of the most recent scientific evidence, in order to derive a science-based cut-off value for a daily exposure to added sugars which is not associated with adverse health effects. The mandate requestor clarified that the intake of interest is added sugars from all sources, i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing. The health endpoints of interest are those already addressed in the EFSA NDA Panel (2010a) opinion, i.e. micronutrient density of the diet, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

Interpretation of the Terms of Reference

The interpretation of the terms of reference can be found in Section 5 of the Protocol for the scientific opinion on the tolerable upper intake level (UL) of dietary sugars (EFSA NDA Panel, 2018), which was subject to public consultation from 9 January to 4 March 2018. A technical meeting with stakeholders was held in Brussels on 13 February 2018, during the consultation period. After consultation with stakeholders and the mandate requestors, EFSA interprets this mandate as a request to provide scientific advice on a UL for (total/added/free) sugars, i.e. the maximum level of total chronic daily intake of sugars (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route. The health endpoints of interest relate to the development of chronic metabolic diseases, pregnancy-related endpoints and dental caries.

If there are no, or insufficient, data on which to base the establishment of a UL, an indication should be given on the highest level of chronic daily intake (from all sources) where there is reasonable confidence in data on the absence of adverse effects (i.e. a science-based cut-off value for a daily exposure which is not associated with adverse health effects or a safe level of intake). If there are no, or insufficient, data on which to base the establishment of a UL or a cut-off value for (total/added/free) sugars from all sources because the evidence available relates to one or few sources only, or to a particular type of sugar (e.g. fructose, glucose, sucrose), and the extrapolation of the results to (total/added/free) sugars from all sources is found to be unjustified, scientific advice could be provided on quantitative intakes in relation to one or few sources of sugars only, and/or in relation to one type of sugar only (e.g. fructose, glucose, sucrose) (**Figure 1**). The Panel wishes to clarify that a UL is not a recommended level of intake.

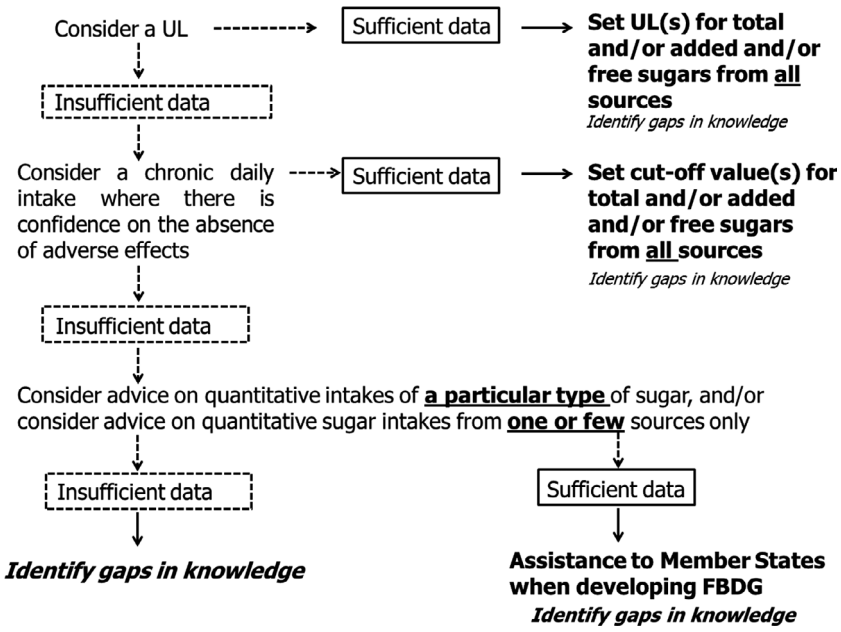


Figure 1: Stepwise process to provide scientific advice on total/added/free sugars

Dietary goals for populations or recommendations for individuals for a nutrient, and for food sources of the nutrient (e.g. FBDGs), are based on considerations of health effects associated with its consumption. DRVs, including ULs, provide the scientific bases for such considerations. However, other factors are also considered, such as the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which dietary goals and recommendations are developed. Establishing dietary goals or recommendations for dietary sugars (e.g. a limit of intake) and FBDGs on sugar-containing foods is part of national nutrition policies and thus in the remit of individual EU Member States, not under EFSA's remit.

Additional information

To address this mandate EFSA was requested to consider, as background information and sources of data, published reports from national and international authorities/bodies addressing the health effects of sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

Data and methodologies

This assessment follows the principles for the application of risk assessment to nutrients in general, and for deriving ULs in particular, which have been described elsewhere (SCF and EFSA NDA Panel, 2006; EFSA NDA Panel, 2010b).

The assessment has been developed following the principles and process illustrated in the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments) (EFSA, 2015). In this context, a draft protocol was developed with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data (i.e. which data to use for the assessment and how to identify and select them), appraising the relevant evidence and analysing and integrating the evidence in order to draw conclusions that will form the basis for the Scientific Opinion. The draft protocol was open for public consultation from 9 January to 4 March 2018. The public consultation included a technical meeting with stakeholders held in Brussels on 13 February 2018. The draft protocol was amended in view of the comments received. All comments received were addressed and published in a technical report (EFSA NDA Panel, 2018), and a final version of the protocol was published (EFSA NDA Panel, 2018).

The six assessment subquestions defined in the Protocol (EFSA NDA Panel, 2018) for this Scientific Opinion on the UL of dietary sugars, the methods used and the sections of the opinion in which they are addressed, are as follows:

No.	Subquestion	Method	Sections
1	What are the levels of (total/added/free) sugars in foods and beverages in Europe?	Food composition data (EFSA Nutrient Composition Database, Mintel's Global New Products Database)	4.1, 4.2, 4.3, 4.4, 4.5
2	What is the distribution of intakes of (total/added/free) sugars from all dietary sources (and by food source) by population group?	Food composition data Food consumption data (EFSA Comprehensive Food Consumption Database)	4.6, 4.7, 4.8
3	What are the digestion, absorption and metabolism of different types of sugars from different sources in humans?	Narrative review	3.1, 3.2, 3.3, 3.4, 3.5
4	What is the relationship between the intake of (total/added/free) sugars and metabolic diseases (disease endpoints and other endpoints) in the target population?	Systematic review	8, 9, 11
5	What is the relationship between the intake of (total/added/free) sugars and dental caries in the target population?	Systematic review	10, 11
6	Which could be the potential mode(s) of action underlying the adverse effects (if any) of (total/added/free) sugars intake?	Narrative review	3.6

The Handbook for Conducting a Literature-Based Health Assessment Using the Office of Health Assessment and Translation (OHAT) from the US National Toxicology Program Approach for Systematic Review and Evidence Integration (NTP, 2019) has been used as reference to conduct the systematic reviews on metabolic diseases and dental caries. The OHAT/NTP tool has been adapted to appraise the internal validity of human intervention and observational studies (Section 7.4). The OHAT approach has also been modified to draw conclusions on hazard identification for metabolic diseases including pregnancy endpoints. The principles for evidence integration and uncertainty analysis, including the adaptations introduced to the OHAT approach to fit this scientific assessment, can be found in Section 8.1.3.

A draft opinion was endorsed by the NDA Panel on 6 July 2021 and was open for public consultation from 22 July to 30 September 2021. The public consultation included a technical meeting with stakeholders held online on 21 September 2021. The draft opinion has been amended in view of the comments received, which have all been addressed and are published in a technical report (**Annex O**).

Protocol amendments

Two amendments have been introduced to the published protocol:

Version of the EFSA Comprehensive Food Consumption Database used in the assessment. The intake assessment of dietary sugars is based on the latest version of the EFSA Comprehensive Food Consumption Database published on 7 February 2020, rather than the one available on 31 December 2018, as written in the protocol. The reason for this amendment is that, having the deadline for the mandate extended by one year (from February 2020 to March 2021), it was feasible to consider most recent European data, collected under the EU Menu project, in the assessment. This includes data from nine new food consumption surveys collected in six European countries. The protocol amendment was endorsed by the NDA Panel on 25 February 2020.

Update of the literature searches for systematic reviews. The literature searches were conducted earlier than planned owing to the high number of hits retrieved in scoping searches to allow incorporation of the new data into the scientific opinion (i.e. they were performed 10 months before the planned endorsement of the scientific opinion instead of the 3 months foreseen in the protocol). The protocol foresees the incorporation of the new studies meeting the inclusion criteria into the opinion by a weight of evidence approach (narratively). Instead, as agreed with the mandate

requestor, only new studies meeting certain criteria have been considered to draw conclusions on hazard identification, but these studies have also been fully incorporated into the opinion, also in meta-analyses and dose-response analyses where appropriate (see Section 7.1 and **Annex A**). The NDA Panel was informed on 21 January 2021.

Questionnaire to National Competent Authorities of European countries

A total of 37 European countries were asked to supply information on current national recommendations for dietary sugars through the EFSA focal points[1] and the EFSA Food Consumption Network[2] using a questionnaire developed for that purpose (**Annex F**). The questionnaire was also designed to gather sugars intake data from national surveys and national food composition data on added and free sugars.

Assessment

1. Introduction

Digestible carbohydrates are the main source of energy in most human diets. Dietary sugars belong to this category of non-essential nutrients. In 2010, a reference intake range for carbohydrates of 45–60 E% was established by EFSA for adults and children older than 1 year of age (EFSA NDA Panel, 2010a). The available data were not sufficient to set an upper limit for (added) sugars intake.

2. Definition/category

2.1. Chemistry

Dietary sugars are a class of carbohydrates with a degree of polymerisation of one (monosaccharides) or two (disaccharides), which are digestible in the small intestine, with the exception of lactose in individuals with low intestinal lactase activity (EFSA NDA Panel, 2010a) (**Table 1**).

Table 1: Main types of dietary sugars

Subgroup	Components	Monomers
Monosaccharides	Glucose	
	Galactose	
	Fructose	
Disaccharides	Sucrose	Glucose, fructose
	Lactose	Glucose, galactose
	Trehalose	Glucose
	Maltose	Glucose

Maltose and trehalose, with two molecules of glucose each, only differ in the configuration of the glycosidic bond.

This assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route only. Among these, glucose and fructose as monosaccharides, and sucrose and lactose as disaccharides, are the most abundant sugars in mixed diets. The energy conversion factor used for labelling purposes for dietary carbohydrates including sugars is 4 kcal/g (17 kJ/g).

According to European legislation (Regulation 1169/2011[3]), sugar alcohols (polyols) such as sorbitol, xylitol, mannitol and lactitol, which are low-calorie sugar replacers that can be used in foods also for purposes other than sweetening, are 'carbohydrates' not included under the term 'sugars' and

[1] https://www.efsa.europa.eu/en/people/fpmembers
[2] https://www.efsa.europa.eu/sites/default/files/dcmfoodconsnetworklist.pdf
[3] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.

will not be considered in this opinion. Alongside polyols, other substances used as sugar replacers and other mono- or disaccharides present in the diet in marginal amounts are not included in the term 'sugars' for the purpose of this assessment (e.g. isomaltulose, D-tagatose).

Mono- and disaccharides have very similar chemical structures. Most disaccharides are isomers, with the same molecular weight, almost the same functional groups and only small structural differences which are responsible for differences in sweetness, solubility and chemical reactivity (Pokrzywnicka and Koncki, 2018). Several methods are available for the analysis of sugars in food and beverages (Hadjikinova et al., 2017; Schievano et al., 2017; Pokrzywnicka and Koncki, 2018; Vennard et al., 2019). High-pressure liquid chromatography (HPLC) is mostly used for routine analyses. It allows a simple, rapid and simultaneous determination of several sugars also at quantitative level (Hadjikinova et al., 2017; Pokrzywnicka and Koncki, 2018; Vennard et al., 2019). HPLC is used in connection with several columns and different detectors. Recently, high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) has been endorsed by the AOAC[4] as the official method for sugar profiling in foods and dietary supplements and it is becoming the primary choice for nutrition labelling (BeMiller, 2017; Vennard et al., 2019).

2.2. Definition of the exposure

This scientific assessment addresses total, added and free sugars, as defined in the protocol (EFSA NDA Panel, 2018). Namely, total sugars are all mono- and disaccharides, as defined in Section 2.1, found in mixed diets; added sugars include mono- and disaccharides added to foods as ingredients during processing or preparation at home, and sugars eaten separately or added to foods at the table; free sugars include added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates (**Figure 2**).

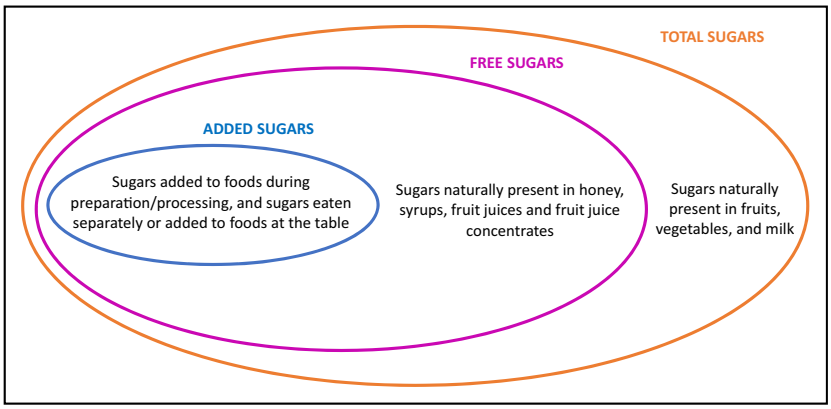


Figure 2: Classification of dietary sugars

3. Physiology and metabolism

3.1. Digestion

Digestion of food functions on two levels, mechanical and chemical. Starting in the mouth, food is mechanically broken down during the process of chewing while salivary amylase, secreted during mastication, initiates the chemical breakdown of starch. In addition to digestive properties, saliva aids in hydrating and lubricating the food to allow for easier swallowing. The partially broken down food, or bolus, travels through the oesophagus which propels it to the stomach. In the stomach, at the mechanical level, peristaltic contractions churn the bolus which allows it to mix with gastric acids, released by parietal cells in the stomach epithelium, resulting in chyme. Food may remain in the stomach from a few minutes up to several hours depending on the amount of food eaten, the physical characteristics and the nutrient composition. As the chyme leaves the stomach, it enters the duodenum, the first segment of the small bowel, where most of the chemical digestion occurs. Already within minutes after swallowing, some of the food enters the duodenum. The pancreas, liver and gall bladder are stimulated to release several enzymes (and bile) that help in digestion.

[4] Available online https://www.eoma.aoac.org/methods/info.asp?ID=52134

Digestible dietary carbohydrates are mainly starch (a polymer of glucose molecules linked by alpha 1-4 and alpha 1-6 glycosidic bonds), disaccharides (sucrose, lactose) and monosaccharides (glucose, fructose). Pancreatic amylase is the primary starch digestive enzyme that cleaves the α 1-4 (but not the α 1-6) glycosidic bonds. End products are maltose, maltotriose and α-limit dextrins, which are small glucose polymers containing α 1-6 glycosidic bonds. Alpha-limit dextrins, maltotrioses and disaccharides are digested into monosaccharides by digestive enzymes present in the brush border membrane of the small bowel: sucrase-isomaltase is involved in the digestion of α-limit dextrins and maltotriose into glucose, and in the digestion of sucrose into glucose and fructose (Boron and Boulpaep, 2016), maltase-glucoamylase in that of maltose into two molecules of glucose, lactase in that of lactose into glucose and galactose and trehalase in that of trehaloseinto two molecules of glucose (Amiri and Naim, 2017). Congenital disaccharidase deficiencies are extremely rare, but lactase expression in the gut decreases drastically during childhood in approximately two-thirds of the world population, leading to adult lactose maldigestion (Storhaug et al., 2017).

Digestion of dietary sugars and starch results in the release of the monosaccharides glucose, galactose and fructose at the surface of small bowel enterocytes.

3.2. Absorption

Sugars (and starch, after digestion to glucose) are absorbed in the blood as monosaccharides. Disaccharides are not absorbed as such, except for traces.

Glucose and galactose are transferred from the gut lumen to the enterocyte by a Sodium-Glucose-coTransporter, SGLT1. This process is driven by the extra-intracellular sodium gradient maintained by the energy-dependent Na^+/K^+ ATPase and results in the complete absorption of glucose and galactose. Fructose is absorbed by facilitated diffusion through a GLUT5 transporter. This absorption depends on the presence of a gut lumen-intracellular fructose gradient and it is not complete. Symptoms of fructose malabsorption frequently occur in individuals with very low fructose intakes but tend to decrease over time upon chronic exposure to fructose due to an increased expression of GLUT5. Co-ingestion of glucose with fructose potentiates fructose absorption, thus decreasing symptoms of fructose malabsorption. Intracellular glucose, galactose and fructose are transported by facilitated diffusion from the enterocyte into the hepatic portal circulation through the same transporter, GLUT2 (Wright et al., 2003).

3.3. Metabolism

Monosaccharides (glucose, fructose, galactose) reaching the hepatic portal circulation are delivered to the liver and eventually entirely metabolised to CO_2 and H_2O.

Glucose can be metabolised in all cells of the human organism. Its metabolism involves a transport from the interstitial fluid to the cell, which is operated by a variety of non-insulin-dependent (mainly GLUT1-3), insulin-responsive (GLUT4) and sodium-glucose (SGLT1-2) membrane transporters. Intracellular glucose is initially metabolised by a member of the hexokinase enzyme family to glucose-6-phopshate (glucose-6-P) (Wilson, 2003). According to the cell type and energy status, glucose-6-P is further metabolised to pyruvate and lactate in the glycolytic pathway, to glucose-1-P and glycogen for storage or metabolised in the pentose monophosphate pathway.

Ingested glucose is already metabolised in part in the gut and liver. Hepatocytes transport glucose through non-insulin-dependent GLUT2 transporters and synthesise glucose-6-P by the enzyme hexokinase IV (also called glucokinase), whose activity is mainly dependent on glucose concentration (Iynedjian, 1993). Glycolysis in the hepatocytes is tightly regulated at the level of the enzyme phosphofructokinase, which is potently inhibited by high intracellular ATP and citrate concentrations. As a consequence, only a portion (usually 10–25%) of absorbed glucose is metabolised in hepatocytes, and the rest escapes hepatic uptake to reach the systemic circulation, where it will increase systemic glycaemia, elicit insulin secretion and stimulate insulin-dependent and non-insulin-dependent glucose disposal in the various organs and tissues (Petersen and Shulman, 2018).

The amount of glucose escaping splanchnic metabolism, thus reaching the systemic circulation and arterial blood can transiently increase blood glucose levels from ca. 5 mmol/L (fasting) to 8–10 mmol/L (postprandial). This increase elicits a marked stimulation of insulin secretion, and arterial glucose will be taken up by peripheral organs, either independently of insulin (brain) or under the control of insulin (skeletal muscle, adipose tissue) (Gerich, 1993).

Different from glucose, fructose cannot be readily phosphorylated by hexokinases and its initial metabolic steps rely on the presence of specific (GLUT5) or non-specific (GLUT2) membrane

transporters (Thorens and Mueckler, 2010) and of specific fructolytic enzymes: ketohexokinase C or fructokinase, which catalyses the conversion of fructose into fructose-1-phosphate (F-1-P); aldolase B, which splits F-1-P into dihydroxyacetone-phosphate and glyceraldehyde, and triokinase, which phosphorylates dihydroxyacetone-phosphate and glyceraldehyde to glyceraldehyde-3-phosphate. Dihydroxyacetone-P and glyceraldehyde-P (triose phosphates) then join the normal glycolytic pathways.

Fructolytic enzymes are expressed in small bowel enterocytes, hepatocytes and kidney proximal tubules, which are the organs primarily involved in fructose metabolism. Part of ingested fructose is already metabolised to glucose (gluconeogenesis), lactate, glyceric acid and fatty acids in small bowel enterocytes. Any fructose escaping gut metabolism reaches the liver through the hepatic portal circulation. In hepatocytes, fructolysis, unlike glycolysis, is not inhibited by intracellular mediators such as ATP or citrate, and almost all fructose transported in liver cells is converted into triose phosphates. An excess of intracellular triose phosphates triggers the synthesis of lactate, glucose, glycogen, glycerol and fatty acids (Ter Horst and Serlie, 2017).

Very little fructose escapes gut and liver metabolism. Fructose concentrations in blood increase transiently up to about 0.5 mmol/L after ingestion of fructose-containing sugars. The fate of this systemic fructose remains unknown. Experiments with intravenous administration of fructose suggest that systemic fructose is mainly metabolised in the kidney (Mayes, 1993), gut and liver, although a portion may also be metabolised in non-fructolytic tissues using alternative metabolic pathways (Helsley et al., 2020). Fructose does not increase blood glucose and insulin concentration to any great extent.

Galactose is almost completely converted into glucose in the liver by way of the Leloir pathway. The enzymes galactose mutarotase, galactokinase, galactose-1-phosphate uridyltransferase and UDP-galactose 4-epimerase are sequentially involved. Defects in the genes encoding for galactokinase, uridylyltransferase or epimerase can lead to galactosaemia, an extremely rare but potentially severe condition (Holden et al., 2003; Sørensen et al., 2011).

Like for fructose, ingestion of a pure galactose load does not increase blood glucose and insulin concentration to any great extent. The concentration of galactose in peripheral arterial blood hardly increases, indicating that the near totality is extracted by splanchnic organs. Tracer experiments with ^{13}C-labelled galactose indicate that ca. 10 g was released into the blood stream as glucose over the 8 h following ingestion of a 50-g galactose load (Gannon et al., 2001).

3.4. Rate of appearance in blood

Glycaemic responses following the intake of carbohydrate-containing foods depend primarily on the amount and type of carbohydrates consumed. Other factors, such as composition (e.g. content of dietary fibre, fat, protein, organic acids and their salts, etc.) and physical properties of the food (e.g. state [liquid, semisolid, solid], cooking methods, processing), which have an impact on gastric emptying, the rate of intraluminal digestion of starches in the gut and the rate of appearance of the mono- and disaccharides at the gut brush border, are also important.

Carbohydrate-containing foods have been classified with respect to their relative impact on blood glucose concentrations by using the glycaemic index (GI), a unitless number between 0 and 100 (Atkinson et al., 2008). Pure glucose is used as reference, while tests are usually standardised to 50 g of digestible carbohydrates.[5] The GIs of pure glucose (100), maltose (~ 105), sucrose (~ 65), lactose (~ 48) and fructose (~ 15), and the GI of different types of honey and syrups diluted in water, mostly reflect their sugars composition. The GI of starchy foods varies widely, from ~ 75 for white wheat bread to ~ 50 for pasta, depending on the rate of digestion of starch among other factors. The glycaemic impact of foods is calculated through the glycaemic load (GL), which accounts for both the GI and the total amount of carbohydrates consumed and is expressed as glucose equivalents.

3.5. Excretion

Trace amounts of disaccharides that reach the systemic circulation are excreted in the urine as such. Glucose reabsorption occurring in the kidneys is almost complete under normal conditions but depends on glycaemia. When blood glucose levels exceed about 10 mmol/L (180 mg/dL), as in uncontrolled diabetes, glucose is lost in urine. The small amounts of galactose and fructose remaining in the systemic circulation after splanchnic extraction and metabolism are filtered in primary urine and

[5] International Organization for Standardization. Food products – Determination of the glycaemic index (GI) and recommendation for food classification: ISO 26642. 1-10-2010.

almost entirely reabsorbed by kidney tubule cells through the SGLT-1 transporter. In normal conditions, only traces of galactose and fructose appear in the urine (Gammeltoft and Kjerulf-Jensen, 1943). When a threshold level of filtered hexoses is reached, as in inherited fructokinase deficiency (essential fructosuria), fructose absorbed in the blood after ingestion is excreted as such in the urine (Tran, 2017).

3.6. Mode(s) of action underlying potential adverse health effects of dietary sugars

3.6.1. Metabolic diseases

Excessive consumption of dietary sugars, and particularly of added sugars, has been proposed to be involved in the development of diet-related chronic diseases (i.e. obesity, diabetes mellitus, dyslipidaemias, hypertension and other cardiovascular diseases) through several mechanisms which are briefly described below.

3.6.1.1. Positive energy balance

A positive energy balance (i.e. energy intake > energy expenditure) is invariably present during the phase of development of obesity. Sugars have been proposed to favour a positive energy balance due to their hedonic properties, leading to an increase in the consumption of energy dense sweet foods and beverages so that energy intake is increased not only due to energy coming from sugars but also from other macronutrients (Freeman et al., 2018; Olszewski et al., 2019).

The mere thought, sight, smell or taste of food starts the cephalic phase of digestion, in which the stomach and gut respond to such stimulus. Nutrient sensing through taste receptors that are located along the entire gastrointestinal tract contributes to the regulation of digestion and impacts on satiety and satiation. Chewing increases the sensory experience of food and contributes to sensory-specific satiation, limiting intake. This sensory experience of (digestion of) food is an important determinant of feeding behaviour and has an impact on deciding what to eat. Sugars stimulate specific taste receptors in the mouth, providing sweet taste and induce nutrient-specific satiation. Nutrient sensing, however, may differ depending on the food source. It has been proposed (although not univocally demonstrated) that sugars in beverages may specifically increase energy intake because liquid foods pass rapidly through the gut limiting sensory detection, such that nutrient sensing impacts less on satiation (de Graaf, 2011; Pan and Hu, 2011).

In addition, stimulation of energy intake may be related to the fact that the fructose component of sugars fails to elicit the release of satiating hormones such as insulin, leptin, PYY or GLP-1 and to inhibit the release of the orexigenic hormone ghrelin (Teff et al., 2004). Compared to glucose, fructose dissolved in water has a lower ability to suppress cerebral blood flow in the hypothalamic nuclei which contribute to the control human feeding behaviour and therefore has been hypothesised to impact less on satiation (Page et al., 2013).

3.6.1.2. Adiposity, ectopic fat deposition, inflammation and insulin resistance

The body stores energy coming from food mainly as fat, primarily in subcutaneous adipose tissue (SAT). Several organs are surrounded by a certain amount of adipose tissue, but these locations are not usually associated with fat storage. Adipose tissue is known to release a large number of adipokines (e.g. hormones, cytokines, extracellular matrix proteins and growth and vasoactive factors) that serve several physiological functions.

Chronic excess energy intake may exceed the storage capacity of SAT, resulting in excessive flow of lipids to other organs. Fat storage shifts then to ectopic sites, including the viscera, liver, muscle, pancreas, kidney, heart and the vascular tree. This phenomenon is collectively described as ectopic fat deposition. Ectopic fat accumulation is associated with adipose tissue dysfunctionality, low-grade local and systemic inflammation, insulin resistance (IR) and end-organ damage (Landecho et al., 2019). It has been postulated that different fat depots may determine different metabolic consequences.

Under conditions of excessive lipid storage, visceral adipose tissue (VAT) contributes to systemic inflammation (through macrophage infiltration and upregulation of the secretion of adipokines). Systemic inflammation and ectopic fat in the liver and skeletal muscle are associated with organ-specific IR, which in turn fosters ectopic fat deposition and inflammation, creating a vicious circle.

Insulin has a central role in glucose and lipid metabolism. Both hepatic and skeletal muscle IR, which can coexist in the same individual to different degrees, induce compensatory hyperinsulinaemia

and increase the risk of developing T2DM. The metabolic response to the intake of dietary sugars (e.g. their effect on glycaemia, insulinaemia, blood lipids), however, can vary widely depending on the metabolic profile of the individual.

The mechanisms by which ectopic fat accumulates and how this affects (and is affected by) IR appear to be tissue specific. In skeletal muscle, altered lipid uptake, impaired capacity to oxidise lipids and accumulation of lipotoxic compounds interfere with insulin signalling and glucose uptake. In the liver, the mechanisms linking lipid metabolism and IR are less well understood. Increased uptake of fatty acids, insulin-induced *de novo* lipogenesis (DNL) and impaired lipid oxidation enhance liver fat accumulation (hepatic steatosis), the main characteristic of non-alcoholic fatty liver disease (NAFLD) (Ipsen et al., 2018). NAFLD can progress to hepatic inflammation and fibrosis (non-alcoholic steatohepatitis, NASH). The prevalence of NAFLD and its progression to NASH is about double in patients with T2DM than in non-diabetic individuals (Cernea and Raz, 2020).

Fructose has been shown to stimulate hepatic DNL to a larger extent than glucose (Hirahatake et al., 2011), and hence has been suspected to be more closely associated with the development of NAFLD (Ter Horst and Serlie, 2017). However, diets supplemented with free fructose or free glucose were shown to have similar effects on intrahepatic fat in short-term experiments in overweight humans. Both free glucose and free fructose increased intrahepatic fat to the same extent when administered in excess of energy needs for weight maintenance but had no effect when administered as part of a weight maintenance diet (Johnston et al., 2013). Ingestion of a hypercaloric high fat diet also increased intrahepatic fat to the same extent as free glucose or free fructose, indicating that energy balance may be a primary determinant of intrahepatic fat concentration (Sobrecases et al., 2010).

Excess VAT, intrahepatic and intramuscular fat are thus strongly associated with systemic metabolic alterations in glucose and lipid metabolism. However, whether ectopic fat in these locations is causally related to the development of systemic metabolic diseases, as well as the relative role of each fat depot, needs to be confirmed (Britton and Fox, 2011). Conversely, ectopic fat depots surrounding the kidney (sinus), the heart and blood vessels and myocardial fat appear to have primarily local effects, inducing organ-specific dysfunction and damage (Britton and Fox, 2011). For example, excess perivascular adipose tissue deposition induces inflammation, oxidative stress, decreased production of vasoprotective adipocyte-derived relaxing factors and increased production of paracrine factors such as resistin, leptin, cytokines (IL-6 and TNF-α) and chemokines. These adipocyte-derived factors initiate and orchestrate inflammatory cell infiltration, including primarily T cells, macrophages, dendritic cells, B cells and NK cells (Nosalski and Guzik, 2017), which negatively impact on the function of the cardiovascular system (Lovren et al., 2015).

It is of note that the preferential storage of fat in non-ectopic vs. ectopic sites depends on several factors, including age, sex, ethnicity, genetic factors, hormonal status, diet and physical activity among others, leading to high inter-individual variability (Trouwborst et al., 2018). For the same age and BMI, VAT, intrahepatic and intramyocellular lipids are higher in men than in women, leading to higher cardiometabolic risk (Schorr et al., 2018).

Short-term intervention studies (3–4 weeks duration) in non-diabetic normal weight and obese individuals have shown that fructose at doses > 80 g/day in isocaloric exchange with other carbohydrates (mainly glucose) increases fasting glucose production and impairs insulin-mediated suppression of hepatic glucose output, indicating hepatic IR. A stimulation of gluconeogenesis may be involved in this process. In hypercaloric conditions, fructose in addition increased fasting serum insulin concentrations. Fructose-induced hepatic IR was, however, not associated with the development of fasting hyperglycaemia in normal weight subjects, or with peripheral (skeletal muscle) IR (Ter Horst et al., 2016). Of interest, consumption of a high fructose but not a high glucose diet for 6 weeks significantly impaired glucose tolerance in overweight subjects (Stanhope et al., 2009). Since impaired suppression of hepatic glucose production is instrumental in the development of impaired glucose tolerance (Mitrakou et al., 1990), this suggests that fructose may specifically be responsible for the development of hepatic insulin resistance. No data are available regarding the effects of a high galactose diet on hepatic insulin resistance.

3.6.1.3. *De novo* lipogenesis

High intakes of sucrose have been shown to increase fasting and postprandial blood triglyceride (TG) concentrations in animal models (Bizeau and Pagliassotti, 2005) and in humans (Stanhope, 2012), most likely due to its fructose component. In humans, fasting and postprandial blood TG concentrations increase at intakes of fructose above 100 g/day and 50 g/day, respectively (Livesey and Taylor, 2008). A higher hepatic DNL, an increased secretion of TG-rich lipoprotein particles (TRL) (VLDL

and chylomicrons) and a lower postprandial clearance of TRL are involved in this process (Chong et al., 2007). Rodent (Federico et al., 2006) and human studies (Theytaz et al., 2014) indicate that intestinal DNL may contribute to this hypersecretion of TRL. Increased TRL concentrations are in turn often associated with increased concentrations of chylomicron remnants, increased concentrations of small, dense LDL particles and low HDL-cholesterol, which may be directly involved in the development of atherosclerotic lesions.

Fructose has also been shown to increase intrahepatic TG concentrations in healthy, normal weight subjects and in overweight subjects within a few days. However, this has been observed only with high amounts of fructose (≥ 30% E) and under hypercaloric conditions (Lecoultre et al., 2013; Yki-Järvinen, 2015).

3.6.1.4. Hyperuricaemia

It has been known for a long time that both ingestion of an acute fructose load and the chronic consumption of a high fructose diet can increase blood uric acid concentrations. Several mechanisms can account for this. After administration of large iv or oral fructose loads, hepatic fructose uptake and phosphorylation to fructose-1-P are markedly increased while the degradation of fructose-1-P to trioses phosphate is slightly delayed. This results in a transient depletion of intrahepatic ATP stores, leading to the formation of AMP and to the degradation of purines (Kedar and Simkin, 2012). In addition, fructose may impair renal uric acid clearance and fractional excretion, as observed in rats (Hu et al., 2009).

Hyperuricaemia is an established risk factor for gout (Shiozawa et al., 2017). The association between high uric acid levels and hypertension, renal disease, cardiovascular diseases (CVD) and T2DM has also been known for some time (Feig et al., 2008a), although it is only recently that the causality of the relationship between serum uric acid levels and the pathogenesis of these diseases has been systematically investigated.

Uric acid levels, even within the normal range, have been proposed as an independent risk factor for the development of primary hypertension, particularly in young individuals. An increase in oxidative stress during uric acid synthesis leading to local and systemic inflammation, reduced availability of nitric oxide and endothelial dysfunction, proliferation of vascular smooth muscle cells and vasoconstriction have been involved in the progression of atherosclerosis. Renal vasoconstriction activates the renin–angiotensin system, increasing blood pressure (Feig et al., 2008a). Uric acid has also been shown to impair insulin-mediated glucose disposal by inducing endothelial dysfunction and by inhibiting insulin-mediated muscle vasodilation (Nakagawa et al., 2005).

Recent meta-analysis of prospective cohort studies has reported dose-response relationships between uric acid levels and risk of both stroke and CHD in both sexes, and the relationship appears to be stronger in women. It is still unclear, however, whether high uric acid levels are independent risk factors for the development of CVD, once traditional risk factors are accounted for (Kuwabara, 2016; Ndrepepa, 2018). The measurement of uric acid in the management of primary hypertension and in the primary prevention of CVD is acknowledged in current European professional guidelines (Williams et al., 2018; Visseren et al., 2021).

3.6.1.5. Other proposed mechanisms

Evidence is mounting that the composition and function of the gut microbiota could play a role in the development of obesity and associated metabolic disorders. The gut microbiome of obese individuals has been shown to be lower in bacterial diversity and gene richness and more capable to harvest energy from the diet than that of normal weight individuals, whereas some bacterial metabolites appear to correlate with metabolic biomarkers of disease (Turnbaugh et al., 2006; Le Chatelier et al., 2013; Vallianou et al., 2019). In addition, dietary factors, including the intake of added sugars, may act as external triggers inducing profound changes in the gut microbiome that have been related to obesity and metabolic disorders (Vallianou et al., 2019). However, the current lack of standards for defining what is considered to be a baseline healthy/stable microbiome precludes linking a particular metabolic disease state with a specific microbiome profile and furthermore establishing any causal relationships.

3.6.2. Pregnancy endpoints

Gestational diabetes mellitus (GDM) is defined as the development of impaired glucose tolerance during pregnancy in a non-diabetic woman. The mechanisms underlying this condition are the existence of a low insulin sensitivity, of a low insulin secretion or both simultaneously in the context of

a diabetogenic stress elicited by the neuroendocrine alterations associated with pregnancy. Obesity and a family history of type 2 diabetes mellitus or GDM are two of many risk factors for the development of GDM. Of note, the occurrence of GDM is itself a risk factor for the development of type 2 diabetes mellitus later in life (Feig et al., 2008b). High intakes of dietary sugars and fats during pregnancy have been associated with increased body weight gain during pregnancy in epidemiological studies. However, evidence is limited to few studies and the role of dietary sugars *per se* on weight gain during pregnancy has not been systematically investigated (Casas et al., 2020).

High birthweight, or macrosomia, is the major complication of diabetes during pregnancy to fetal metabolism. It is secondary to hyperglycaemia-driven fetal hyperinsulinaemia, which stimulates anabolism and the growth of fetal adipose tissue (Kc et al., 2015). High birthweight is widely recognised as a risk factor for later childhood obesity and type 2 diabetes (Wang et al., 2021).

Low birthweight and more specifically a small weight related to gestational age (SGA) occurs because of intrauterine growth retardation (IUGR). It results from chronic fetal undernutrition during gestation, which is most often due to placental insufficiency secondary to decreased uteroplacental blood flow, or to maternal protein/energy undernutrition (Krishna and Bhalerao, 2011). The unfavourable uterine environment causing growth restriction results in programming that predisposes IUGR infants to long-term health issues such as poor physical growth, metabolic syndrome, cardiovascular disease, neurodevelopmental impairment and endocrine abnormalities, warranting careful monitoring (Kesavan and Devaskar, 2019). Accelerated weight gain secondary to catch-up growth is also associated in SGA infants with a higher risk for overweight and obesity later in life (Nordman et al., 2020).

Protein/energy undernutrition during pregnancy is rare in European countries nowadays, and the majority of cases of European intrauterine growth retardation develop as a consequence of pre-eclampsia, a condition of unknown aetiology characterised by increased vascular resistance in placental blood vessels leading to placental hypoperfusion (Huppertz, 2008; Maršál, 2017). Both type 1 and type 2 diabetes increase the risk of pre-eclampsia. Few epidemiological studies have reported a correlation between the intake of dietary sugars and increased risk of pre-eclampsia during pregnancy (Casas et al., 2020). Excess energy intake may also directly contribute to the development of placental insufficiency, as reported in pregnant mice fed a high fat, high sucrose diet (Musial et al., 2017). This may be related to fructose-induced alterations of placental metabolism, including increased uric acid production, lipid accumulation and oxidative stress (Asghar et al., 2016).

3.6.3. Dental caries

Dental caries is the localised loss of dental hard tissues as a result of acids produced by bacterial fermentation of sugars in the mouth. The tooth is composed of three mineralised tissues – enamel, dentine and cementum. Dentine forms the bulk of the tooth including the roots and is covered by a thin layer of cementum. Enamel forms the hard, outer crown of the tooth and comprises hydroxyapatite crystals, composed of calcium and phosphate in a dispersed organic matrix.

The oral cavity contains a diverse microbiota, with a complex biogeography that differs across different areas, but whose dynamic equilibrium appears to be crucial to avoid the onset of specific diseases such as periodontitis and dental caries. Such microbiota, when developed along a tooth surface, constitutes what is clinically known as dental plaque (Kilian et al., 2016; Sanz et al., 2017; Zhang et al., 2018). An essential factor in the aetiology of dental caries is the dental plaque biofilm, which is made up of a pellicle, plaque microbiota and an extracellular matrix. The pellicle, comprised of adsorbed salivary proteins, is the first layer to form onto the enamel surface. Microorganisms then become attached to the pellicle and multiply, forming a continuous layer increasing in depth. The microorganisms make up 70% of plaque. Dental plaque contains over 500 different types of bacteria, yet the majority do not have a direct role in dental caries development but influence the properties of the plaque. Thirty per cent of plaque consists of the plaque matrix which is largely composed of glucans derived from dietary sucrose by the action of glucosyltransferases from plaque bacteria. Mutans streptococci and Lactobacillus acidophilus are major bacteria associated with dental caries playing a key role in the initiation and progression of dental caries; however, many other types of bacteria in the oral biofilm can metabolise sugars to acid (Roberts, 2015). Mutans streptococci produce acids from dietary sugars, synthesise glucan from sucrose and create ideal conditions for other cariogenic bacteria such as lactobacilli, bifidobacteria and some non-mutans streptococci.

Dietary sugars diffuse into the dental plaque where they are metabolised by plaque microorganisms to organic acids (mostly lactic acid) which diffuse into the enamel causing subsurface demineralisation and initiating the caries process (Pitts et al., 2017). Enamel hydroxyapatite usually begins to

demineralise at around pH 5.5, which is sometimes referred to as the 'critical pH'. Saliva contains several buffer systems that increase plaque pH, thus promoting remineralisation in porous areas where demineralisation has occurred. A demineralised lesion may therefore be remineralised in the early stages. However, if acid conditions and resulting demineralisation dominate, the enamel becomes more porous until finally the surface gives way and a cavity forms. The rate of demineralisation is affected by the concentration of hydrogen ions (i.e. pH at the tooth surface) and the duration for which the plaque pH falls below the critical pH. Another factor is the amount of calcium, phosphate and fluoride available in plaque, because high levels of these minerals in plaque will help resist demineralisation. There is some evidence to suggest that sucrose is more cariogenic compared with other mono- and disaccharides partly due to it being the sole substrate for glycan synthesis (Zero, 2004). However, there is not enough evidence to rank the cariogenic potential of sugars and likely no benefit of substituting one for another (Koulourides et al., 1976). In theory, the form of the sugars containing food and its oral retentiveness (stickiness) could impact the cariogenic potential by extending the length of exposure of the acidogenic bacteria to sugars substrate in the mouth. However, epidemiological evidence to support this is lacking.

Dental caries requires sugars and acidogenic bacteria to occur, but is influenced by the composition of the tooth, the quantity and composition of saliva and the time sugars are available for fermentation. Furthermore, behavioural factors, e.g. toothbrushing, interdental cleaning, the use of plaque revealing solutions or fluoride use, can further affect caries incidence, by altering the oral microenvironment, i.e. reducing the amount of plaque on tooth surfaces, making oral hygiene easier or modifying the mineral composition of tooth surfaces and possibly bacterial activity.

4. Dietary sources and intake data

4.1. Dietary sources

Glucose and fructose are found naturally in fruits, berries, some vegetables and honey. Sucrose is naturally present in sugar cane and sugar beet, in honey and in many vegetables, berries and fruits. However, the most prevalent dietary source consists of sucrose added at the table and to processed foods, as a sweetener to improve palatability, as a food preserver and to confer functional characteristics to foods. Galactose is found in fermented and lactase-hydrolysed milks but is rare. Lactose is naturally found exclusively in milk and dairy products (Cummings and Stephen, 2007; EFSA NDA Panel, 2010a).

Maltose and trehalose are naturally present in small amounts in some foods. Maltose is found naturally in e.g. barley, wheat, germinating grain, maltodextrins and glucose syrups, while trehalose is found in yeast products, mushrooms and crustaceans. Trehalose can be used to replace sucrose in foods to reduce the sweet taste while keeping similar technological properties (Cummings and Stephen, 2007; EFSA NDA Panel, 2010a).

Glucose–fructose (or fructose–glucose) syrups[6] are increasingly used as a substitute for sucrose in processed foods and beverages due to their technological characteristics such as longer shelf-life, higher stability in solutions and lower price. These syrups are derived from the hydrolysation of starch into individual glucose units, about half of which are then enzymatically converted to fructose. In the United States, such syrups are known as 'high fructose corn syrups' (HFCS) as they are produced from corn, and to differentiate them from corn syrups, which contain 100% glucose. In the EU, where glucose–fructose syrups are consumed three times less frequently than in the United States (kg/capita), they are not necessarily produced from corn, and are referred to as 'isoglucose'[7]. The percentage of fructose contained in the syrups varies across countries and no defined composition is available. Typically, most syrups contain either 42% fructose, as those used in processed foods, or 55% fructose, as those used in SSBs. Compared to sucrose (50% glucose and 50% fructose), the proportion of the two monosaccharides is fairly similar, but in HFCS and isoglucose, they are not bound together (free monosaccharides). Following the abolition of the EU sugar quota system in 2017, which had controlled the sugar market since 1968, sugar production and exports are no longer limited. It has been estimated that, by 2026 (i.e. within 10 years from the sugar quota abolition), the internal production of isoglucose will more than double, reaching 10% of the EU sweetener market. Consumption of free fructose in Europe is likely to increase in parallel (Sanders and Lupton, 2012;

[6] Council Directive 2001/111/EC of 20 December 2001 relating to certain sugars intended for human consumption.
[7] Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (Single CMO Regulation) – Part II.

European Commission, 2017,2018). Free fructose is generally perceived as sweeter than sucrose in foods and beverages on a weight basis (Hobbs, 2009).

4.2. Methodological considerations

Estimates of intake of total, added and free sugars from all dietary sources were obtained using data from the EFSA Comprehensive Food Consumption Database in combination with the food composition databases for total, added and free sugars as described in the protocol and illustrated in **Figure 3**. The methodology used is fully described in **Annex B**.

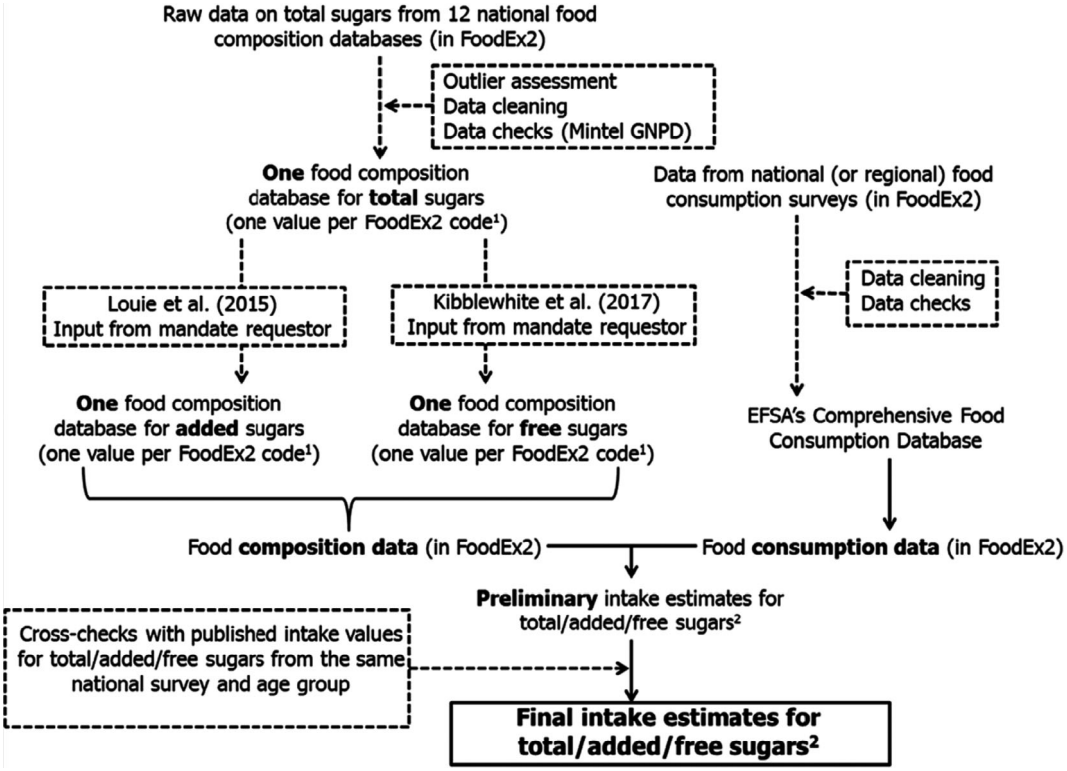


Figure 3: Methodology used to estimate intakes of total, free and added sugars in European countries

Solely for the purpose of developing the food composition databases for added and free sugars, the definitions of added and free sugars were modified as illustrated in **Figure 4**. This is because the exact product consumed was not specified at national level (e.g. cookies, with no specification of the type or brand), so that the ingredient used for sweetening purposes (e.g. sucrose, fructose, syrups, honey, fruit juice concentrates, other) was not specified, and thus, the amount of added and free sugars originating from the different ingredients could not be assigned.

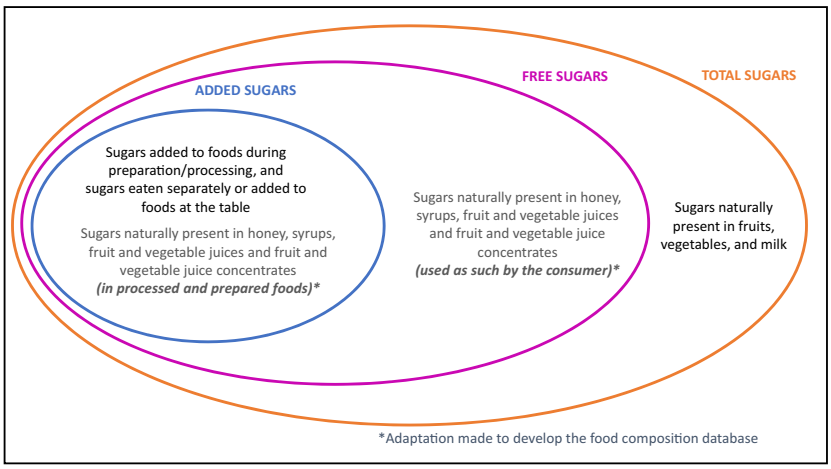


Figure 4: Adaptation of the definitions of added and free sugars for the development of the food composition database

The procedure by Wanselius et al. (2019) developed from previous methods for estimation of added sugars content in foods by Louie et al. (2015) and for estimation of free sugars content by Kibblewhite et al. (2017) was systematically used as the basis for the estimation of added and free sugars.

The food composition databases on total, added and free sugars and details on the characteristics of the food consumption surveys included in the EFSA Comprehensive European Food Consumption Database that was used to estimate intakes of dietary sugars (name, population group covered, number of subjects, number of consumption days recorded and dietary method used) can be found in **Annex C. Annex C** also includes information on the FoodEx2 levels and corresponding categories used to link food composition and food consumption data (i.e. linking categories). Intake estimates of total, added and free sugars in the whole population and in consumers of selected food groups are in **Annex D** and **Annex E**, respectively. Data are provided by age group, consumption survey and country.

Data on the content of single mono- and disaccharides in foods in the EFSA Nutrient Composition Database are scarce and not adequate to provide estimates of intake for individual types of sugars. This paucity of data was confirmed in the questionnaires completed by the National Competent Authorities of European Countries (**Annex F**).

The latest version of the EFSA Comprehensive Food Consumption Database, updated in 2020, contains results from a total of 69 different dietary surveys carried out in 25 different European countries covering 134,929 individuals. Consumption data were collected using repeated 24-hour dietary recalls or dietary records covering from 2 to 9 days per subject. Because of the differences in the methods used for data collection, direct country-to-country comparisons are not always possible. In addition, data on total energy intake reported by data providers were used to calculate intakes of dietary sugars as E%. Since different methodologies, assumptions and national food composition databases may have been used to calculate energy intakes for each survey, between-country comparisons for sugars intakes expressed as E% should be read with caution.

Food groups contributing to the intake of dietary sugars have been constructed by clustering the linking categories in different ways (**Table 2**). For the whole population, the purpose was to identify major sources of dietary sugars and calculate intakes of sugars coming from both core food groups (i.e. food groups supplying most macro- and micronutrients in the diet as recommended in FBDGs) and non-core food groups (i.e. food groups that could be removed from the diet without substantially affecting its nutritional quality and for which FBDGs generally advise to limit consumption). Non-core food groups being major contributors to the intake of added and free sugars have been broken down further to identify consumer groups of interest (consumers). The Panel acknowledges that the above-mentioned classification is functional to this opinion, and that the contribution of specific foods to nutrient intakes may differ across population groups and countries depending on dietary patterns and traditions.

Table 2: Food groups contributing to the intake of dietary sugars in the whole population and food groups used to define consumer groups[(a)]

Food groups (whole population)		Food groups (consumers)	
Short name	**Description**	**Short name**	**Description**
SUGARS AND CONFECTIONERY	Sugar and similar (i.e. table sugar, honey and syrups), confectionery and water-based sweet desserts	SUGAR AND SIMILAR	Table sugar, honey and syrups
		CONFECTIONERY	Confectionery and water-based sweet desserts
SSSD+SSFD	Soft and fruit drinks sweetened with sugar	SSSD+SSFD	Soft and fruit drinks sweetened with sugar
FINE BAKERY WARES	e.g. cakes, biscuits, pastries	FINE BAKERY WARES	e.g. cakes, biscuits, pastries
FRUIT/VEG JUICES	Fruit/vegetable juices and nectars	FRUIT/VEG JUICES	Fruit/vegetable juices and nectars
FRUIT/VEG_processed	Processed fruits and vegetables excluding beverages		
FRUIT/VEG_fresh	Fresh fruits, vegetables		
CEREALS	Cereal and cereal-based products including bread but excluding fine bakery wares		
MILK AND DAIRY	Milk and dairy products including dairy alternatives		
BABY FOODS	Foods for infants and young children		
ALCOHOLIC BEV	Alcoholic beverages		
OTHERS	Others		

(a): Detailed composition of each food group could be found in **Annex D (Tables 6, 7 and 8)**.

The intake of 'fruit and vegetable juices' was estimated together. In about 88% of the consumption occasions, these were coded by data providers as fruit juices, which in FoodEx2 are 100% fruit juices, with no added sugars. The remaining consumption occasions were coded as fruit nectars (25–99% fruit, with added sugars; 3%), vegetable juices (2%), mixtures of fruit and vegetable juices (0.5%), or by using FoodEx2 codes at higher levels that made it impossible to identify whether the juices consumed were with added sugars or not (e.g. 'fruit juices and nectars', 7%). Therefore, consumption of 'fruit and vegetable juices' mostly refers to fruit juice with no added sugars (100% fruit juice). It is important to highlight that participants in the food consumption surveys might not have the knowledge or information to differentiate between fruit juices with no added sugars and fruit nectars with added sugars, and/or the question in the food consumption survey may have not been specific enough to retrieve that information. The Panel notes that consumption of fruit nectars is likely to have been underestimated using the EFSA Comprehensive Database and the consumption of 100% fruit juices overestimated leading to underestimation of the intake of added sugars from 'fruit and vegetable juices', whereas the intake of free sugars is not affected by this uncertainty.

4.3. Estimates of intake of total, free and added sugars from all dietary sources

Intakes of total, free and added sugars by European country and population group in grams per day, as E%, and as non-alcohol E%, both from all sources and from specific food groups, as well as the percent contribution of these food groups to the total intakes, are shown in **Annex D**.

Intakes of added and free sugars by country and population group in grams per day, as E%, and as non-alcohol E% are also provided for consumers in relation to five food groups which have been identified as major contributors to the intake of added and free sugars. Consumers were defined as subjects who had consumed at least one food product within the food group at least once within the survey period. The percent contribution of each food group to the intake of free and added sugars from all sources in consumers of the food category only is provided in **Annex E**.

A summary of the intake of total, added and free sugars from all sources in g/day across European surveys by population group and sex is given in **Tables 3** and **4**, and as percent of total energy (E%) for both sexes combined in **Table 5**.

Table 3: Daily intakes of total, free and added sugars across European dietary surveys by population group – females

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 month to < 12 month (n = 13)	39	87	78	103	1	18	5	44	1	14	4	35
Toddlers, ≥ 12 month to < 36 months (n = 16)	58	100	93	141	11	54	31	104	8	39	21	89
Other children, ≥ 3 to < 10 years (n = 19)	61	116	97	179	29	79	61	135	22	67	49	120
Adolescents, ≥ 10 to < 14 years (n = 19)	69	126	107	214	31	89	74	156	25	77	59	145
Adolescents, ≥ 14 to < 18 years (n = 17)	56	118	96	210	25	78	65	177	21	68	58	145
Adults, ≥ 18 years to < 65 (n = 22)	59	119	101	215	24	67	61	166	19	51	50	125
Older adults, ≥ 65 years (n = 21)	54	109	96	185	17	53	52	122	13	43	43	95
Pregnant women (n = 5)	71	97	117	163	32	50	76	113	25	44	66	92
Lactating women (n = 2)	95	112	144	190	50	52	90	118	27	43	60	98

(a): The 95th percentile estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

Table 4: Daily intakes of total, free and added sugars across European dietary surveys by population group – males

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 month to < 12 month (n = 13)	43	81	81	132	2	19	9	41	1	14	8	35
Toddlers, ≥ 12 month to < 36 month (n = 16)	62	105	96	154	14	68	37	105	10	45	27	92

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Other children, ≥ 3 to < 10 years (n = 19)	67	134	101	220	31	86	62	156	23	74	46	139
Adolescents, ≥ 10 to < 14 years (n = 19)	67	142	130	258	27	104	85	178	22	92	72	178
Adolescents, ≥ 14 to < 18 years (n = 17)	78	148	146	284	36	109	95	252	30	96	77	174
Adults, ≥ 18 to < 65 years (n = 22)	68	131	132	270	29	86	72	219	24	67	70	163
Older adults, ≥ 65 years (n = 21)	59	117	105	206	17	63	51	142	11	51	43	131

(a): The P95 estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

Table 5: Daily intakes of total, free and added sugars across European dietary surveys by population group – males and females combined[a]

Population group, age range (n surveys)	Total sugars (E%)				Free sugars (E%)				Added sugars (E%)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 to < 12 month (n = 13)	24	44	36	94	1	11	4	31	1	11	3	30
Toddlers, ≥ 12 months to < 36 month (n = 15)	20	32	30	50	4	18	10	36	3	13	8	29
Other children, ≥ 3 to < 10 year (n = 16)	16	31	23	43	8	20	14	33	6	17	11	28
Adolescents, ≥ 10 to < 14 years (n = 15)	15	26	23	41	8	18	15	30	5	16	12	28
Adolescents, ≥ 14 to < 18 year (n = 13)	14	26	23	45	8	18	15	38	6	15	13	27
Adults, ≥ 18 to < 65 year (n = 17)	12	25	23	42	6	15	13	33	5	10	12	23
Older adults, ≥ 65 year (n = 17)	13	23	25	36	4	11	11	24	3	9	9	18
Pregnant women; 5 (n = 4)	14	21	23	32	6	10	14	22	5	9	10	20
Lactating women (n = 2)	19	23	30	34	10	10	19	21	6	8	11	18

(a): The P95 estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

The population group 'elderly adults' defined in the protocol encompasses the age categories 'elderly' and 'very elderly' described in the EFSA Comprehensive database (EFSA, 2011). Individuals aged 65 years and older will be referred to as older adults in this opinion.

A summary of the intake of total, added and free sugars from specific food groups across European surveys by population group can be found in **Appendix A**. A summary of the intake of added and free sugars from the five food groups contributing the most to the intake of added and free sugars in consumers across European surveys by population group is depicted in **Appendix B**.

4.3.1. Adults and older adults

4.3.1.1. Whole population

In adults, mean intakes of total, added and free sugars in absolute amounts were higher in males than in females within each survey, as expected from the higher body size and energy intake, whereas mean intakes of total sugars as E% were systematically higher in females than in males.

For **total sugars**, mean intakes ranged from 12 E% in Croatian males to 25 E% in German females. The P95 ranged from 23 to 42 E%. Overall, the major contributor to total sugars intake was fresh fruits and vegetables (from 14% in the Netherlands to 39% in Romania), followed by sugars and confectionery (from 11% in Slovenia and Sweden to 29% in Hungary) and milk and dairy products (from 10% in Latvia and Romania to 26% in Finland). The contribution of cereals, processed fruits and vegetables and alcoholic beverages to the intake of total sugars was low (≤ 9% each), as well as the variability across countries. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy and cereals) to the intake of total sugars ranged between 31% in Germany and 54% in Spain, whereas the contribution of beverages (i.e. SSSD, SSFD, fruit and vegetable juices) ranged from 8% in Italy to 29% in Germany **(Annex D)**.

Mean intakes of **added and free sugars** ranged from 4 E% in Cypriot females to 10 E% in Dutch males and females, and from 5 E% in Croatian males to 15 E% in German females, respectively. The P95 ranged from 12 to 23 E% and from 13 to 33 E%, respectively. By definition, the food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% to 5 E% (P95 from 1 E% to 24 E%). The major contributor to the intake of added sugars in virtually all countries was sugar and confectionery (from 20% in Austria to 57% in Italy), followed by SSSD+SSFD (from 8% in Latvia and Italy to 34% in Belgium) and fine bakery wares (from 2% in Denmark to 30% in Austria), with high variability across countries. The contribution of cereals (≤ 9%), fruit and vegetable juices (≤ 5%) and alcoholic beverages (≤ 3%) to mean intakes of added sugars was low, with low variability across countries. The contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) to the intake of added sugars ranged between 8% in Latvia and 35% in Croatia, whereas their contribution to the intake of free sugars ranged from 16% in Italy and Latvia to 46% in Germany **(Annex D)**.

In the older adults, mean and P95 intakes of total, added and free sugars as E% were comparable to those in adults, but generally lower. Beverages combined contributed less to **total** sugars intake (between 4% in Italy and 15% in Germany), particularly SSSD+SSFD, while core food groups combined contributed more (from 37% in Austria up to 66% in Greece). Sugars and confectionery contributed more to **added** sugars intake (between 10% in Austria and 66% in Italy), as well as fine bakery wares and processed fruits and vegetables (from 2% in Denmark to 45% in Austria and from 2% in Portugal to 26% in Sweden, respectively), while the contribution of beverages combined was lower (from 3% in Finland to 22% in Cyprus and Romania).

4.3.1.2. Consumers of selected food groups

In adults, intakes of added and free sugars from all sources and from food groups identified as the major contributors to the intake of added and free sugars in the whole population have also been calculated for the population of consumers of each food group **(Appendix B, Annex E)**. In virtually all countries, mean intakes of added and free sugars from all sources (g/day) were higher in adult consumers of SSSD+SSFD than in consumers of any other food group. Exceptions were Czech Republic, Hungary, Romania and the United Kingdom, where the highest intakes of added and free sugars were among consumers of confectionery, and the Netherlands, where the highest intakes of free sugars were among consumers of fruit and vegetable juices. Intakes of added sugars were higher from SSSD+SSFD than from any other food group in consumers in all countries (mean intakes up to 40 g/day, P95 up to 123 g/day). Likewise, intakes of free sugars were higher from SSSD+SSFD than from any other food group in consumers in most countries, except for Finland and Germany. In these

countries, intakes of free sugars were higher from fruit and vegetables juices than from any other food group in consumers, with mean intakes of 27 g/day (P95 76 g/day) and 45 g/day (P95 134 g/day) in Finland and Germany, respectively. The contribution of SSSD+SSFD to added sugars and of fruit and vegetables juices to free sugars was up to 51% and up to 46%, respectively, in consumers of these beverages.

As for adults, **older adults** consumers of SSSD+SSFD had generally the highest mean intakes of added and free sugars from all sources (g/day). Intakes of added sugars from SSSD+SSFD and of free sugars from fruit and vegetable juices were higher than from any other food group in consumers in most countries, but lower than in adults (up to 25 g/day, P95 up to 71 g/day and up to 30 g/day, P95 up to 94 g/day, respectively). SSSD+SSFD contributed slightly more to added sugars intake (up to 53%) and fruit and vegetable juices slightly less to free sugars intake (from 2% to 42%) in consumers of these beverages in the older adults compared to adults **(Appendix B, Annex E)**.

4.3.2. Infants

4.3.2.1. Whole population

In infants aged from ≥ 4 to < 12 months, mean intakes of total, free and added sugars in absolute amounts were generally higher in males than in females, but comparable between sexes when expressed as E% (differences up to ±1 E% in most countries), with few exceptions.

Mean **total sugar** intake as E% ranged from 24 E% in Italian females and Danish males, to 44 E% in German males and females. The P95 ranged between 36 E% and 94 E%. The major contributors to total sugar intake where baby foods (from 12% in Latvia to 65% in France), milk and dairy (from 13% in Finland to 60% in Estonia), followed by fresh fruits and vegetables (above 10% in all countries but France and Estonia, where it was only 3% and 8%, respectively, and up to 28% in Slovenia). The contribution of SSSD+SSFD (≤ 3%), cereals (≤ 3%) and fine bakery wares (≤ 4%) to the mean intake of total sugars was low. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy, cereals and baby foods) to the intake of total sugars ranged between 66% in Bulgaria and 97% in Portugal and Estonia, whereas the contribution of SSSD+SSFD and fruit and vegetable juices combined was ≤ 9% in all countries **(Annex D)**.

Mean intakes of **added and free sugars** in infants ranged from ≅ 0 E% in Cypriot females to 11 E% in Finnish males, and from 1 E% in Cypriot and Estonian males and females and Spanish females to 11 E% in Finnish males, respectively. The P95 for added sugars ranged between 3 E% and 30 E% and for free sugars from 4 E% to 31 E%, respectively. The food groups contributing the most to the difference between the intake of added and free sugars were sugars and confectionery (intake from ≅ 0E% to 9 E%, P95 from ≅ 0 E% to 22 E%), owing to the contribution of honey and syrups to the intake of free (but not added) sugars, and fruit and vegetable juices (intake from ≅ 0 E% to 2 E%, P95 from ≅ 0 E% to 14 E%). The contribution to mean added sugars intake of fruit and vegetable juices, processed fruits and vegetables, SSSD+SSFD and cereals was low in most countries (≤ 6%, ≤ 9%, ≤ 9% and ≤ 10%, respectively), with exceptions for fruit and vegetable juices (up to 23% in Italy), processed fruits and vegetables and cereals (up to 19% and 16% in Estonia, respectively), and for SSSD+SSFD (up to 25% in Germany). The contribution of baby foods to the mean intake of added sugars was very variable across countries, owing to the high heterogeneity of the individual foods grouped under this category and to differences in food choices among countries (e.g. selection of regular foodstuffs vs. foods specially formulated for infants and young children). It ranged from ≅ 0 E% in Bulgaria, Denmark, Latvia, Portugal, Finland and Spain, where only consumption of baby foods with no added or free sugars was reported, to 52% in France **(Annex D)**.

Major contributors to the intake of **added** sugars, with high variability across countries, were milk and dairy (from 3% in Bulgaria and Italy to 58% in Spain), sugars and confectionery (from 1% in Spain and Portugal to 72% in Bulgaria) and fine bakery wares (from 0% in Italy to 36% in Portugal). In Finland, foods were disaggregated into their main components by the data providers **(Annex B)**, and consequently, the contribution from sugars and confectionery to added sugar intake was 82%, whereas the contribution from fine bakery wares and milk and dairy was 0%. In most countries, consumption of SSSD+SSFD in infants was negligible (≤ 1%). Among countries reporting any significant consumption of these beverages, the contribution of SSSD+SSFD and fruit and vegetable juices combined to the intake of added sugars ranged from 1% in Denmark and Estonia to 25% in Germany. The contribution of these beverages combined to the intake of free sugars ranged from 2% in Finland to 37% in Germany **(Annex D)**.

4.3.2.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) in infants were higher in consumers of SSSD+SSFD than in consumers of any other food group in all countries with a significant consumption of these beverages. The exceptions were the United Kingdom and Slovenia, where confectionery was the highest contributor to the intake of free sugars from all sources. Mean intakes of added and free sugars were, in most countries, higher from SSSD+SSFD (added sugars: intake up to 31 g/day, P95 up to 6 g/day and free sugars: up to 35 g/day, P95 up to 7 g/day) than from any other food group in consumers. The contribution of SSSD+SSFD to added sugar intake and free sugar intake in consumers was up to 100% (Portugal) **(Appendix B, Annex E)**.

4.3.3. Toddlers and children

4.3.3.1. Whole population

In toddlers (12 to < 36 months) and in other children (≥ 36 months to < 10 years, from now on children), mean intakes of total, free and added sugars in absolute amounts were generally higher in males than in females, but comparable between sexes when expressed as E% (differences up to ±1 E% in most countries), with few exceptions.

In **toddlers**, mean **total sugar** intakes as E% ranged between 19 E% in Italian females and 33 E% in German males. The P95 ranged between 30 E% and 50 E%. The major contributor to total sugar intake was milk and dairy in almost all countries (from 17% in Cyprus to 37% in Portugal), followed by fresh fruits and vegetables (from 9% in France to 30% in Slovenia) and baby foods (from 1% in Denmark to 32% in Cyprus) with high variability across countries. The contribution of cereals and fine bakery wares to total sugar intake was low, with low variability across countries (≤ 6% and ≤ 10%), followed by processed fruits and vegetables (≤ 14%). The contribution of SSSD+SSFD to the intake of total sugars was ≤ 8% in all countries but Germany and the Netherlands (16% and 19%, respectively). Fruit and vegetable juices contributed generally more to total sugar intake (from 3% in the United Kingdom (DNSIYC 2011) and Portugal to 19% in Belgium and Bulgaria) than SSSD+SSFD, with high variability across countries. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy, cereals and baby foods) ranged between 45% in Bulgaria and 84E% in Portugal, whereas the contribution of beverages (i.e. SSSD, SSFD, fruit and vegetable juices) ranged between 4% in Finland and 29% in Germany **(Annex D)**.

Mean intakes of **added and free sugars** in toddlers ranged from 2 E% in Cypriot females to 13 E% in German males and females and Dutch females, and from 3 E% in Cypriot females to 18 E% in German males, respectively. The P95 ranged between 8 E% and 29 E% for added sugars and between 10 E% and 36 E% for free sugars. The food groups contributing the most to the difference between the intake of added and free sugars were fruit and vegetable juices (mean intake of free sugars from 0 E% to 4 E%, P95 from 2 E% to 24 E%). The major contributors to added sugars intake were sugars and confectionery (< 10% only in Spain and Cyprus, and up to 49% in Denmark), milk and dairy (< 10% only in Bulgaria, and up to 48% in Spain) and fine bakery wares (≥ 10% in all countries but Denmark, Estonia and Finland, and up to 34% in Cyprus), with high variability across countries. The contribution to mean added sugars intake of fruit and vegetable juices, processed fruits and vegetables, baby foods and cereals was low in most countries (≤ 5%, ≤ 7%, ≤ 8% and ≤ 8%, respectively), with exceptions for fruit and vegetable juices and baby foods (up to 20% and 15%, respectively, in Italy), processed fruits and vegetables (up to 15% on Latvia) and for cereals (up to 20% in Cyprus). In Finland, where foods were disaggregated by the data providers (Section 5.2), the contribution from sugars and confectionery to added sugars intakes was 61%, whereas the contribution from baby foods and fine bakery wares was negligible. The contribution of SSSD+SSFD to added sugar intakes was < 10% in half the countries and ranged from 0% in Finland to 42% in the Netherlands, with high variability across the countries. The contribution of beverages combined to added and free sugar intakes ranged from 0% in Finland to 44% in the Netherlands, and from 13% in Finland to 53% in Germany, respectively **(Annex D)**.

In children, despite a generally lower intake of total sugars as E%, mean intakes of added and free sugars were generally higher than in toddlers. Compared to toddlers, beverages combined contributed more (up to 32% in Germany (VLS)) to total sugars intake, whereas the contribution of core food groups combined (i.e. fresh fruits and vegetables, milk and dairy, cereals) was lower (from 37% in Germany (ESKIMO) to 65% in Cyprus). Baby foods, barely consumed by this population group, were combined with other minor contributors to the intake of total sugars in the miscellaneous group 'others'. As in toddlers, milk and dairy contributed the most to the intake of total sugars (up to 40%),

but its contribution was lower in children than in toddlers in most countries, with few exceptions. The contribution of SSSD+SSFD to added sugar intakes in children (up to 39% in the Netherlands) was generally higher compared to toddlers in almost all countries. The food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% in Portugal to 5 E% in Germany (ESKIMO) and Finland (P95 from 6 E% to 22 E%). There was a general trend towards a higher contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) to added and free sugar intakes in children compared to toddlers in most countries (up to 24% higher in Denmark and up to 26% higher in Finland, respectively). Notable exceptions in children were two countries where the very high contribution of beverages to added and to free sugars intakes reported in toddlers dropped slightly (up to 40% in the Netherlands and up to 44% in Germany (ESKIMO), respectively) **(Annex D)**.

4.3.3.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) **in toddlers** were higher in consumers of SSSD+SSFD and in consumers of confectionery than in consumers of any other food group in almost all countries **(Appendix B, Annex E)**. Exceptions were Finland, where the highest mean intakes of added sugars were among consumers of fine bakery wares, and Estonia and the United Kingdom (NDNS 1–3),[8] where the highest intakes of free sugars were among consumers of fruit and vegetable juices. Mean intakes of added and free sugars were, respectively, higher from SSSD +SSFD (up to 21 g/day, P95 up to 59 g/day) and fruit and vegetable juices (up to 24 g/day, P95 up to 47 g/day) than from any other food group in consumers, with a few exceptions. The contribution of SSSD+SSFD to added sugar intake and of fruit and vegetable juices to free sugar intake in these consumer groups was, respectively, up to 46% and up to 48%.

Mean intakes of added sugars from all sources (g/day) **in children** were mainly higher in consumers of SSSD+SSFD than in consumers of any other food group, while mean intakes of free sugars were highest in consumers of SSSD+SSFD or fruit and vegetable juices, with few exceptions. Intakes of added and free sugars in children were higher from SSSD+SSFD (mean intakes up to 29 g/day, P95 up to 67 g/day and up to 31 g/day, P95 up to 72 g/day, respectively) than from any other food group in consumers in most countries. The contribution of SSSD+SSFD to the mean added and free sugars intakes in these consumer groups was up to 41% and up to 38%, respectively **(Appendix B, Annex E)**.

4.3.4. Adolescents

4.3.4.1. Whole population

In adolescents aged ≥ 10 to < 14 years (younger adolescents), mean intakes of total, added and free sugars in absolute amounts (g/day) were the same or higher in males than in females in most countries, while in adolescents aged ≥ 14 to < 18 years (older adolescents), as in adults, they were higher in males than in females in all countries. Mean intakes of total sugars as E% were the same or higher in females than in males (up to +5 E%) in older and younger adolescents, with few exceptions in younger adolescents only.

In **younger adolescents**, mean intakes of **total sugars** ranged from 15 E% in Cypriot and Italian males and females to 27 E% in Estonian males and females and Finnish males. The P95 ranged from 23 to 41 E%. The major contributors to mean total sugar intake were milk and dairy (from 11% in Austria to 32% in Finland), fresh fruits and vegetables (from 8% in Sweden to 26% in Estonia[9]), sugars and confectionery (from 7% in Spain to 24% in Germany) and SSSD+SSFD (from 3% in Latvia to 27% in the Netherlands). The contributions from alcoholic beverages (≤ 2%), processed fruits and vegetables (≤ 11%) and cereals (≤ 12%) were low, with low variability across countries. Collectively, the contribution from core food groups (i.e. fresh fruits and vegetables, milk and dairy and cereals) was between 33% in Belgium and 58% in Greece. The contribution from SSSD+SSFD and fruit and vegetable juices combined to total sugars intake ranged from 14% in Latvia to 34% in the United Kingdom and the Netherlands **(Annex D)**.

Mean intakes of **added and free sugars** in younger adolescents ranged from 5 E% in Cypriot males to 16 E% in Dutch males, and from 8 E% in Cypriot and Italian males and females to 19 E% in Dutch males, respectively. The P95 ranged from 12 to 28 E% for added sugars and from 15 to 30 E%

[8] NDNS ROLLING PROGRAMME YEARS 1-3.
[9] DIET-2014-EST-C.

for free sugars. The food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% in the Czech Republic to 5 E% in Germany (P95 from 5 to 22 E%). The major contributors to mean added sugars intake were sugars and confectionery (from 13% in Portugal to 56% in Finland) and SSSD+SSFD (from 7% in Latvia to 41% in the Netherlands), followed by fine bakery wares (≥ 10% in most countries and up to 32% in Greece) and milk and dairy (≥ 10% in most countries and up to 26% in Spain). The lowest contributions to mean added sugar intakes were from alcoholic beverages (≤ 1%), cereals (≤ 11% in all countries but Cyprus, where it was 23%), processed fruits and vegetables (≤ 11%) and fruit and vegetable juices (≤ 12%). The contribution from beverages to added and free sugar intakes ranged between 10% in Cyprus and 42% in the Netherlands, and between 24% in Latvia and 49% in the United Kingdom, respectively **(Annex D)**.

In older adolescents, mean intakes of total, added and free sugars as E% were comparable to those of younger adolescents in all countries. Only in Germany, the P95 for total and free sugars were notably higher (up to 46 E% and 39 E% in females, respectively). The contribution from beverages combined to the intake of total and free sugars was similar in younger and older adolescents in all countries but Germany, where for older adolescents it was as high as 43% and 59%, respectively **(Annex D)**.

4.3.4.2. Consumers of selected food groups

In younger adolescents, no consistent pattern was found when calculating the highest mean intake of added and free sugars from all sources (g/day) for the consumers of different food groups, by country. For example, in Finland, the highest mean intake of added and free sugars from all sources was reported for consumers of fine bakery wares, whereas in Spain, the highest mean intake of added and free sugars from all sources was reported for consumers of confectionery and in Germany for consumers of SSSD+SSFD **(Appendix B, Annex E)**. Intakes of added sugars from SSSD+SSFD in consumers were higher than intakes from any other food group (mean intakes up to 37 g/day, P95 up to 97 g/day), whereas intakes of free sugars from either SSSD+SSFD (up to 39 g/day, P95 101 g/day) or fruits and vegetable juices (up to 26 g/day, P95 71 g/day) were higher than from any other food group in consumers in most countries. The contribution of SSSD+SSFD to added and free sugars intake was up to 56% and up to 47% in this consumer group, respectively.

In older adolescents, mean intakes of added and free sugars from all sources (g/day) were higher in consumers of SSSD+SSFD than in consumers of any other food group in most countries. Mean intakes of added sugars were higher from SSSD+SSFD than from any other food group in consumers (up to 40 g/day, P95 up to 118 g/day) whereas the highest intakes of free sugars were from either SSSD+SSFD (up to 41 g/day, P95 up to 118 g/day) or fruits and vegetable juices (up to 55 g/day, P95 146 g/day), with a few exceptions. These intakes were generally higher compared to younger adolescents. The contribution of SSSD+SSFD to added and free sugars intake was also higher than in younger adolescents (up to 59% and up to 48% in this consumer group, respectively) **(Appendix B, Annex E)**.

4.3.5. Pregnant and lactating women

4.3.5.1. Whole population

In the only five surveys available on **pregnant women** (Austria, Cyprus, Latvia, Portugal and Spain), the mean intake of **total sugars** ranged from 14 E% in Cyprus to 21 E% in Austria, with the P95 ranging from 23 to 32 E%, respectively. Mean intakes of total sugars in pregnant women compared to non-pregnant women from the same countries were generally higher in absolute amounts but similar when expressed as E%. Major contributors to total sugar intake were fresh fruit and vegetables (from 22% in Spain to 30% in Cyprus), milk and dairy products (from 16% in Austria to 31% in Portugal) and sugars and confectionery (from 9% in Austria to 16% in Latvia). The contribution from processed fruit and vegetables and cereals was low (≤ 9% for both). Core food groups collectively, i.e. fresh fruits and vegetables, cereals and milk and dairy, contributed between 52% in Spain and 60% in Cyprus, whereas the contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) was between 8% in Latvia and 22% in Austria **(Annex D)**.

Mean **intakes** of **added and free sugars** ranged from 5 E% in Cyprus to 9 E% in Latvia and from 6 E% to 10 E% in the same countries, respectively. The P95 ranged from 10 to 20 E% and from 14 to 22 E%, respectively. As for total sugars, mean absolute intakes of added and free sugars were generally higher in pregnant women than in non-pregnant women from the same countries, but similar

when expressed as E%. As for other population groups, fruit and vegetable juices contributed the most to the difference between the intake of added and free sugars, although the intake of these was very low in pregnant women (mean intakes between 1 E% and 2 E%; P95 from 4 to 13 E%). The major contributors to added sugars intake were fine bakery wares (from 22% in Spain to 29% in Cyprus), sugar and confectionery (from 17% in Austria to 31% in Latvia) and SSSD+SSFD (from 5% in Latvia to 32% in Austria). The contribution from processed fruit and vegetables (≤ 6% for all but Latvia which was 11%) and from fruits and vegetable juices (≤ 5%) was very low or null in most countries. The contribution from beverages combined to added and free sugar intakes ranged from 5% in Latvia to 32% in Austria, and from 15% to 46% in the same countries, respectively **(Annex D)**.

In the only two surveys available for **lactating women** (from Estonia and Greece), mean and P95 intakes of total, added and free sugar as E% were similar to pregnant women. Likewise, compared to non-lactating women from the same country, mean intakes in absolute amounts were higher in lactating women but similar when expressed as E%. Compared to pregnant women, core food groups collectively contributed less to total sugar intake (46% in Greece and 53% in Estonia) and SSSD+SSFD contributed less to the intake of added sugar (≤ 8%). The contribution of fine bakery wares (13% in Estonia and 39% in Greece) and sugars and confectionery (52% in Estonia and 27% in Greece) to the intake of added sugars was highly variable **(Annex D)**.

4.3.5.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) in **pregnant women** were higher in consumers of SSSD+SSFD than in consumers of any other food group in all countries except Cyprus, where consumers of confectionery had the highest intakes. Intakes of added and free sugars were higher from SSSD+SSFD than from any other food group in consumers (mean intakes up to 30 g/day, P95 up to 85 g/day for both). SSSD+SSFD contributed up to 55% and up to 46% to the intake of added and free sugars, respectively, in consumers of these beverages **(Appendix B, Annex E)**.

In Estonia, **lactating women** consumers of SSSD+SSFD had the highest mean intake of added and free sugars from all sources (61 and 69 g/day, respectively), and intakes of added and free sugars from sugars and similar were the highest of all food groups in consumers (16 g/day, P95 48 g/day, and 19 g/day, P95 49 g/day, respectively). The mean intakes of added and free sugars from SSSD +SSFD were substantially lower in lactating women consumers than pregnant women consumers. The contribution of sugars and similar to the mean added and free sugars intakes in these consumer groups was, respectively, 37% and 36%. In Greece, the highest mean intake of added and free sugars from all sources (g/day) was in lactating women consumers of confectionery and in consumers of sugars and similar, respectively. Intakes of added sugars from fine bakery wares were the highest of all food groups (12 g/day),[10] while the highest intakes of free sugars were from fruits and vegetable juices (19 g/day)[10] in consumers. The contribution of fine bakery wares to the mean added sugars intake was 42% and the contribution of fruit and vegetable juices to free sugars intake was 37% in consumers of these food groups, respectively.

4.4. Overview of published data on intake of total, added and free sugars collected by Member States

EFSA requested Member States to provide intake data on dietary sugars from national dietary surveys, as estimated using national food composition databases. The aim was to compare such data with sugar intake estimates obtained for the same national surveys and population groups calculated by EFSA using the EFSA food composition databases for total, added and free sugars.

National (aggregated) sugars intake data were received from 18 countries, for a total of 27 national surveys. Of these, only 14 surveys were in the EFSA Comprehensive Database **(Annex C)**. For some surveys, however, a comparison between national sugars intake data and data calculated by EFSA was not possible due to major differences in the exposure assessed and/or in the age ranges for which intakes were calculated. For the remaining surveys, an exact comparison between identical age ranges was not possible in most cases. Thus, the most appropriate age ranges reported in national surveys were selected on a case-by-case basis in order to allow a meaningful comparison. Details can be found in **Annex F**. In total, nine national surveys were available for comparison, including all population groups covered by the intake assessment (n = 7). Of these, six national surveys (seven population

[10] P95 could not be calculated as the number of participants in this survey is below 60.

groups) report on total sugars, three national surveys (three groups) on free sugars and five national surveys (three groups) on added sugars.

Overall, mean intakes for **total sugars** calculated by EFSA were in line with those reported in national surveys. Mean intakes calculated by EFSA across surveys, age groups and sexes were, in most cases, within +/− 12% the values reported in national surveys. Exceptions were values calculated by EFSA for toddlers in France, which were 19 and 15% lower than national values reported for males and females, respectively.

For **added sugars,** EFSA values were generally lower than national values, across all surveys and population groups (up to 25%) possibly owing to the type of food composition data used and the different definitions of added sugars applied across countries. Exceptions were national values reported in the survey in Portugal, which were 11% lower than EFSA values for the older adults and did not differ from those calculated by EFSA for children. Added sugars intake reported for male and female children in Spain (ENALIA, 3–9 years), were, respectively, 49% and 46% higher than those estimated by EFSA. This substantial difference could be attributed to the type of food composition data and the different definition of added sugars used in the national publication.

Similar to added sugars, EFSA values for **free sugars** were generally lower than national values, across all surveys and population groups (up to 21%). Exceptions were national values reported in the survey in Portugal, which were between 8% and 17% higher than EFSA values for adults and older adults of both sexes.

4.5. Uncertainty analysis

Sources of uncertainty and their potential impact on the final intake estimates, where possible, are identified and discussed below.

Consumption data

Uncertainties and limitations arising from the use of the EFSA Comprehensive Food Consumption Database have been described in detail elsewhere (EFSA et al., 2011), and relate to the following methodological aspects:

- **Sampling strategy and response rate:** Using sampling strategies which are convenient (e.g. use of household as sampling unit rather than individuals, target recruitment through universities, pharmacies or factories vs. using national population registers) and low response rates may lead to survey samples which are not representative of the general population at national level. This could lead to over- or underestimation of the intakes in the general population at national level.
- **Representativeness over different weekdays and seasons:** Surveys not covering weekdays and weekend days, or conducted on one season only, may not capture habitual intakes mostly for foods which are consumed in one season only or on special occasions (e.g. weekends). However, most surveys in the Comprehensive Database, especially those conducted more recently, cover a whole year period with an appropriate proportion of weekdays and weekend days.
- **Methodology used to assess dietary intakes:** dietary recall vs. food records (see **Annex B**).
- **Use of standard portion sizes:** This can lead to over- or underestimation of the actual quantity consumed.
- **Inclusion of consumption surveys covering only few days**: This leads to overestimation of high percentiles of chronic intake, whereas it is expected to minimally affect mean intakes of nutrients widely distributed in the diet, such as dietary sugars. For foods not consumed daily, intakes could be over- or underestimated depending on whether consumption days are captured in the survey. This has also an impact on the number (and percentage) of consumers of non-core food groups identified in the surveys.
- **Other systematic errors**: Underreporting has been shown to be associated with sex, age, educational level and BMI (e.g. obese subjects and male subjects underreport more frequently than lean subjects and females). Underreporting also varies among food categories: Foods with high sugars or fat content and sweeteners added to beverages are more prone to be underreported (EFSA, 2009).

Composition data

- The EFSA Nutrient Composition Database contains data on total sugars from national food composition databases up to 2012. Recipes and ingredients (which can affect the sugar content of food products) might change to a certain extent over time, which could lead to either underestimation or overestimation of the actual intake of total sugars. However, major contributing food categories were checked in the Mintel's Global New Products Database for confirmation, which is expected to minimise the uncertainty associated with changes in recipes and ingredients over time.
- For this opinion, food composition data from 12 European countries were pooled, and thus, a consistent number of food products was taken into account per food category, leading to a more robust database which considers product variability, assuming a global food market. However, the use of national composition tables representing typical local products can introduce differences between the intake estimated by Member States and those estimated by EFSA for the present opinion, as shown in **Annex F**. Intakes of total sugars calculated by EFSA are generally lower than those calculated by Member States, with some exceptions.
- Composition tables contain average values for a food category, which may under- or overestimate the actual sugar content of a certain food product consumed by one subject. However, it is expected that the uncertainty introduced by this factor is minimised when mean intakes are calculated for the population.
- The classification of total sugars as added or free also involves assumptions, i.e. when the exact recipe of a product is unknown (e.g. cake) so that the amount of added and free sugars originating from the different ingredients could not be assigned. The classification of all the ingredients used for sweetening purposes as added sugars is expected to have no impact on the intake of free sugars, but could result in an overestimation of the consumption of added sugars that is proportional to the use of honey, syrups, fruit juices and fruit juice concentrates for sweetening purposes. The impact of this uncertainty on the overall intake estimates for added sugars is judged to be low. Similarly, when step 10 of the methodology is applied (the content of added or free sugars was assumed to be equal to 50% of total sugars, as indicated in **Annex C**), the free or added sugar content of the food could have been under- or overestimated.

Linkage of composition and consumption data

- Assumptions were made while assigning the total, free and added sugars content of foods to the consumption events. Some consumption records were only coded on a very generic level (FoodEx2 level 1 or 2) and it was not possible to identify the exact product consumed. In these cases, an average level of the lower FoodEx2 levels was assigned to the record (e.g. 'Alcoholic drinks' FoodEx2 level 1 category or 'Fine bakery wares' on FoodEx2 level 2).
- Both composition and consumption data were coded in the FoodEx2 system. Their matching was carried out through the linking categories, which took into consideration both the FoodEx2 basic codes on different levels and all possible sugar-related facet descriptors. However, 'sugar free' products and those made 'with reduced sugars' could not always be distinguished, which might have led to overestimation of the intake of total, free and added sugars. EFSA estimates of sugars intakes were generally lower than those calculated by Member States, and thus, it is expected that this factor does not introduce a major uncertainty in the intake estimates used in this opinion.

5. Methodological considerations when estimating intakes of dietary sugars and their sources and their relationship to disease endpoints in observational studies

5.1. Dietary assessment methods

Food frequency questionnaires (FFQs) are the most used dietary assessment method to estimate the intake of sugars and their sources in observational studies. Multiple 24-h recalls are sometimes used and, less commonly, diet records or dietary history.

Each dietary assessment method has its own characteristics and sources of errors, which are summarised in **Table 6**. Issues specific to the estimation of the consumption of dietary sugars from specific sources, total sugars and specific sugars types (e.g. free/added sugars, fructose) are further discussed in the following sections.

Table 6: Characteristics of dietary assessment methods and related sources of bias

	Diet records	24-h recalls	Food frequency questionnaires (FFQ)[a]	Diet history
Method	• Subjective real-time measure using open-ended, self-administered diet diary record • 'Weighed food consumption records' include weighing foods on scales • Participant literacy and full cooperation required; high burden • Children can contribute to the recording from around 10 years of age, but adults need to provide details of the foods consumed.	• Subjective retrospective measure using open-ended questionnaires administered by a trained interviewer • Participant literacy not required when interviewer-administered; low burden for the participant • Can be used to assess diets of children by questioning the parent/carer, but a problem arises if the parent/carer is not with the child all day. Children can provide some information themselves from around 10 years of age.	• Subjective retrospective measures using closed-ended questionnaires, self- or interviewer-administered • Participant literacy not required when interviewer-administered; low burden • Can be used to assess diets of children by questioning the parent/carer	• Subjective measures using open- and closed-ended questionnaires, administered by a trained interviewer • Low participant literacy required; high burden
Collected data	• Actual intake throughout a specific period; detailed • At least 2 separate days (preferably including a weekend day) needed to assess within-subject variability • If a suitable number of records are collected over a long period, usual intake can be estimated • Estimated records include careful description of amount of food • Foods need to be linked with nutrient composition data by trained staff	• Actual intake over the previous 24-h; detailed (open-ended) • At least 2 separate days (preferably including a weekend day) needed to assess within-subject variability • If a suitable number of recalls are collected over a long period, usual intake can be estimated • Foods need to be linked with nutrient composition data by trained staff	• Usual intake estimates over a relatively long period (e.g. 6 months, 1 year); level of details is variable depending on the purpose for which the FFQ was developed • Description of portion size with a choice of sizes or a modification of frequency to account for size • A standard list of foods is used to represent each food group, from this a representative nutrient intake for a portion of the food group is calculated	• Usual intake estimates over a relatively long period; level of details is variable depending on the purpose for which the questionnaire was developed • A FFQ or diet records may also be administered to verify information • Foods need to be linked with nutrient composition data by trained staff

	Diet records	24-h recalls	Food frequency questionnaires (FFQ)[a]	Diet history
Errors due to random within-person variation	• Foods consumed occasionally (twice a week or less; e.g. cakes or sweet beverages in occasional consumers) may be over- or underestimated and lead to subject misclassification • Generally reduces the strength of the association	• Foods consumed twice a week or less (e.g. cakes or sweet beverages in occasional consumers) may be over- or underestimated and lead to subject misclassification • Generally reduces the strength of the association	• Lower than with other dietary assessment methods if questions are well designed	• Describes usual diet so deals with within person variability as part of the method
Reporting errors	• Subjects may change their habitual intake for ease of recording or to increase social acceptability; selective reporting • May result in systematic within- and between-person errors; can bias the association in any direction	• Recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes; • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction	• Questionnaire misunderstanding, recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes • Errors due to FFQ design (e.g. a short FFQ may underestimate the true variation in dietary intake and the individual's total daily energy intake) • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction	• Recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes • Long interview may tire the respondent and affect accuracy • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction
Handling of measurement errors	• Errors due to random within-person variation can be limited if adequate number of days of recording are collected. • Weighed food records provide most accurate measures of portion sizes. A good description can be made if food not weighed. • Use of a food portion size atlas or similar information can aid description	• Errors can be limited if interviewers are well-trained, use adequate probing questions (e.g. regarding commonly forgotten foods such as adds-on (e.g. sugar, honey added by the consumer at the table), snacks, beverages) and by using an automated system. • Pictures/models can help improving the accuracy of portion size recalls	• Regression calibration (preferably derived from an internal calibration study based on a random sample of the main study)	• Errors can be limited if interviewers are well-trained, use adequate probing questions (e.g. regarding commonly forgotten foods such as adds-on (e.g. sugar, honey added by the consumer at the table), snacks, beverage) • Pictures/models can help improving the accuracy of portion size recalls

(a): Only studies using semi-quantitative FFQ were eligible for this opinion.

5.1.1. Sources of error in estimating the intake of dietary sugars

5.1.1.1. Food consumption data

Misreporting of food intake is a common problem in subjective dietary assessment methods and it is difficult to quantify. Selective reporting and recall bias may affect the identification of foods eaten and the estimation of portion sizes, in particular when using FFQs and 24-h recalls. Sources of sugars perceived as less healthy (e.g. SSBs, fine bakery wares, confectionery) may be more prone to selective underreporting (Poppitt et al., 1998), while those perceived as healthy (e.g. fruits and vegetables) may be overreported (Miller et al., 2008). Foods and beverages consumed between meals (e.g. snacks) and add-ons (e.g. sugar, honey added at the table) are also more prone to underreporting (Millen et al., 2009; Gemming and Ni Mhurchu, 2016). This can affect estimates of both sugars from specific sources and specific sugar types. For instance, intake of added sugars may be underestimated due to selective underreporting of significant contributors to added sugars intakes that are perceived as less healthy, as well as unintentional omissions (Poppitt et al., 1998). The direction and magnitude of the error (i.e. over- vs. underestimation) can be difficult to predict for exposures such as total sugars or total fructose, for which food contributors may be affected by reporting biases in opposite directions.

FFQs focusing on specific sources of sugars (e.g. SSBs) rather than on the whole diet can be quicker to administer and may appear more reliable for the specific source. However, such questionnaires do not allow the estimation of total energy intake (TEI), diet quality and the possibility to adjust for these factors (Section 5.1.3) (Cade et al., 2002).

5.1.1.2. Food composition data

The content of total sugars is available in most food composition databases (FCDs) because of its mandatory declaration on food labels. A source of error in the intake estimates relates to the quality and representativeness of the FCD used for the calculation of intake estimates, especially when it does not contain the foods/drinks consumed by the population under study (Ahuja and Perloff, 2008) or has not been regularly updated to reflect product reformulation and market trends (e.g. use of sugar substitutes) (Sylvetsky and Rother, 2016; Samaniego Vaesken et al., 2019).

In contrast to total sugars, the content of free and added sugars is not readily available in most FCDs. Methods have been developed to classify sugars in foods as added or free based on the ingredient lists or recipes (e.g. disaggregation method, 10-step systematic method) (Kibblewhite et al., 2017; Amoutzopoulos et al., 2018; Wanselius et al., 2019; Yeung and Louie, 2019). A common limitation of these methods is the reliance on food composition information which may not be available for all food products consumed or may be outdated due to changing formulations. These methods require assumptions (e.g. regarding the proportion of specific ingredients) and subjective decisions (e.g. when using borrowed values from similar food products) to be made, which may introduce biases. The method used to assign content of added and free sugars to foods is seldomly described in observational studies and thus the extent of potential inaccuracies is difficult to assess. Also, the use of different definitions and nomenclatures across studies hampers comparisons.

Similarly, sugar types (e.g. fructose, sucrose, glucose) are not readily available in most FCDs. Whereas some FCDs may rely on food analysis, others are built borrowing values from other countries or even from other regions of the world. This information is often not provided in studies' methods.

5.1.2. Assessment of measurement error and risk of bias

Elements considered when assessing errors of sugars intake estimates and related risk of bias in the relationship between the exposure and the health endpoint include the followings:

- Validity and reproducibility of the dietary assessment methods

The use of a tool which has been validated for the study population is critical to minimise errors in the intake estimates. Ideally, the questionnaire is validated for the intake of the nutrient of interest and for energy intake against objective measures. Urinary excretion of fructose and sucrose have been proposed as biomarkers of sugars intake (see Section 5.2). The doubly labelled water method can be used to validate dietary assessment methods for energy. However, biomarkers of sugars intake are limited and seldomly used as reference for validation to date (Section 5.2). The doubly labelled water method is also rarely used for validation of TEI. Instead, dietary assessment methods are commonly validated against each other. In that case, validation data are not necessarily available for the exposure of interest but for related dietary variables which are used as proxy indicators (e.g. validity

data on total carbohydrates for sugars or sources of sugars; validity data on main fructose food sources for fructose). Data on the reproducibility of the method, by comparing its results at different time points, are also important to assess its reliability.

- Repetition of the dietary assessment to assess habitual intake

In studies on sugars intake and incidence of chronic diseases, intake estimates should represent long-term intakes. Intake estimates based on a single dietary measurement do not allow to capture changes in subjects' consumption habits over time. Although macronutrient intakes can be assumed to be relatively stable over adulthood, consumption habits of individual foods may change rapidly. In studies investigating the association between a particular food source of sugars and the risk of disease, repeated dietary assessment is recommended to obtain a more representative estimate of individuals' habitual consumption.

- Measures to address potential systematic errors

It has been described that underreporting of food intake happens more commonly and to a greater extent in overweight and obese individuals than in normal weight subjects (Macdiarmid and Blundell, 1998; Murakami and Livingstone, 2015; Wehling and Lusher, 2019). Other factors such as smoking habits, level of education, social class, social desirability, physical activity and dietary restraint have also been associated with misreporting of food intake (Macdiarmid and Blundell, 1998; Tooze et al., 2004; Hebert et al., 2008). Although several methods have been applied to account for misreporting of energy intake, including the exclusion of implausible reporters (e.g. based on arbitrary cut-offs regarding energy intake estimates) or the adjustment or stratification of analysis according to the plausibility of reporting, these methods are not equivalent and their ability to minimise the impact of differential reporting bias on the observed nutrient–health relationships is unclear (Jessri et al., 2016; Ejima et al., 2019). Analyses taking different approaches of accounting for misreporting to assess stability of results (i.e. sensitivity analysis) are recommended.

- Calibration

In some studies, two methods (e.g. FFQ and diet records) are used in combination, so that a shortcoming of one method may be compensated to a certain extent by the second method, which can increase the accuracy of the intake estimates. Measurement errors in self-reported sugars intake may also be assessed, and possibly corrected for, using a biomarker of sugars intake (Section 5.2). However, available markers need further validation and have seldomly been used in epidemiological studies so far (Kuhnle et al., 2015; Tasevska, 2015).

- Temporal proximity of the intake estimation to the incidence of the disease

Intake measurements taken close to the incidence of the disease may be at risk of being influenced by changes in the dietary habits of the individual related to the underlying condition (reverse causality). Sensitivity analyses excluding incident cases identified during the first years of follow-up allow to address this concern.

5.1.3. Consideration of energy intake and other dietary factors in observational analyses

A general methodological issue when investigating the association between nutrient intakes, including sugar (or sugars from specific sources), and health endpoints is the risk for confounding by energy intake, intake of other nutrients and/or associated dietary patterns.

Several statistical approaches are available to account for energy intake in nutrient-disease risk models (Willett et al., 1997). The choice of the model requires consideration of the hypothesis investigated, i.e. whether energy intake may act as a confounder or as a mediator of the relationship. The characteristics and interpretation of the different models are outlined in **Table 7**.

Table 7: Models applied to account for energy intake in observational studies and their interpretation[(a)]

	Characteristics	Interpretation
Multivariable model, unadjusted for TEI	• Intake variable: nutrient (food) intake estimate	• The association may be confounded by TEI when TEI is associated with disease risk • The model allows for the mediation of TEI in the exposure–disease relationship
Multivariable model, adjusted for TEI	• Intake variable: nutrient (food) intake estimate • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, bias in the risk estimates may result from incomplete control of confounding by TEI
Nutrient residuals model	• Intake variable: residuals from the regression of the nutrient (food) intakes of the individuals on their total energy intakes • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, adjustment for TEI occurs before categorisation
Multivariable nutrient density model	• Intake variable: energy intake from the nutrient (food) divided by the total energy intake of each individual • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, adjustment for TEI occurs before categorisation • Lack of adjustment for TEI can bias the association in the opposite direction if TEI is associated with the disease
Energy partition model	• Intake variable: nutrient (food) intake estimate • Energy intake from other nutrients included as a covariate	• Apparent effect of the nutrient (food) while maintaining energy from other nutrients (foods) constant (i.e. reflects both the energy and non-energy contribution of the nutrient) • When the intake variable is categorised, bias in the risk estimates may result from incomplete control of confounding by TEI

(a): Adapted from (Willett et al., 1997).

Most observational studies consider TEI as a potential confounder of the association between sugars intake and disease risk. Sugars intake estimates are typically standardised for energy before categorisation, using the nutrient residual model or the nutrient density model adjusted for TEI.

In contrast, most studies investigating disease risk associated with sources of sugars (e.g. SSBs, FJs) provide models with and without adjustment for TEI, thus exploring the role of TEI as a potential mediator in the causal pathway between the consumption of the sugar source and the health endpoint. Notably, studies investigating disease risk associated with specific sources of sugars seldomly standardised the intake values for TEI (based on residuals from the regression on TEI or energy density) before categorising participants according to their intake. In this case, the adjustment is based on categorical variables, which may bias the intake–disease association due to incomplete control for confounding by TEI (Willett et al., 1997).

Confounding by dietary components is typically controlled by adjusting for individual dietary factors or for (aggregated) dietary pattern scores. As for other potential confounders, the adjustment strategy (e.g. choice of covariates, model selection) requires prior consideration, justification and sound statistical methods.

The incorrect use of these models in statistical analyses, but also measurement errors in dietary assessments, can increase, attenuate or even invert the true relationship. For instance, when the

nutrient density model is applied, the lack of adjustment for TEI, when it is associated with the disease, can invert the direction of the association (Willett et al., 1997). The fact that reporting errors in dietary assessments are usually biased and affect in different ways both the measurement of the nutrient of interest and the measurement of relevant covariates (e.g. TEI, intake of other nutrients or foods) makes it difficult to adjust for measurement error in regression analyses and also to predict the direction and magnitude of the bias of the nutrient–disease relationships.

Calibration and validation studies can be used to understand measurement error properties of different dietary assessment methods and apply adequate correction factors, so that well-designed and conducted studies can provide meaningful information about relationships between habitual consumption of specific components of the diet and disease endpoints, provided that appropriate statistical methods are used (Kipnis et al., 1997; Day et al., 2004).

5.2. Biomarkers of intake

5.2.1. Fructose and sucrose in urine

Urinary sucrose and fructose have been shown to correlate with the intake of dietary sugars but urinary glucose has not.

Urinary sucrose and fructose in 24-h urine samples (24uSF) cannot be used as a recovery biomarker because only a very small fraction of the sugars ingested are excreted, and thus, analytical values are quantitatively far from absolute intakes. Daily intake of dietary sugars, however, could be predicted from 24uSF by using calibration equations developed in feeding studies (Tasevska et al., 2005, 2009). This assumes that the biases of the biomarker are stable between individuals and across populations (Tasevska, 2015).

Calibrated measures of 24uSF have been used to assess the measurement error of dietary self-reports (dietary food records, 24-h recalls, FFQs) in the OPEN (Tasevska et al., 2011) and NPAAS (Tasevska et al., 2014a) cohorts, both regarding the accuracy of the measurements and their relationship with the risk of disease. Two and three individual, complete 24-h urine samples were available in the OPEN and NPAAS cohorts, respectively. Correlation coefficients between calibrated 24uSF and self-reported intake for total sugars were low for all dietary instruments (between 0.2 and 0.6), and generally lower for women than for men, suggesting that women misreported sugars consumption more than men. The average from multiple (2 and 3 days) 24-h dietary recalls was found to perform better than dietary food records or FFQs, also in relation to disease risk (Tasevska, 2015).

Urinary sucrose and fructose in spot urine samples and in overnight urine collections have been proposed to classify individuals in categories of intake for use in observational studies to investigate the relationship between sugars intake and disease risk, rather than to quantify habitual consumption of dietary sugars (Kuhnle et al., 2015; Ramne et al., 2020). The use of a composite measure of added sugars intake and urinary fructose and sucrose in overnight samples has also been explored (Freedman et al., 2010; Ramne et al., 2020).

Both spot urine and 24-h collections reflect recent intakes (in the previous 6–8 h up to the previous day), so that the number of collections needed to adequately capture habitual intakes (or how well habitual intakes are captured by a single urine collection) could vary widely depending on intra- and inter-individual day-to-day variation in sugars intake.

The Panel acknowledges the potential of fructose and sucrose in urine as a reliable biomarker of intake for dietary sugars. The Panel notes, however, that calibration equations to calculate the intake of dietary sugars from 24uSF have been developed in few studies with small sample sizes, and that the assumption that biases in the biomarker are stable between individuals and across populations needs to be ascertained. The Panel also notes that the validity of sucrose and fructose concentrations in spot urine samples and overnight urine collections as biomarkers of intake, either when used alone (as surrogate markers to classify individuals in categories of intake) or in combination with self-reported intakes (for calibration purposes), needs further exploration of the potential sources of error associated with these measurements, as well as of their (random, non-random) impact on subject misclassification in epidemiological studies (Davy and Jahren, 2016; Ramne et al., 2020).

5.2.2. Carbon stable isotope ratio

The carbon stable isotope ratio ($^{13}C/^{12}C$ or $\delta\ ^{13}C$) measured in biological samples (e.g. serum, urine, hair) has been proposed as a biomarker of added sugars intake in populations consuming added sugars mainly refined from C4 plants which are naturally rich in ^{13}C (e.g. maize, sugar cane, sorghum),

as in North America. However, correlations between sugars intake and δ ^{13}C may be biased by many confounding factors, including other dietary nutrients naturally enriched with ^{13}C (including maize starch, oils and protein), and the performance of this biomarker has not been yet investigated under controlled feeding conditions. In addition, δ ^{13}C in biological samples may be of little use in geographical areas largely depending on sugar beet, a C3 plant, as source of added sugars (e.g. Europe, Japan) (Dragsted et al., 2018).

6. Overview of dietary reference values and recommendations

While setting dietary reference intakes (DRIs) for carbohydrates in 2005, the US Institute of Medicine (IoM) concluded that the data available at the time on dental caries, behaviour, cancer, risk of obesity and risk of dyslipidaemia were insufficient to set a UL for total or added sugars. An upper limit of intake for added sugars of 25E% was suggested by considering that the intake of some micronutrients was below the DRI in US population subgroups exceeding that level of added sugars (IoM, 2005).

Other national and international authoritative bodies have given recommendations for individuals or proposed population goals for dietary sugars. Dietary goals or recommendations for a nutrient are based on considerations of health effects associated with its consumption, as well as the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed (EFSA NDA Panel, 2010b). An overview of population goals or recommendations for dietary sugars established by individual bodies can be found in the protocol for this opinion (see **Appendix A** in the **Protocol**). A tabulated summary is given in **Table 8**.

In 2010, when establishing DRVs for carbohydrates and dietary fibre, the EFSA NDA Panel (EFSA NDA Panel, 2010a) concluded that the data available at the time on dental caries, micronutrient density of the diet, body weight, blood lipids, glucose and insulin responses and risk of type 2 diabetes were insufficient to set a UL for total or added sugars. Different from other authoritative bodies, EFSA did not establish dietary goals or recommendations for dietary sugars (e.g. a limit of intake) because this is part of national nutrition policies and in the remit of individual EU Member States, and not under EFSA's remit.

In Europe, some countries provide qualitative recommendations for consumers to limit the intake of dietary sugars and/or their sources, including sweets, desserts and sugar-containing beverages (sugar-sweetened soft and fruit drinks, fruit juices and dairy drinks), whereas others provide quantitative recommendations for added or free sugars (typically < 10 E%), and more rarely for total sugars (from 15 to 20 E%). Further information on existing recommendations for dietary sugars and their sources in European countries can be found in the portal of the European Commission on Food-Based Dietary Guidelines[11] and **Annex F** of this opinion.

Table 8: Summary of existing population goals or recommendations for dietary sugars or their sources

Guideline	Target population	Sugar fraction	Population goal/ Recommendation	Basis (endpoint)
German Nutrition Society (Hauner et al., 2012)[(a)]	General population	SSBs	Limit consumption	Obesity Risk of T2DM
Nordic Council of Ministers (2014)	General population	Added sugars	Recommendation for individuals of < 10 E%	Micronutrient density
Health Council of the Netherlands (2015)	General population	SSBs	Limit consumption	Obesity Risk of T2DM
SACN (2015)	General population (> 2 years)	Free sugars	Population goal of ≤ 5 E%	Energy intake
ANSES (2016)	Adults	Total sugars[(b)]	Recommendation for the adult population of ≤ 100 g/day	Fasting triglycerides

[11] https://ec.europa.eu/jrc/en/health-knowledge-gateway/promotion-prevention/nutrition/food-based-dietary-guidelines

Guideline	Target population	Sugar fraction	Population goal/ Recommendation	Basis (endpoint)
HHS/USDA (2015)(c)	General population	Added sugars	Recommendation for individuals of < 10 E%	Micronutrient density
WHO (2015)	General population	Free sugars	Recommendation for individuals of < 10 E% < 5E% conditional	Body weight Dental caries
American Heart Association (Vos et al., 2016)	Children	Added sugars	Recommendation for individuals of 25 g/day ≥ 2 years Avoid < 2 years	Energy intake Adiposity Dyslipidaemia CVD risk
ESPGHAN (Fidler Mis et al., 2017)	Children	Free sugars	Recommendation for individuals of ≤ 5 E% ≥ 2 years (lower for < 2 years)	Dental caries Weight gain (SSBs) CVD and T2DM (fructose)

FBDG: food-based dietary guidelines; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; SSBs: sugar-sweetened beverage.

(a): Since the protocol was published, the German Nutrition Society in consensus with the German Obesity Society and the German Diabetes Society, updated its recommendation in 2019 and endorsed the WHO (2015) recommendation, stating that the intake of free sugars should be limited to less than 10% of total energy intake (Ernst et al., 2019).

(b): Excluding lactose and galactose.

(c): Since the protocol was published, HHS/USDA has updated its recommendation, keeping the same bases to establish a limit of 10 E% for added sugars (HHS/USDA, 2020).

7. Hazard identification: methodological considerations

As specified in the protocol, subquestions 4 and 5 were planned to be answered by performing systematic reviews and, possibly, dose-response meta-analyses if the available data allowed doing so. The conceptual framework for the systematic reviews on sugars intake in relation to disease endpoints and other endpoints is summarised in **Figure 5**.

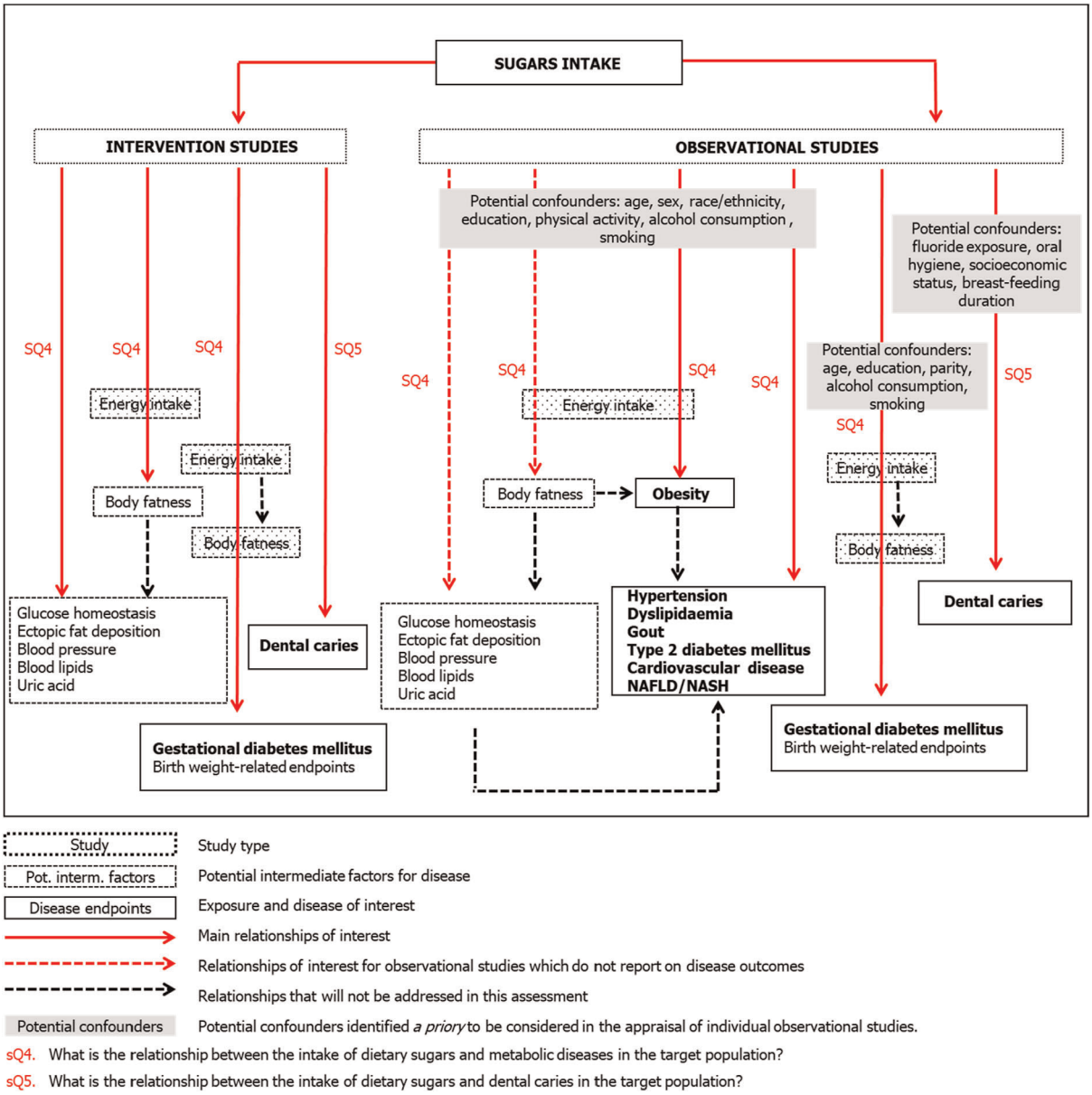


Figure 5: Conceptual framework for the systematic reviews on sugars intake in relation to disease endpoints and other endpoints

7.1. Literature searches

Literature searches were designed to identify studies published in English and conducted in humans. Specific search strings were used in Cochrane Library, Embase, PubMed and Scopus to limit by type of study and publication type. Date limits were applied based on previous systematic reviews as described in Section 9.2 of the protocol.

Literatures searches for sub-Q4 (metabolic diseases) were designed to address each type of endpoint. The searches were conducted on 23 July 2018. The results by endpoint and database were combined and exported into EndNote reference manager software, as well as all individual references cited in published reports from national and international authorities/bodies addressing the health effects of sugars, and in systematic reviews and meta-analyses published since 2010 on this topic. A variation of the method described in Bramer et al. (2016) was performed to identify duplicates in EndNote. After de-duplication, a total of 23,811 records were identified and imported into DistillerSR® Web-Based Systematic Review Software (Evidence Partners, Ottawa, Canada).

Literature searches were conducted for subquestion 5 (dental caries) on 24 and 25 July 2018 as described above. A total of 2,141 records were identified after removing the duplicates and imported into DistillerSR®.

Literature searches were updated on 28 and 31 August 2020 for subquestion 4 and on 13 and 16 October 2020 for subquestion 5 using the same methodology as described for the original searches. The complete search strings used in the bibliographic databases, the results of the updated literature searches and details on how the new studies identified were used for this scientific opinion can be found in **Annex A**.

Briefly, a full incorporation of the new evidence into the scientific assessment was not possible within the agreed timeline owing to the high number of pertinent studies identified and the high number of exposure–endpoint tandems for which new evidence became available. Therefore, in consultation with the mandate requestor, the Panel decided to incorporate into the assessment new publications meeting the inclusion criteria only when:

a) the BoE from the original search did not support a positive relationship between the exposure and the risk of disease and
b) the BoE from the updated search could change that conclusion.

In all other circumstances (e.g. when there was already evidence from the original search for a positive and causal relationship between the exposure and the risk of disease; or when the new evidence was unlikely to change conclusions of no support for a positive and causal relationship between the exposure and the risk of disease), the new studies are only summarised and discussed narratively in **Annex A**. The Panel acknowledges that this approach is conservative but considers it appropriate for a safety assessment.

7.2. Study selection and requests for additional information

The eligibility criteria for the selection of human intervention and observational studies on metabolic diseases and dental caries are listed in Section 9.1 of the protocol.

The flow charts for the selection of intervention and observational studies on metabolic diseases and dental caries are shown in **Appendix C**. For metabolic diseases, after full-text screening and exclusions during data extraction, the final number of articles included in the assessment was 156, of which 61 reported results from 49 intervention studies, and 95 referred to observational studies. Nine additional publications on observational studies identified through the update of the literature search were incorporated into the assessment, leading to a total of 104 publications reporting on 66 individual cohorts. For dental caries, 12 publications met the inclusion criteria: One was an intervention study and 11 articles reported on seven individual cohort studies.

At full-text screening and during data extraction, authors were contacted for additional information, where appropriate. Details about this process and the decisions taken based on the additional information provided are given in **Annex G**. For all the references on dental caries, authors were contacted to provide individual data for dose-response analyses (Section 10).

Details on the references excluded at full-text screening and the reasons for exclusion are given in **Annex H**. In some cases, the exclusion refers only to certain exposures, endpoints or specific exposure–endpoint combinations, and not to the whole study.

7.3. Strategies for data extraction and analysis

7.3.1. Intervention studies on metabolic diseases

A total of 49 intervention studies reported in 61 publications were included after full-text screening. Of these, 43 were conducted in adults and six in children and/or adolescents. A list of the studies reported in more than one reference, the main reference that is used as unique identifier for the study in this opinion and the endpoints used for the present assessment that are not extracted from the main reference but from linked references can be found in **Appendix D**.

The studies included were very heterogeneous in several aspects including the type of research question investigated, the dietary conditions in which they were conducted regarding the target energy intake, the fraction of the diet that was manipulated, the type of sugar or sugar source investigated, the type of control used, the study design (parallel, cross-over), the study population, the endpoints assessed and the variables used for the assessment and the duration of the intervention.

7.3.1.1. Research question

The intervention studies included were originally designed to answer one or more of the following questions:

Q1: The effect of the **amount of sugar from one or more sources**. These are studies comparing a type of sugar (e.g. sucrose) or a sugar source (e.g. honey, HFCS) to a 'zero' sugar control, which could be another energy-equivalent macronutrient (e.g. starch) or an energy-reduced or energy-free control (e.g. water, artificially sweetened beverages, no intervention) and studies comparing different amounts of the same type of sugar (e.g. fructose, glucose, sucrose).

Q2: The effect of the **type of sugar**. These are studies comparing the same amount of different monosaccharides (e.g. fructose vs. glucose).

As per protocol, the main question to be addressed to derive a UL for dietary sugars is the effect of the amount of sugars on the endpoint (**Q1**). A secondary objective was, where data allowed, to assess the effect of different types of sugars (**Q2**) and the effect of the amount of sugars from one or more sources **(Q1)**. Other questions that the studies included were originally designed to address are:

Q3: The effect of **sugars given as monosaccharides or as disaccharides**. These are studies comparing mixtures of glucose and fructose as either sucrose (as disaccharides) or HFCS (as monosaccharides).

Q4: The effect of **replacing one source of sugars by another**. These are studies comparing the same amount of foods containing different types and amounts of sugars (e.g. 20% of energy from the diet as fruits and vegetables or as fruit juices; 70 g of either sucrose or honey, the latter containing about 46 g of mixed sugars; same amount of HFCS and rare sugars syrup, the latter containing less sugars and a different monosaccharide composition), studies comparing the same amount of sugars with different monosaccharide composition (e.g. sucrose vs. corn syrup, sucrose vs. fructose or glucose) and studies comparing the effect of the same amount of a monosaccharide (e.g. fructose) from different sources (e.g. as free fructose, from sucrose, from HFCS).

However, these questions are not relevant for the present assessment.

The complete list of intervention studies that passed the full-text screening step and the question that each study investigated can be found in **Appendix E**.

7.3.1.2. Target energy intake

As per protocol, studies aiming at energy restriction or weight loss were excluded. The studies included could be classified in four main groups in relation to the dietary conditions in which they were conducted:

a) Isocaloric with neutral energy balance: Studies designed to maintain body weight by matching total energy intake to energy requirements (i.e. neutral energy balance) in all study arms
b) Isocaloric with positive energy balance: Studies designed to increase energy intake (i.e. positive energy balance) in all study arms
c) Hypercaloric: Studies designed to increase energy intake in the sugar arm (i.e. positive energy balance) and to maintain body weight in the control arm (i.e. neutral energy balance)
d) *Ad libitum:* Studies providing no instructions or restrictions regarding total energy intake to all study arms.

7.3.1.3. Fraction of the diet that is manipulated in the study

An inclusion criterion for intervention studies was the quantification of the amount of sugars provided. However, the amount of sugars reported in the publication that was consumed in the study arms (expressed in g/day or as E%) may refer to the whole diet (for whole-diet interventions) or only to the fraction of the diet that was manipulated (e.g. some beverages, some foods and beverages, some solid foods). The only study in which the whole diet was manipulated used a total liquid diet replacement (Thompson et al., 1978). In all other cases, only a fraction of the diet, variable from study to study, was the subject of the intervention, and thus, only the amount of sugars consumed with that fraction of the diet is reported in the publication. Only in few instances, there was enough information provided to calculate the amount of sugars consumed from the whole diet (total sugars) in all the study arms.

The amount of sugars provided with the intervention always refers to added sugars, except for studies using honey (free sugars, Majid et al. (2013)), studies which targeted non-milk extrinsic sugars (free sugars, Markey et al. (2016); Umpleby et al. (2017)) or a whole liquid diet (total sugars as free sugars, Thompson et al. (1978)).

7.3.1.4. Type of sugar investigated

The sugars administered to intervention arms were as follows: fructose, glucose, mixtures of glucose and fructose, sucrose, HFCS, corn syrup, rare sugars syrup, honey, fruit juice, sugar-sweetened beverages, non-milk extrinsic sugars, simple carbohydrates. For data analysis, the intervention has been classified as follows with respect to the type of sugar administered:

a) Glucose
b) Fructose
c) Mixtures of glucose and fructose, where these monosaccharides are in an approximate ratio of 1:1 as found in mixed diets (including sucrose, HFCS, honey, sugar-sweetened beverages, fruit juice, non-milk extrinsic sugars, simple carbohydrates)

Study arms using corn syrup (Thompson et al., 1978), rare sugars syrup (Hayashi et al., 2014) or fruit juice (Hollis et al., 2009; Houchins et al., 2012) were not considered for answering Q1 or Q2 as they were planned to investigate Q4 only (see also Section 7.3.1.6 on data selection).

7.3.1.5. Type of control

During data extraction, the type of controls used in the studies were classified as follows: water, artificial sweeteners, no sugar, starch, fat and mixed macronutrients. For data analysis, these arms were assigned a zero value for the amount of (added or free) sugars given with the intervention.

7.3.1.6. Data selection

Mean effect estimates were computed for each study by selecting one intervention arm and one reference arm, as follows:

Q1. Effect of the **amount of sugar**. Comparisons are made between:

a) one arm with a zero (added or free) sugars value (reference) and one arm with a sugars value > 0 (intervention), which could be any type of sugar; if more than one arm with zero (added or free) sugars is available for a given study, the arm being more comparable to the intervention is selected as reference (e.g. ASSD is selected as reference for SSSD, rather than water or no intervention); if two or more arms with a sugars value > 0 are available for the same study, the arm with the highest sugars value is selected as intervention; if the highest sugars value corresponds to two or more arms investigating different types of sugars, sucrose or fructose were selected as intervention rather than HFCS, corn syrup or glucose because sucrose and fructose are the main energy-containing sweeteners used in Europe, at least until the end of the sugar quota.
b) two arms with different doses of the same sugar (e.g. sucrose); if more than two arms are available for the same study, the arm with the lowest dose (reference) is compared to the arm with the highest dose (intervention); if the same doses are investigated for different sugars within a study, sucrose or fructose were selected rather than HFCS or glucose for the reasons given above.

Q2. Effect of the **type of sugar**. Comparisons are made between arms which provide the same dose of glucose (reference) and fructose (intervention).

The main characteristics of the intervention studies on metabolic diseases included in the assessment and the study arms selected to address each question are shown in **Appendix E**.

The amount of sugars provided with the intervention always refers to added sugars, except for studies using honey (free sugars, Majid et al. (2013)), studies which targeted non-milk extrinsic sugars (free sugars, Markey et al. (2016); Umpleby et al. (2017)) or a whole liquid diet (total sugars as free sugars, Thompson et al. (1978)).

The four intervention studies (seven comparisons; (Lowndes et al., 2014a,b; Angelopoulos et al., 2015) which compared the effect of sugars administered as either sucrose or HFCS (Q3) were kept in the body of evidence because they could also address Q1, Q2 or both. However, the four studies that could only answer Q4 about the source of sugars (e.g. honey vs. sucrose; fruits and vegetables vs.

fruit juice) will be not considered further (Yaghoobi et al., 2008; Houchins et al., 2012; Hayashi et al., 2014; Rasad et al., 2018).

7.3.1.7. Data analysis

In most intervention studies, and particularly in those conducted under controlled energy conditions, the amount of sugars given with the intervention to each subject is adjusted to total energy intake and expressed as E%. In other studies, the intervention is a fixed amount of sugars expressed in g/day. To make meaningful comparisons across studies, amounts of sugars in g/day were transformed into amounts of sugars as E% using mean total energy intakes for the study group at baseline reported in the individual studies whenever possible. If no information on total energy intake at baseline was available, assumptions were made based on sex (1,800 kcal was assumed for females; 2,200 kcal was assumed for males and 2,000 kcal was assumed for females and males combined). However, the same E% from sugars in different studies could correspond to very different E% from sugars in the whole diet, depending on the energy contribution of the dietary fraction that was manipulated to total energy intake and on the macronutrient composition of the dietary fraction that was not manipulated. For most of the studies included, such information is not available. In addition, the target dose of sugars to be administered with the intervention, rather than the amount of sugars consumed (often not reported in studies conducted ad libitum) was used for data analysis.

In this context, the only variable that could be investigated in relation to Q1 for different endpoints was the target (rather than the achieved) difference in sugar intakes between study arms, assuming that the dietary fraction that was not manipulated in the studies is comparable across arms regarding the macronutrient composition and, thus, the sugar content both at baseline and at the end of the intervention. The second assumption is that between-arm differences in endpoint variables reflect the change that would occur in a group of individuals increasing their sugar intake. This was effectively so in studies where the intervention aimed at increasing sugars intake, but not in studies where the intervention aimed at reducing sugars intake.

A correlation coefficient of 0.82 has been used to calculate the precision of the mean effect in cross-over studies and in parallel studies when the between-arm difference was computed using changes between baseline and end of the intervention. In both cases, the correlation coefficient is necessary to account for the dependency between two measurements of the same outcome variable (e.g. body weight, fasting blood glucose) in the same individual. Owing to the uncertainty in the level of correlation between repeated measurements for all the outcome variables considered in this assessment and the limited evidence that is available to provide an accurate and precise estimate for each of them, an Expert Knowledge Elicitation (EFSA, 2014) was conducted with the members of the Working Group on sugars. Estimates of the plausible range for the correlation coefficient (between 0.50 and 0.99) and of the value that with highest probability corresponds to the true mean across endpoints (0.82) were elicited. A sensitivity analysis using the extremes of the plausible range has also been conducted when estimating the pooled mean effects (forest plots) and the parameters of the dose-response models.

Further details on the statistical analysis of RCTs can be found in **Annex L**.

7.3.2. Observational studies on metabolic diseases including pregnancy endpoints

A total of 104 publications reporting on 66 different cohorts were included after full-text screening. These comprise mostly prospective cohort (PCs) and three prospective case-cohort (PCCs) studies. For convenience, PCs will be used as umbrella term for observational studies in the text, unless reference is made to specific studies with a PCC design.

A summary of the cohorts, together with the references reporting on each cohort, the general characteristics of the subjects recruited at baseline, the exposures and endpoints assessed and the methods used for the exposure assessment can be found in **Appendix J**.

7.3.2.1. Exposure

The studies included have investigated either dietary sugars from all sources or specific sources of sugars. In the former, quantified sugar intakes are used as independent variables in the studies, whereas studies on specific sources of sugars (e.g. sugar-sweetened soft drinks, fruits, chocolate, jam) generally use the amount of food as independent variable.

Standard exposure categories were defined for data extraction as shown in **Table 9**. The exposure described in the studies was approximated to the closest standard category to allow comparisons across studies. The same terminology was used for data extraction in intervention studies, where appropriate.

Table 9: Exposure categories for data extraction

Exposure category	Includes	Excludes
Total sugars	Monosaccharides (i.e. glucose, fructose and galactose) and disaccharides (i.e. sucrose, lactose and maltose)	Sugar alcohols (polyols), other substances used as sugar replacers and other mono- or disaccharides present in the diet in marginal amounts
Added sugars	Mono- and disaccharides used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table	Sugars from intact fruit, vegetables and milk; sugars naturally present in honey, syrups, fruit juice and fruit juice concentrates
Free sugars	Mono- and disaccharides added to foods by the manufacturer, cook or consumer plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.	Sugars from intact fruit, vegetables and milk
Sucrose	Sucrose naturally contained in foods and sucrose added to foods and beverages	–
Fructose	Free fructose plus half of sucrose	–
Free fructose	Fructose naturally present as monosaccharide in foods and beverages and fructose added to foods and beverages as monosaccharide	Fructose in sucrose
Free glucose	Glucose naturally present as monosaccharide in foods and beverages and glucose added to foods and beverages as monosaccharide	Glucose in sucrose
Sugar-sweetened soft drinks (SSSDs)	Carbonated and non-carbonated sugar-sweetened drinks such as soda, iced tea, sports drinks and energy drinks or any subgroup thereof	Alcoholic beverages, milk and milk beverages, coffee and hot tea, fruit drinks and fruit juices
Sugar-sweetened fruit drinks (SSFDs)	Fruit squashes, cordials, lemonades, punches or any combination of these	SSSDs and fruit juices
Sugar-sweetened fruit juices (SSFJs)	Fruit juices, concentrates and nectars with added sugars or any combination of these	Fruit drinks and 100% fruit juices
100% fruit juices (100% FJs)	Unsweetened fruit juices	SSFDs and SSFJs
Total fruit juices (TFJs)	SSFJs and 100% FJs	SSSDs and SSFDs
Fruit juices (FJs)	100% FJs, SSFJs or TFJs	SSSDs and SSFDs
Artificially sweetened soft drinks (ASSDs)	Sugar-free carbonated and uncarbonated drinks such as soda, iced tea, sports drinks and energy drinks or any subgroup thereof	Sugar-sweetened soft drinks, alcoholic beverages, milk and milk beverages, coffee and hot tea, fruit drinks and fruit juices
Sugar-sweetened beverages (SSBs)	Water-based beverages and fruit juices with added sugars. Include SSSDs, SSFDs, SSFJs and TFJs (when SSFJs and 100% FJs are not reported separately) or any combination thereof	100% fruit juices (except if SSFJs and 100% FJs are not reported separately)
Artificially sweetened beverages (ASBs)	Sugar-free, water-based sweetened beverages	Water-based beverages and fruit juices with added sugars

Dietary sugars

Sugars in the diet have been classified in observational studies considering their chemical structure (e.g. glucose, fructose, lactose, maltose, sucrose), whether they are consumed as monosaccharides, disaccharides or both (e.g. free fructose vs. total fructose), whether they occur naturally in foods or have been added to foods (e.g. 'natural' fructose vs. added fructose), whether they come from solid foods or from liquids, or a combination of the above (e.g. added free fructose).

This heterogeneity in the classification of the exposure results in a high number of specific exposure–endpoint couples which cannot be systematically addressed within the time and resources available. In addition, for several exposure–endpoint couples, only one study was available. Therefore, the Panel took the following decisions regarding data extraction:

a) Not to extract data on lactose, maltose and galactose. The rationale for this decision are as follows:

   i) Maltose is a very minor component of the diet and galactose is only found in small amounts in fruits and vegetables (Acosta and Gross, 1995).
   ii) Lactose, maltose or galactose is generally not used as sweeteners and was not used in any of the intervention studies included in the assessment.
   iii) There is no hypothesis by which lactose or maltose *per se* could increase the risk of metabolic diseases other than contributing to total sugars in the diet or the glucose pool in the body.

b) Not to extract data on added sucrose, added fructose or added sugars from specific foods (e.g. beverages, cereals, milk, sweets, table sugar). The reasons for this decision are:

   - The study reporting on added sucrose also reports on added sugars from all sources and sucrose from all sources (Tasevska et al., 2014b).
   - The study reporting on added fructose also reports on fructose from all sources and this was extracted as the exposure of interest (Bahadoran et al., 2017).
   - The very few studies which report on added sugars from specific foods also report on added sugars from all sources, which was extracted as the exposure of interest. In addition, the food groups for which the intake of added sugars was reported were not comparable across studies (**Appendix J**).

c) Not to extract data on added sugars from solids and/or added sugars from liquids when data on added sugars from all sources were available.
d) Not to extract data on added free fructose because the only study reporting on this exposure also reports on fructose from all sources, which was extracted as the exposure of interest (Tasevska et al., 2014b).

Data have been extracted, where available, for the following categories of dietary sugars: total sugars, added sugars, free sugars, sucrose, fructose (as monosaccharide and bound to glucose), free fructose (as monosaccharide) and free glucose (as monosaccharide) from all dietary sources. Data have also been extracted for added sugars from solids and/or liquids from studies not reporting on added sugars from all sources.

Sources of sugars

When the exposure category used in the studies as independent variable for analysis was the amount of a food source for which the sugar content had not been quantified, the following approach was followed for data extraction and analysis.

For beverages, the nomenclature of the exposure of interest was standardised as described in **Table 9**. When the amount of SSSDs, SSFDs, SSFJs, TFJs and 100% FJs consumed was reported, either for each beverage group separately or for any combination of these groups, data were extracted for the most aggregated exposure category available within the SSBs category (e.g. for SSSD and SSFD combined rather than for the two categories separately) and within the FJ category (for fruit juices combined rather than for each individual juice type; for TFJs rather than for 100% FJs or SSFJs separately). Using data from the EFSA food composition and consumption databases, the sugar content in these beverages was assumed to be 10 g/100 mL (round number).

Data were not extracted for the following beverages:

a) Combined categories including beverage groups with very different sugar content and for which a reliable estimate of the sugar intake was not feasible, not knowing the relative

contribution of each of the beverage groups to the combined exposure (e.g. categories including coffee and tea not specifying if sweetened or unsweetened; categories including both SSSD and ASSD combined; categories including plain milk, milk shakes and flavoured milk).

b) Vegetable juices, either alone or in combination with fruit juices, because the sugars content is significantly lower compared with other beverages (mean 3.7 g/100 mL) and their relative contribution to total juices is unknown.

c) Milk, because the intake is typically reported for skim and whole milk separately and there is no hypothesis by which lactose *per se* could increase the risk of metabolic diseases.

Data were not extracted for individual **solid foods** or food groups for the following reasons:

a) Combined categories included foods or food groups with very different sugar content. Not knowing the relative contribution of each food or food group to the combined exposure, reliable estimates of sugars intake were not feasible (e.g. sweets and deserts, candies and cakes).

b) Foods for which sugar intakes could have been calculated were either small contributors to total sugar intakes, were investigated in relation to the metabolic disease endpoints for other reasons than their sugar content or both (e.g. individual fruits, chocolate, syrups, jams).

c) The few studies quantifying sugar intakes from individual solid foods or food groups were heterogeneous regarding the exposure of interest and the endpoint assessed, so that only one study was available for each specific exposure–endpoint relationship. In addition, these studies were also reporting on (total/added/free) sugars from all sources, which was extracted as the exposure of interest.

Artificially sweetened beverages

Health effects of artificially sweetened beverages (ASBs) consumption are out of the scope of this assessment. Data on ASBs from the same PCs reporting on SSBs have been extracted in evidence tables whenever available to explore whether (and the extent to which) any relationship between SSBs and risk of disease could be attributed to the sugar fraction of these beverages in these particular studies. However, it should be noted that such data do not allow drawing conclusions about the relationship between the intake of ASBs and risk of disease because the systematic reviews conducted for this assessment did not address that question (e.g. evidence for ASBs has not been systematically collected).

7.3.2.2. Data selection

Data have been extracted in evidence tables from the PCs included in the assessment for all exposures and endpoints of interest with the following exceptions:

1) When data for the same cohort, exposure and endpoint were reported in more than one publication, the publication with the longest follow-up was kept.

2) If two publications reported on the same cohort, exposure and endpoints which are closely related (e.g. BMI and BMI z-scores), the publication reporting on the endpoint which was more appropriate for the study population was kept (e.g. BMI z-scores rather than BMI for adolescents).

3) Data from publications on single cohorts (e.g. EPICOR, HPFS) that are part of pooled analysis in other publications (e.g. EPIC and Harvard Pooling Project in relation to SSBs and CHD risk, respectively) have not been extracted to avoid considering these cohorts twice.

7.3.2.3. Data analysis

Data from PCs were meta-analysed by EFSA to explore linear and non-linear dose-response relationships between exposures and endpoints of interest in comprehensive uncertainty analyses whenever possible (see Section 8.1.3). Details on the statistical analysis of observational studies on metabolic diseases can be found in **Annex M**.

For dose-response relationships explored in individual studies by the authors, only PCs reporting on measures of risk across categories of intake (and not PCs reporting on continuous exposure–endpoint relationships) have been considered. This is because in the former, linearity of the dose-response relationship is not assumed but tested.

7.3.3. Studies on dental caries

One publication reporting on a human intervention study and 11 publications reporting on seven prospective cohort studies met the inclusion criteria for this assessment. Although only studies investigating the relationship between quantitative amounts of dietary sugars intake and dental caries were included, data on frequency of consumption were also extracted from these studies when available.

Individual data were requested from the authors of all prospective cohort studies. This was to explore the possibility of conducting pooled analyses to identify dose-response relationships between the intake of sugars and risk of dental caries and/or levels of intake at which the risk of dental caries is not increased.

7.4. Appraisal of the internal validity of the included studies

As specified in the protocol, a customised version of the OHAT/NTP risk of bias (RoB) tool was used to appraise the internal validity of eligible studies.[12] The appraisal addressed eight RoB questions for RCTs and five RoB questions for prospective cohort studies (PCs) and prospective case-cohort studies (PCCs) (**Table 10**). Questions related to randomisation (for intervention studies) and confounding (for observational studies) and questions related to detection bias for the exposure and the endpoint were considered the most critical for the allocation of studies to RoB tiers (i.e. key questions). For each study and exposure–outcome relationship, the RoB questions were answered by choosing one of the options depicted in **Figure 6**.

Table 10: Sources of bias and the corresponding questions used to address them, by study design(a)

Selection bias	RCTs	PCs/PCCs
1. Was administered dose or exposure level adequately randomised?	X*	
2. Was allocation to study groups adequately concealed?	X	
3. Did selection of study participants result in appropriate comparison groups?		(b)
Confounding bias		
4. Did the study design or analysis account for important confounding?		X*
Performance bias		
5. Were the research personnel and human subjects blinded to the study group during the study?	X	
Attrition/Exclusion Bias		
6. Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection bias		
7. Can we be confident in the exposure characterisation?	X*	X*
8. Can we be confident in the outcome assessment?	X*	X*
Selective Reporting Bias		
9. Were all measured outcomes reported?	X	(c)
Other Sources of Bias		
10. Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	X	X

RCTs: randomised controlled studies; PC: prospective cohort studies; PCC: prospective case-cohort studies.
(a): Adapted from OHAT/NTP RoB tool (NTP, 2019).
(b): This question from OHAT/NTP RoB tool was not retained as it was not applicable to the study designs included in the assessment.
(c): Because this question was found to be seldomly relevant for the observational studies included in the assessment, it was addressed under question 10 'other sources of bias' as selective reporting.
*: Key questions, i.e. questions considered as the most critical for the allocation of studies to RoB tiers.

[12] Available online: https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/riskbias/index.html

++	**Definitely Low** risk of bias	There is direct evidence of low risk-of-bias practices (May include specific examples of relevant low risk-of-bias practices)
+	**Probably Low** risk of bias	There is indirect evidence of low risk-of bias practices OR it is deemed that deviations of low risk-of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
-/NR	**Probably High** risk of bias	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g. not reported or 'NR') provided about relevant risk-of bias practices
--	**Definitely High** risk of bias	There is direct evidence of high risk-of-bias practices (May include specific examples of relevant high risk-of-bias practices)

(a): Source: OHAT/NTP RoB tool[13]

Figure 6: Answer format for the risk of bias (RoB) questions[(a)]

The judgements to the RoB questions were combined into an overall RoB judgement for each study and exposure–outcome relationship, according to the OHAT/NTP 3-tier system (**Table 11**). As a result, studies were classified as being at low (tier 1), moderate (tier 2) or high (tier 3) RoB.

Table 11: Tiering approach, by study design

	RCTs	PCs/PCCs
Tier 1, low risk of bias	Study rated as 'definitely low' or 'probably low' risk of bias for the key questions[(a)] **AND** Most other applicable questions answered 'definitely low' or 'probably low' risk of bias	Study rated as 'definitely low' or 'probably low' risk of bias for the key questions[(b)] **AND** At least one of the other applicable questions answered 'definitely low' or 'probably low' risk of bias
Tier 2, moderate risk of bias	Study met neither the criteria for tiers 1 or 3	Study met neither the criteria for tiers 1 or 3
Tier 3, high risk of bias	Study rated as 'definitely high' or 'probably high' risk of bias for the key questions[(a)] **AND** Most other applicable questions answered 'definitely high' or 'probably high' risk of bias	Study rated as 'definitely high' or 'probably high' risk of bias for at least two of the key questions[(b)] **AND** At least one of the other applicable questions answered 'definitely high' or 'probably high' risk of bias

RCTs: randomised controlled studies; PCs: prospective cohort studies; PCCs: prospective case-cohort studies.
(a): Key questions, i.e. questions considered most critical for the allocation of studies to RoB tiers for RCTs, related to randomisation (question 1), exposure characterisation (question 7) and outcome assessment (question 8).
(b): Key questions, i.e. questions considered most critical for the allocation of studies to RoB tiers for PCs and PCCs, related to confounding (question 4), exposure characterisation (question 7) and outcome assessment (question 8).

The appraisal forms, including the explanations for expert judgements, can be found in **Annex I**. As foreseen by the OHAT/NTP guidance, the criteria for the RoB questions were customised in the light of the specificities of the review questions. For RCTs, minimal adaptations to the original tool were introduced, mostly to accommodate the appraisal of studies with a cross-over design (questions 1, 2 and 8), the special characteristics of the exposure of interest (question 5) and the outcome assessment (question 6). For observational studies, the criteria to rate the confidence in the exposure characterisation (question 4) and in the outcome assessment (question 5) were adapted to encompass the methods for dietary assessment and outcome ascertainment used in eligible studies, and associated risk of bias. To that end, the criteria for the appraisal of the exposure characterisation captured the critical elements outlined in Section 5. The question addressing 'other threats' to internal validity (question 7) was used to address the risk of bias related to potential over-adjustment of the model in the statistical analysis and selective reporting **(Annex I)**.

The outcome of the appraisal of human studies in relation to the risk of bias can be found in **Annex K**.

[13] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

8. Hazard identification: chronic metabolic diseases

8.1. Body of evidence

8.1.1. Intervention studies

A summary of the main characteristics of the randomised controlled trials (RCTs) on metabolic diseases included in the assessment, the identification of the questions that each study could address (Q1–Q4) and the study arms used in this opinion as intervention and control to address Q1 (effect of the amount of sugar) and Q2 (effect of fructose vs. glucose) can be found in **Appendix E**.

A summary of the results of the intervention studies on metabolic diseases per endpoint cluster is shown in **Appendix F**. The results are presented in line with the primary objective of the study and according to the data analyses performed by the authors.

The intervention studies included in the body of evidence can be summarised as follows:

a) Studies providing different amounts of sugar (e.g. fructose; mixtures of fructose and glucose as sucrose, sugars from SSBs, honey; non-milk extrinsic sugars, simple carbohydrates from the whole diet). Of these, four studies targeted free sugars and the rest manipulated only the added sugars fraction (Q1).
b) Studies providing similar amounts of fructose and glucose (Q2).

These studies allow investigation of the following exposures in relation to the endpoints of interest:

a) Added and free sugars
b) Fructose
c) SSBs (as mixtures of glucose and fructose in beverages)

In the RCTs available, the sugar fraction manipulated was either added sugars or free sugars. In this context, an assumption will be made that the sugar fraction not manipulated in the study remained constant through the intervention and comparable among study arms. This applies to sugars in intact fruits, vegetables and milk in all the studies and to sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates when used as such by the consumer in all the studies except those assessing free sugars. That was the case in the few RCTs which reported on the amount of total sugars in the background diet. The sugar fraction not manipulated with the intervention in those studies ranged from 2.5 to 12E%, and the intake of total sugars across arms ranged from 2.5 to 50E%.

It should be noted that, since added sugars are a fraction of free sugars, and free sugars are a fraction of total sugars, changes in the intake of added sugars in an intervention will also imply changes in the intake of free and total sugars. However, sugars in whole fruits, vegetables and milk have not been manipulated with the intervention in any of the studies, and this is an important fraction of total sugars intake. Therefore, the Panel considers that these studies do not allow conclusions on total sugars as a whole.

Conversely, since the intakes of added and free sugars widely overlap, the Panel considers that RCTs addressing Q1 can be combined to draw conclusions on added and free sugars, even if the majority of the studies manipulated only the added sugars fraction. The Panel also considers that the data available from RCTs do not allow comparison of health effects based on the classification of dietary sugars as added or free.

From the only study which investigated 100% FJs vs. a sweetened drink or no drink (Hollis et al., 2009), the sweetened drink was selected as the high sugar arm for comparability across studies. This single study was considered insufficient to draw conclusions from RCTs on fruit juices.

For studies conducted in usual consumers of SSBs who were asked to replace these with non-caloric alternatives, the target for the control was assumed to be the usual consumption of SSBs at baseline and the target for the intervention the complete removal of those beverages.

It should be noted that RCTs conducted under isocaloric conditions aim to investigate the effect of sugars in isocaloric exchange with other macronutrients (primarily starch) and thus independently from their energy content, whereas RCTs conducted ad libitum investigate the effect of introducing sugars to (or removing sugars from) the diet in free living conditions. This includes the contribution of sugars to TEI but also the effect of any dietary modifications resulting from the intervention (e.g. changes in TEI and/or the composition of the diet), which were generally not controlled for.

8.1.2. Observational studies

The main characteristics of the observational studies included in the assessment are in **Appendix J**. The results by type of exposure and endpoint are shown in the evidence tables (**Annex J**).

The PC studies included in the body of evidence (BoE) allow investigation of the following exposures in relation to the endpoints of interest:

a) Total sugars
b) Added sugars, sucrose as a surrogate exposure for added sugars and free sugars (and non-milk extrinsic sugars) from all sources.
c) Fructose, either as total fructose or as free fructose from all sources
d) SSBs, including (a) SSSDs, SSFDs, SSFJs or any combination of these; and (b) TFJs when combined with SSSDs and/or SSFDs
e) Fruit juices, including 100% FJs or TFJs.

It is acknowledged that the above-mentioned classification is data driven. Like intervention studies, few PCs have investigated the relationship between free sugars from all sources (DONALD, (Herbst et al., 2011) and (Goletzke et al., 2013b); Mr and Ms Os (Liu et al., 2018); and/or free sugars from liquids (KoCAS, (Hur et al., 2015); DONALD, (Goletzke et al., 2013b)) and the endpoints of interest. Only the Mr and Ms Os cohort investigated both added sugars and free sugars from all sources. Therefore, studies on free sugars will be assessed together with studies on added sugars to draw conclusions on both sugar fractions because these two exposures widely overlap. As for RCTs, the Panel considers that the data available from PCs do not allow comparison of health effects based on the classification of dietary sugars as added or free.

In the PCs available, SSFJs were always considered under SSBs, i.e. in combination with SSSDs and/or SSFDs, whereas only a few PCs include TFJs under SSBs, always in combination with SSSDs and SSFDs. In this context, SSBs mostly denote water-based beverages with added sugars, under the assumption that 100% FJs were a minor contributor to the combined intake. In all PCs addressing FJs, these were reported by the authors (either in the publications or following clarification upon EFSA's request) as 100% FJs or TFJs. The Panel notes that, as for food consumption surveys, study participants might not have the knowledge or information to differentiate between fruit juices with no added sugars and fruit nectars with added sugars, and/or the question in FFQs may have not been specific enough to retrieve that information. However, the Panel notes that, although 100% FJs and SSFJs (e.g. nectars) differ in the content of added sugars, the amount of free sugars in these beverages is similar, and thus, 100% FJs and TFJs will be considered together under FJs for the purpose of this opinion.

PCs investigating the relationship between a food source (SSBs, FJs) and an endpoint allow conclusions on the food source and not necessarily on the sugar fraction of the source. Data on ASBs from the same PCs reporting on SSBs will be summarised in the text and discussed when drawing overall conclusions on hazard identification in order to explore whether any relationship between the intake of SSBs and risk of disease could be attributed, at least in part, to the sugar fraction of these beverages. However, the Panel wishes to reiterate that such data do not allow drawing conclusions about the relationship between the intake of ASBs and risk of disease because the systematic review was not set for that purpose, ASBs being out of the scope for this assessment.

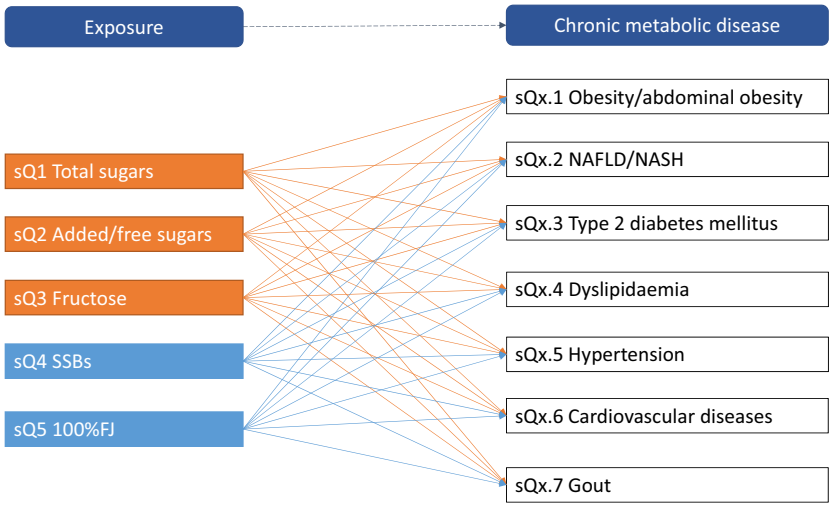
In PCs where the exposure has been introduced in multivariable regression models as a **continuous variable**, adjustments for TEI have been conducted in different ways and at different steps in the process. A review of the methods used to adjust for TEI in nutritional epidemiology, together with their strengths, limitations and potential for confounding of the association between the intake of the nutrient and the endpoints associated with TEI can be found in Willett et al. (1997) and in Section 5.1.3 of this scientific opinion. Most PCs on dietary sugars (total, added and free sugars; glucose and fructose) have investigated these nutrients keeping TEI constant in the analysis (i.e. in isocaloric exchange with other macronutrients), whereas most PCs on specific sources of sugars (SSBs and FJs) have explored whether these could be associated with the endpoint with and without considering their contribution to TEI (i.e. keeping and not keeping TEI constant). It should be noted, however, that in most PCs that have analysed the exposure as a **categorical variable**, the intake of dietary sugars has been standardised for TEI before assigning individuals to categories of intake, whereas the intake of beverages has not. In the first case, TEI is kept constant in the analysis, testing the hypothesis that dietary sugars may be associated with disease risk by mechanisms other than contributing to excess energy intake. In the second, TEI is not kept constant in the analysis because

introducing TEI as a covariate later in the process results in incomplete adjustment for TEI. This approach addressed the hypothesis that specific sources of sugars may be associated with disease risk also by contributing to excess energy intake.

8.1.3. Principles applied to assess the body of evidence: evidence integration and uncertainty analysis

The hazard identification step aims at identifying adverse health effects, i.e. increased risk of chronic metabolic diseases, caused by the intake of dietary sugars. The following question is addressed: Is the intake of (total/added/free) sugars (and/or their sources, e.g. SSBs, FJs) positively and causally associated with the risk of chronic metabolic diseases at the levels of sugar intake and in the population subgroups investigated in the studies eligible for this assessment?

The question is broken down into a series of subquestions (sQ) addressing specific exposure–disease relationships, as illustrated in **Figure 7**.



Each arrow represents one specific subquestion. Five types of exposure and seven metabolic diseases have been identified based on the evidence availability resulting from the study selection process. sQx = subquestion by exposure.

Figure 7: Exposure–disease relationships investigated for hazard identification

Within each sQ, randomised controlled trials (RCTs) and prospective cohort studies (PCs) are organised in separate lines of evidence (LoE), which are classified in the following hierarchical order (**Figure 8**):

- **Standalone (main) LoE:** Studies on disease endpoints (e.g. incidence of hypertension, incidence of T2DM). These studies could, on their own, answer the sQ directly.
- **Standalone (surrogate) LoE:** Studies on endpoints which are surrogate measures of the disease risk (e.g. blood pressure for hypertension, fasting glucose for T2DM). These studies also could, on their own, answer the sQ, on the assumption that a sustained increase in the surrogate measure over time (e.g. blood pressure) would eventually lead to an increased risk of disease (e.g. hypertension). However, the Panel is aware of the uncertainty inherent in this assumption and this will be considered in the overall uncertainty analysis for each sQ.
- **Complementary LoE:** Studies on endpoints which are relevant to the disease but less direct than those included in standalone LoE (e.g. risk factors, upstream indicators, other biologically related endpoints). These studies, on their own, cannot answer the sQ but can be used as supporting evidence to the standalone LoEs.

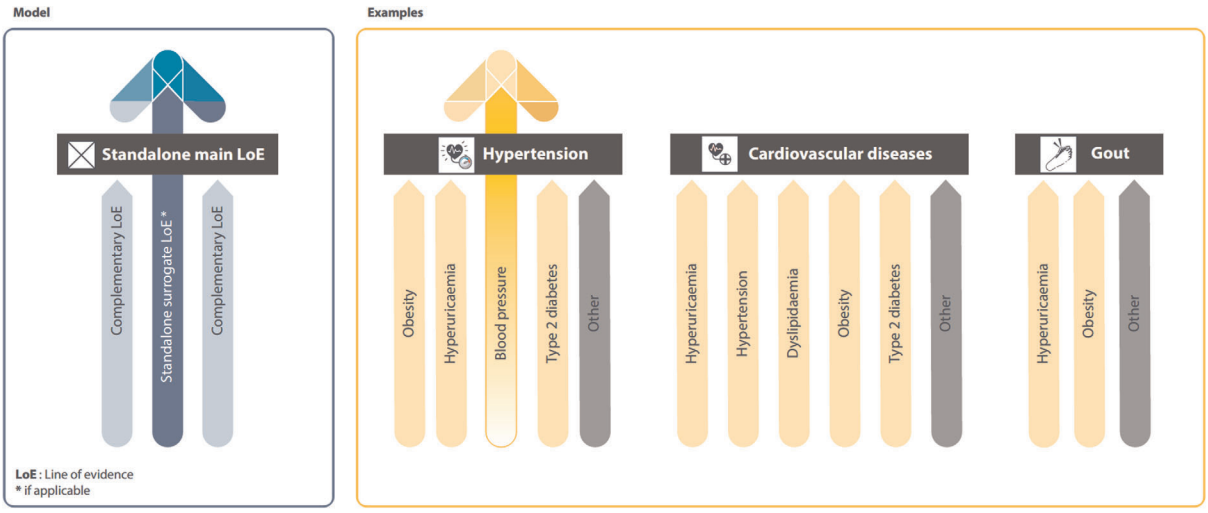
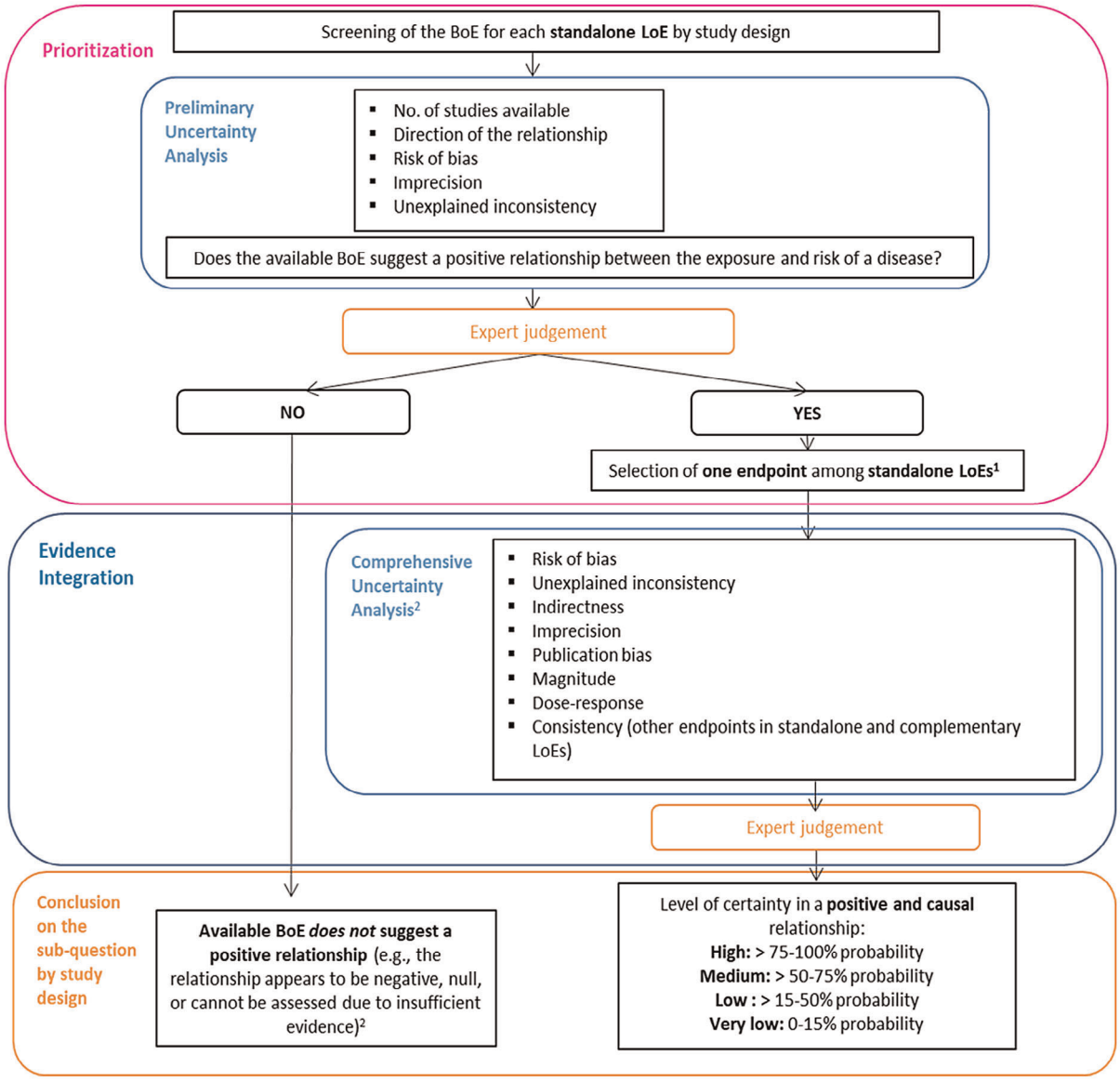


Figure 8: Graphical representation of standalone and complementary lines of evidence with some examples

Conclusions on each sQ are reached by study design (RCTs separately from PCs), by considering the uncertainties in the BoE and in the methods and by integrating the relevant LoEs. A stepwise approach is applied as illustrated in **Figure 9**. It involves a prioritisation step to identify sQs for which the available BoE suggests a positive relationship between the exposure and risk of disease based on a preliminary uncertainty analysis (UA) and expert judgement. A comprehensive UA (adapted from the OHAT approach as described below) is then applied to the selected sQs to express the level of certainty that a positive and causal relationship exists (see **Figures 10 and 11**). The Panel considers that sQs for which the available BoE does not suggest a positive relationship (e.g. the relationship appears to be negative, null or cannot be assessed due to insufficient evidence) cannot be used to inform the setting of a UL/safe level of intake for dietary sugars or to provide advice on quantitative intakes for their sources (i.e. SSBs and FJs) based on safety considerations. These sQs will be used to identify data gaps and research needs, where appropriate.



[1]For subquestions with more than one standalone LoE, and for standalone LoEs with endpoints which are biologically related, the comprehensive uncertainty analysis is undertaken for the endpoint with the highest level of evidence for a positive relationship with the exposure. The endpoint will be selected by expert judgement i.e. considering the number of studies available, and the strength, consistency and biological plausibility of the relationship.

[2]Complementary LoEs are assessed and discussed considering the factors underpinning the preliminary UA to provide a complete picture of the evidence base available for the sQ and inform the identification of data gaps. Yet, in the absence of evidence from Standalone LoE, evidence from complementary LoEs cannot be used to conclude on a positive and causal relationship between the exposure and the risk of disease.

Figure 9: Stepwise approach for evidence integration and uncertainty analysis applied to each subquestion by study design

The prioritisation step focuses on standalone LoEs. Data from complementary LoEs are not considered at this step because, on their own, they cannot answer the sQ and thus cannot be used to conclude on a positive and causal relationship between the exposure and the risk of disease. However, when the BoE for standalone LoEs does not suggest a positive relationship between the exposure and the risk of disease, complementary LoEs will nevertheless be assessed and discussed considering the factors underpinning the preliminary UA as depicted in **Figure 9**, in order to provide a complete picture of the evidence base currently available for the sQ and inform the identification of data gaps.

In the preliminary UA, the judgement applied to determine whether the BoE suggests a positive relationship between the exposure and the risk of disease includes considerations around the statistical

significance of study results. EFSA recommends that less emphasis is placed upon the reporting of statistical significance and more on statistical (point) estimation (i.e. effect estimate) and associated interval estimation (i.e. confidence interval) (EFSA Scientific Committee, 2011). In fact, point estimates and related confidence intervals are reported in evidence tables and plots, and full use of them is made during the judgement. However, for practical reasons, the terms 'non-significant' and 'significant', which usually imply making reference to a conventional cut-off for the p value of the statistical test applied, are used when reporting the results of individual studies in the preliminary UA.

The principles for the UA (**Figure 10**) have been derived from the OHAT 7-step framework for systematic review and evidence integration (NTP, 2019). The latter includes three steps to reach conclusions on hazard identification: (i) 'rating the confidence[14]' in the body of evidence, i.e. expressing the likelihood that the true effect is reflected in the apparent relationship (step 5); (ii) translating confidence ratings into 'level of evidence' for 'health effect' or 'no health effect' (step 6); (iii) integrating evidence from human and animal studies, along with other relevant data (e.g. mechanistic data) (step 7).

The following adaptations have been applied to the OHAT approach:

a) The assessment is restricted to the identification of adverse health effects in the BoE, i.e. positive and causal relationship between the exposure and risk of disease. This involves a prioritisation step, as described above, and a comprehensive UA to conclude on the level of certainty for the positive and causal relationship identified in the BoE. In contrast to OHAT, whenever a positive relationship is not identified for an sQ at the prioritisation step, no comprehensive UA is undertaken and no conclusions are made about other possible relationships (i.e. null denoting no health effect; negative, denoting a beneficial health effect) (see **Figure 10**).
b) Consequently, this assessment combines steps 5 and 6 from OHAT. The final level of certainty expresses the probability that a positive and causal relationship exists between the exposure and risk of disease, considering the limitations in the BoE and in the methods used to address it. The Bradford Hill criteria on causality as used in the OHAT approach (strength, consistency, temporality, biological gradient, biological plausibility, experimental evidence for causal association; Table 14 in OHAT handbook (NTP, 2019) are applied to judge on causality.
c) In line with OHAT's principles, the BoE on a particular sQ is given an initial level of certainty based on study design. In the OHAT's framework, the 'initial confidence rating' is expressed through four qualitative descriptors, i.e. 'high', 'moderate', 'low', 'very low'. It is assigned by considering four features of the design i.e. exposure is experimentally controlled, exposure occurs prior to the endpoint, endpoint is assessed at individual level and an appropriate comparison group is included in the study. As a result, OHAT proposes that RCTs start with a 'high' confidence rating (likely to comply with all four the above-mentioned criteria), while prospective cohort studies (where the exposure is unlikely to be controlled) start with a 'low' to 'moderate' confidence rating (Table 8 in OHAT handbook (NTP, 2019), depending on whether the exposure precedes the outcome or not. The Panel agrees with the rationale behind this initial rating but notes that qualitative descriptors bear some ambiguity (EFSA Scientific Committee, 2018). Therefore, OHAT's 'initial confidence ratings' have been translated into 'initial levels of certainty' expressed as approximate probabilities (**Figure 10**).
d) Similarly, the final level of certainty for a positive and causal relationship between the exposure and risk of disease is expressed in terms of probabilities, rather than using qualitative descriptors (**Figure 10**).
e) Among the criteria considered to downgrade the certainty in the BoE, the evaluation of indirectness is restricted to how the endpoint assessed in the studies relates to the main (disease) endpoint. External validity will be considered when drawing overall conclusions on hazard identification (Step 7 in OHAT). The other criteria, i.e. risk of bias across studies, unexplained inconsistency, imprecision and publication bias, are used according to OHAT's principles. Criteria for downgrading the certainty in the BoE will be considered first and will be systematically addressed in comprehensive UAs.
f) Among the criteria considered to upgrade the certainty in the BoE, consistency is assessed by considering the consistency in the evidence available on endpoints which are biologically

[14] The concept of 'confidence' as used in OHAT framework is equivalent to the concept of 'certainty' in EFSA's terminology (EFSA guidance on U).

related under each sQ (i.e. standalone LoEs and complementary LoEs which pertain to the sQ of interest, as outlined in **Table 12**). At this step, the consistency across LoEs is considered for each type of study design separately. Consistency of the evidence across study designs is considered in a final integration step (see below and **Figure 10**). The other criteria, i.e. magnitude, dose-response, residual confounding and other related factors, are used according to OHAT's principles. Criteria for upgrading the certainty in the BoE will be systematically considered but only reported on when deemed relevant to the BoE.

g) The level of certainty in a positive and causal relationship between the exposure and disease risk in this assessment is based on human data alone. Consistent with the OHAT framework, mechanistic data and mode of action are not required to reach hazard identification conclusions for each specific exposure–disease endpoint. This information will be discussed narratively when summarising the overall conclusions on hazard identification. However, different from the OHAT framework, it will not be used to upgrade or downgrade the level of certainty on the relationship between the intake of dietary sugars and disease risk because mechanistic data have not been systematically searched for or appraised, as foreseen in the protocol.

h) A comprehensive UA will not be undertaken on a BoE consisting of less than three independent studies because some criteria that should be considered to downgrade the certainty in the BoE cannot be assessed (e.g. heterogeneity). In that case, the initial level of certainty assigned to the relationship will be 'very low' (0–15% probability) to reflect the limited BoE available. In this case, the characteristics of the available studies (e.g. sample size, magnitude of the effect, risk of bias) and the biological plausibility of the relationship (including mode of action) will be considered to upgrade the level of certainty where appropriate. When the BoE for an exposure–disease relationship is limited to one or two studies, data supporting its biological plausibility become a critical feature of the available evidence that could increase the Panel's level of certainty on the relationship.

i) Step 7 in OHAT is not applied.

A schematic representation of the approach for assessing the final level of certainty in the hazard identification conclusions by study design is provided in **Figure 10**.

Initial level of certainty by study design	Factors decreasing certainty	Factors increasing certainty	Final level of certainty
High: > 75-100% probability RCTs Moderate: > 50-75% probability PCs *assessing the exposure (or change thereof) prior to the endpoint* Low: > 15-50% probability PCs *assessing changes in the exposure and concurrent changes in the endpoint* Very low: 0-15% probability	• risk of bias across studies (limitations to internal validity) • Unexplained inconsistency (heterogeneity) • indirectness of the endpoint to the main (disease) endpoint • imprecision • publication bias	• large magnitude of the effect (or a strong association/response) • dose-response (monotonic or not) • residual confounding or other factors that would increase certainty in the estimated effect (for PCs only) • consistency (across endpoints in standalone and complementary LoEs)	**High:** > 75-100 % probability **Moderate:** >50-75 % probability **Low:** > 15-50% probability **Very low:** 0-15 % probability

(a): Adapted from OHAT (NTP, 2019).

Figure 10: Approach applied to assign the final level of certainty in a causal relationship(a)

This type of approach cannot be implemented according to fixed objective criteria – expert judgement is needed, which implies some subjectivity in each decision. However, it provides a reproducible and transparent framework for expressing uncertainty in the evidence and in the methods.

Hazard identification conclusions for each sQ across study designs will be primarily based on the evidence with the highest certainty on the relationship. Consistent results across study designs can result in higher certainty on the causality of a positive relationship (**Figure 11**). Limitations in the BoE regarding the external validity of the results with respect to the exposure level and setting (population subgroup) will be discussed in the hazard characterisation step (Section 11).

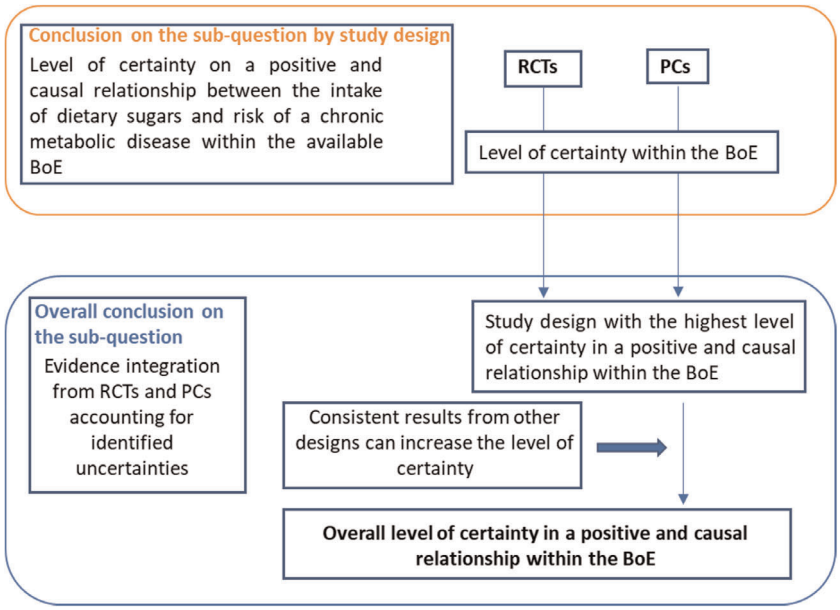


Figure 11: Approach for evidence integration and uncertainty analysis across study designs applied to each subquestion

Table 12 outlines the subquestions (sQ) and the LoEs considered in relation to each metabolic disease. The table also provides information on the eligible studies by type of design and exposure, the number and type of studies available for each LoE and identifies data gaps in the BoE.

For the risk of obesity, two disease endpoints are included in the standalone (main) LoE: (a) incidence of obesity based on BMI cut-offs, and (b) incidence of abdominal obesity based on WC cut-offs, as either one on its own could answer the sQ. Measures of body weight/BMI and WC are included in the standalone (surrogate) LoE. Measures of body fat and abdominal fat are considered as complementary LoEs.

Changes in skeletal muscle fat and visceral adipose tissue are considered in a complementary LoE for the sQ on the risk of NAFLD/NASH because these two variables are reported in studies which investigate the effect of sugars on liver fat.

Measures of glucose homeostasis have been grouped in LoE which follow the natural history of type 2 diabetes, i.e. from those that are expected to be impaired first to those expected to be impaired later in time:

a) Measures of insulin sensitivity obtained either in steady-state conditions (during an euglycaemic hyperinsulinaemic clamp) or in non-steady state conditions (e.g. during an intravenous glucose with frequent sampling/minimal model assessment (IVGTT)).
b) Indices of insulin sensitivity/resistance and indices of insulin secretion/beta cell function, either derived from the fasting state (e.g. HOMA-IR, HOMA-beta) or from an OGTT (e.g. Matsuda index of insulin sensitivity).
c) Measures of glucose tolerance, either derived from the fasting state (fasting glucose and insulin) or from an oral glucose tolerance test (OGTT), including glucose and insulin at 120 min and areas under the curve (AUC) for glucose and insulin.
d) Measures of blood glucose control, including fructosamine, glycated albumin and glycated haemoglobin.

LoE c) is considered standalone (surrogate) because cut-off values for fasting glucose and for glucose at 120 min during an OGTT are used for the diagnosis of diabetes. Within this LoE, measures of fasting insulin and insulin at 120 min during an OGTT will be considered as complementary. In contrast, LoEs (a) and (b) are considered complementary because, on their own, they cannot answer the sQ about the risk of T2DM. Although measures of blood glucose control (LoE d) are relevant endpoints, these are not expected to change significantly in non-diabetic individuals (RCTs in diabetics were not eligible). Indeed, the four RCTs with an appropriate duration that investigated the effect of added sugars on measures of blood glucose control, with sugar doses ranging from 6 to 24 E%, did not show significant differences between the high and low sugar arms on fructosamine (Gostner et al., 2005; Stanhope et al., 2009), glycosylated albumin (Swanson et al., 1992) or glycated haemoglobin (Hernandez-Cordero et al., 2014). Consequently, this LoE will not be considered further.

Risk of T2DM is considered as complementary LoE for the risk of dyslipidaemia because high fasting TG and low HDL-cholesterol are characteristic of insulin resistance states (such as the metabolic syndrome) and T2DM.

For LoEs with more than one endpoint (e.g. measures of glucose tolerance, blood lipids) studies reporting on at least one endpoint which is pertinent to the LoE (e.g. fasting glucose, HDL-cholesterol) have been counted. Studies reporting on multiple endpoints that belong to the same LoE (e.g. total cholesterol, triglycerides and HDL-cholesterol; incidence of obesity, incidence of abdominal obesity) have been counted only once.

Table 12: Subquestions for hazard identification, lines of evidence and number of studies included by study design

sQ1: Is the intake of **total sugars** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) Randomised controlled trials (RCTs) providing different amounts of total sugars through the manipulation of free sugars and sugars in intact fruits, vegetables and milk – None
b) Prospective cohort studies (PCs) on total sugars from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ1.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**3**
LoE3. Complementary	Body fat, abdominal fat	0	2
sQ1.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	**1**
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity (sQ1.1)	sQ1.1.	sQ1.1
sQ1.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**4***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	**1**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
sQ1.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c and derived indices	0	**2**
LoE3. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
sQ1.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	SBP and/or DBP	0	**1**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0	0

LoE4. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
sQ1.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint), CHD or stroke	0	**8**
LoE2. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
LoE4. Complementary	Risk of dyslipidaemia (sQ1.4)	sQ1.4	sQ1.4
LoE5. Complementary	Risk of hypertension (sQ1.5)	sQ1.5	sQ1.5
LoE6. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ1.5)	LoE3 for sQ1.5	LoE3 for sQ1.5
sQ1.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ1.5)	LoE3 for sQ1.5	LoE3 for sQ1.5
LoE3. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1

sQ2: Is the intake of **added and free** sugars positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) Randomised controlled trials (RCTs) providing different amounts of added and free sugars from foods, beverages or food and beverages
b) Prospective cohort studies (PCs) on added sugars, sucrose (as surrogate for added sugars) and free sugars from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ2.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**11(+2)**	**8**
LoE3. Complementary	Body fat, abdominal fat	5	4
sQ2.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**4**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/3	0
LoE4. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
sQ2.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**4**
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**17**	**2**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	5	2
LoE4. Complementary	Measures of insulin sensitivity	7	0
LoE5. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
sQ2.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**24**	**3**
LoE3. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
sQ2.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	SBP and/or DBP	**10**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/7	0
LoE4. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
sQ2.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**

LoE2. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
LoE4. Complementary	Risk of dyslipidaemia (sQ2.4)	sQ2.4	sQ2.4
LoE5. Complementary	Risk of hypertension (sQ2.5)	sQ2.5	sQ2.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ2.5)	LoE3 for sQ2.5	LoE3 for sQ2.5
sQ2.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ2.5)	LoE3 for sQ2.5	LoE3 for sQ2.5
LoE3. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1

sQ3: Is the intake of **fructose** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing similar intakes of fructose and glucose from foods, beverages or food and beverages
b) RCTs comparing different amounts of fructose from foods, beverages or food and beverages
c) PCs on fructose, free fructose and free glucose (as comparator for free fructose) from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ3.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**2**	**2**
LoE3. Complementary	Body fat, abdominal fat	1	1
sQ3.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/2	0
LoE4. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
sQ3.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**3**
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**10**	0
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	5	1
LoE4. Complementary	Measures of insulin sensitivity	6	0
LoE5. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
sQ3.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**10**	**1**
LoE3. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
sQ3.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**3**
LoE2. Standalone (surrogate)	SBP and/or DBP	**5**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/5	0
LoE4. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
sQ3.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
LoE4. Complementary	Risk of dyslipidaemia (sQ3.4)	sQ3.4	sQ3.4
LoE5. Complementary	Risk of hypertension (sQ3.5)	sQ3.5	sQ3.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ3.5)	LoE3 for sQ3.5	LoE3 for sQ3.5

sQ3.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ3.5)	LoE3 for sQ3.5	LoE3 for sQ3.5
LoE3. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1

sQ4: Is the intake of **SSBs** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing different amounts of SSBs or mixtures of fructose and glucose in beverages
b) PCs on SSBs or on added sugars from beverages

LoE	Endpoints	RCTs (n)	PCs (n)
sQ4.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**10**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**6(+2)**	**21**
LoE3. Complementary	Body fat, abdominal fat	4	6
sQ4.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat/visceral adipose tissue	2/2	0/1
LoE4. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
sQ4.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**14***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**7**	1
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	3	2
LoE4. Complementary	Measures of insulin sensitivity	3	0
LoE5. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
sQ4.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**5**
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**7**	**4**
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
sQ4.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**7**
LoE2. Standalone (surrogate)	SBP and/or DBP	**4**	**1**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/3	1/0
LoE4. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
sQ4.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**10**
LoE2. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
LoE4. Complementary	Risk of dyslipidaemia (sQ4.4)	sQ4.4	sQ4.4
LoE5. Complementary	Risk of hypertension (sQ4.5)	sQ4.5	sQ4.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ4.5)	LoE3 for sQ4.5	LoE3 for sQ4.5
sQ4.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ4.5	LoE3 for sQ4.5
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1

sQ5: Is the intake of **FJs** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing different amounts of fruit juices – None
b) PCs on fruit juices

LoE	Endpoints	RCTs (n)	PCs (n)
sQ5.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**2**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**10**
LoE3. Complementary	Body fat, abdominal fat	0	3
sQ5.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
sQ5.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**9***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	0
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
sQ5.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**1**
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	0	0
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
sQ5.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**2**
LoE2. Standalone (surrogate)	SBP and/or DBP	0	0
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ1.1	sQ1.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
sQ5.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
LoE4. Complementary	Risk of dyslipidaemia (sQ5.4)	sQ5.4	sQ5.4
LoE5. Complementary	Risk of hypertension (sQ5.5)	sQ5.5	sQ5.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ5.5)	LoE3 for sQ5.5	LoE3 for sQ5.5
sQ5.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ5.5)	LoE3 for sQ5.5	LoE3 for sQ5.5
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1

BMI, body mass index; CHD, coronary heart disease; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; LoE, line of evidence; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCs, prospective cohorts; RCTs, randomised controlled trials; SBP, systolic blood pressure; sQ, subquestion; T2DM, type 2 diabetes mellitus; TG, triglycerides; total-c, total cholesterol.
*: Includes prospective case-cohort studies. Grey cells denote the absence of eligible studies. Number of studies in standalone LoEs are in **bold**.

8.2. Risk of obesity

Body weight and BMI (or BMI standardised by age and sex and expressed as BMI z-scores for studies conducted in children) were eligible endpoints in RCTs with an intervention period of at least 6 weeks. Body weight and BMI were not assessed as endpoints in studies conducted under neutral energy balance because these studies were designed to maintain body weight constant (i.e. target energy intakes were adjusted to that end, even weekly in some studies). Percent body fat (%BF) and waist circumference (WC) were eligible endpoints in studies conducted ad libitum and in studies conducted under neutral energy balance. This is because both endpoints could theoretically change together with body weight or independently of it through changes in body composition and body fat redistribution. Measurements of %BF using bioelectrical impedance analysis (BIA) or skinfold thickness were not eligible for intervention studies because these techniques are generally not appropriate to assess small changes in body fat when used alone, particularly in obese subjects and/or when significant changes in body water compartments occur.

8.2.1. Total sugars

sQ1.1. Total sugars and risk of obesity

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**3**
LoE3. Complementary	Body fat, abdominal fat	0	2

8.2.1.1. Observational studies

Three prospective cohorts of children investigated the association between the intake of total sugars and BMI (SCES, (Gopinath et al., 2013); NGHS, (Lee et al., 2015); KoCAS, (Hur et al., 2015)), of which two also assessed WC (SCES, NGHS) and two %BF (SCES, KoCAS). The studies used either the nutrient residuals model or the standard multivariable model (in continuous analysis) to adjust for TEI, and thus kept TEI constant. The evidence table, including the effect estimates and confidence intervals, is in **Annex J**.

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. PCs. The SCES cohort (RoB tier 2) reports non-significant associations (negative in females, positive in males) between total sugars intake at baseline and change in BMI or WC over the 5-year follow-up. In the NGHS cohort (RoB tier 1), a non-significant (positive) association was found between 1-year changes in total sugars intake and concurrent changes in BMI z-scores and WC in the most adjusted models. Associations between absolute intake of total sugars at baseline and BMI z-scores at the end of the 4-year follow-up were positive and non-significant in the KoCAS (RoB tier 3).

Preliminary UA. The Panel notes the limited number of studies available, that the direction of the relationship is inconsistent across studies, and that none shows significant associations between the intake of total sugars and BMI (or BMI z-scores) or WC. The heterogeneity of these studies with respect to the exposure–endpoint relationships investigated (baseline intake vs. changes in the endpoint, changes in intake vs. changes in the endpoint, baseline intake vs. endpoint at the end of follow-up) precludes the calculation of pooled mean estimates across studies, as evidence is sparse by type of relationship.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity. **No comprehensive UA is performed**.

LoE3. Complementary: Body fat, abdominal fat. PCs. The Panel notes that the BoE is limited to two PCs (SCES, KoCAS), which are inconsistent regarding the direction of the association between total sugars intake and %BF (negative in SCES, significant in males only, RoB tier 2; positive in KoCAS, RoB tier 3).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and %BF.

8.2.1.2. Overall conclusion on sQ1.1

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity. Total sugars were not investigated under other dietary conditions (e.g. not keeping TEI constant in the analysis).

8.2.2. Added and free sugars

sQ2.1. Added and free sugars and risk of obesity

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**11 (+2)**	**8**
LoE3. Complementary	Body fat, abdominal fat	5	4

8.2.2.1. Intervention studies

LoE 2. Standalone (surrogate): Body weight/BMI, waist circumference. RCTs. Changes in body weight were investigated in 11 studies of which six manipulated sugars from beverages and five from a combination of solid foods and beverages. Seven RCTs were conducted in overweight/obese individuals and two were in children and adolescents. Between-arm differences in added sugar intakes ranged from 6 to 24 E%. Of these, two studies investigated changes in WC. WC was also measured in two studies conducted under neutral energy balance. The results of the individual studies are in **Appendix F**.

Preliminary UA

At the end of the intervention, body weight was higher in the high sugars arm relative to the low sugars arm in all the 11 studies considered. The effect was statistically significant in three studies. Six RCTs were at low RoB (tier 1) and five at moderate RoB (tier 2). The mean pooled effect (95% CI) is 1.15 kg (0.53, 1.77; I^2 = 29%) **(Appendix G, Figure G.1a)**. The results on BMI followed the same pattern in the six studies which assessed this endpoint, as expected in studies conducted mainly in adults **(Appendix G, Figure G.1b)**. The mean pooled effect (95% CI) is 0.38 kg/m^2 (0.10, 0.66).

In the four studies which investigated changes in WC, between-arm differences in added sugars intake ranged from 6 to 22 E% **(Appendix G, Figure G.1c)**. Within each dietary condition (i.e. ad libitum, under neutral energy balance), the two studies available showed changes in WC in opposite directions. One RCT was at low RoB (tier 1) and three RCTs were at moderate RoB (tier 2). The mean pooled effect (95% CI) is 0.25 cm (−0.47, 0.97; I^2 = 50%). Changes in WC were consistent with changes in body weight within each study conducted ad libitum, and consistent with changes in %BF within each study conducted under neutral energy balance.

The Panel considers that the available BoE suggests a positive relationship between the intake of added and free sugars and risk of obesity.

Comprehensive UA

Selection of the endpoint. Owing to the low number of studies having WC as an endpoint and the lower reliability of this measurement as compared to body weight, the Panel selected body weight as the key endpoint for the comprehensive UA in relation to sQ2.1 (**Table 13**).

Dose-response relationship. In the linear dose-response meta-regression analysis conducted by EFSA (**Annex L**), the intake of added or free sugars expressed as E% could not significantly explain the variability in the between-arm differences in body weight changes (the fit of the model measured by the Akaike information criteria (AIC), equal to 36.1, was not dissimilar from that of the model with no explanatory variables, AIC equal to 36.5). Thus, evidence does not support a linear dose-response relationship between the intake of added or free sugars as E% ad libitum and body weight change (estimated regression coefficient 0.0479, 95%CI: −0.0623; 0.1582, p = 0.3941). Consequently, the impact of other variables as possible modifiers of the effect was not explored. A non-linear dose-response was not investigated based on the graphical exploration of the data. Dose-response was not investigated in individual studies.

LoE3. Complementary: Body fat, abdominal fat. RCTs. Five studies assessed changes in %BF, of which two were at neutral energy balance and three ad libitum. Between-arm differences in added sugars intake ranged from 10 to 23 E% **(Appendix G, Figure G.1d)**. In all studies except one, %BF was higher in the high sugars arm relative to the low sugars arm at the end of the intervention relative to baseline. The mean pooled effect (95% CI) is 0.22% (−0.05, 0.50; I^2 = 0%). Changes in %BF were generally consistent with changes in body weight within each study conducted ad libitum, and consistent with changes in WC within each study conducted under neutral energy balance.

Consistency across LoEs. The Panel notes that changes in body weight were generally consistent with changes in WC and % BF within each study, but few RCTs investigated these endpoints.

Table 13: sQ2.1. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods.

What is the level of certainty in a positive and causal relationship between intake of **added and free** sugars *ad libitum* and the risk of obesity at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint:** body weight **11 RCTs, 1,328 participants.** Pooled mean effect estimate (95% CI) = 1.15 kg (0.53, 1.77) assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be > 0.82. **(Appendix G, Figure G.1a)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	6 studies in tier 1; 5 studies tier 2 (**Appendix I, Table I.1**) Between low and moderate Key questions: • Randomisation: low • Exposure assessment: generally low • Outcome assessment: mixed low and probably high Probably high for allocation concealment and blinding	Serious
Unexplained inconsistency	Low statistical heterogeneity (I^2 = 29% for the pooled mean effect). Mean effect estimates are similar across studies and 95%CI largely overlap.	Not serious
Indirectness	Surrogate endpoint	Serious
Imprecision	Low. It could be even lower because the correlation coefficient for this endpoint is expected to be > 0.82 **(Appendix G, Figure G.1a)**.	Not serious
Publication bias	Funnel plot suggests low risk of publication bias (**Appendix H, Figure H.1**). Public (n = 3), private (n = 3) and mixed (n = 4) funding (NR for one study).	Undetected
Upgrading factors	None identified	None
Final certainty	Started high, downgraded one level for indirectness. RoB was not considered sufficiently serious to downgrade because it was between low and moderate, and generally low for 2 out of the 3 key questions.	**Moderate (> 50–75% probability)**

Conclusion sQ2.1. RCTs. The level of certainty in a positive and causal relationship between the intake of added and free sugars and risk of obesity is **moderate** (rationale in **Table 13**). The studies were conducted ad libitum. Between-arm differences in added and free sugars intake were between 6 and 24 E%. Most RCTs were in overweight/obese adult subjects, and two were in children and adolescents.

8.2.2.2. Observational studies

Eight PCs investigated the association between added sugars (QUALITY, (Wang et al., 2014); NGHS, (Lee et al., 2015)), free sugars (DONALD, (Herbst et al., 2011); KoCAS, (Hur et al., 2015)), added and free sugars (Mr and Ms OS, (Liu et al., 2018) or sucrose (PHHP, (Parker et al., 1997); EPIC-Norfolk, (Kuhnle et al., 2015); NSHDS, (Winkvist et al., 2017)) and body weight, BMI or BMI z-scores. Of these, three also investigated WC (QUALITY, NGHS, EPIC-Norfolk), and three either BF, abdominal fat or both (DONALD, QUALITY, Mr and Ms OS). Evidence tables are in **Annex J**.

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. PCs. The four studies on added or free sugars were conducted in children (DONALD, QUALITY, NGHS, KoCAS), whereas the study on added and free sugars was in the older adults (Mr and Ms OS) and the three studies on sucrose were in adults (PHHP, EPIC-Norfolk, NSHDS).

Sugars intake was analysed as continuous variable in all the studies. Six PCs used either the nutrient residuals model (DONALD, EPIC-Norfolk) or the standard multivariable model (QUALITY, KoCAS, PHHP, NGHS) to adjust for TEI, and thus kept TEI constant. Two studies used the multivariable energy density model not including TEI as covariate (NSHDS, Mr and Ms OS).

Six studies investigated the association between added sugars, free sugars or sucrose intake at baseline and either the change in endpoint over follow-up (PHHP, QUALITY, Mr and Ms OS) or the endpoint at the end of follow-up (EPIC-Norkfolk, DONALD, KoCAS), while two studies investigated the association between change in added sugars or sucrose intake and change in endpoints over follow-up (NSHDS, NGHS).

Preliminary UA

Negative (DONALD, KoCAS, EPIC-Norfolk) or null (QUALITY, PHHP) associations between the intake of added sugars, free sugars or sucrose at baseline and measures of body weight are reported in all studies except one (Mr and Ms OS). Plot can be found in **Appendix K, Figure K.1a** (EPIC-Norfolk and PHHP could not be included). The EPIC-Norfolk study reported a positive association when sucrose in spot urine samples was used as a marker of sucrose intake. The direction of the associations observed with WC were consistent with those for body weight measurements within each study (QUALITY, NGHS, EPIC-Norfolk). Positive (NGHS) and negative (NSHDS) associations between changes in the intake of added sugars or sucrose and measures of body weight were reported. The Panel notes that in NSHDS and Mr and Ms OS, multivariable nutrient density models were applied without adjustment for TEI (NSHDS, Mr and Ms OS).

Two PCs were in RoB tier 1 (NGHS, QUALITY), five in tier 2 (DONALD, EPIC-Norfolk, PHHP, NSHDS, Mr and Ms OS) and one in tier 3 (KoCAS) for these endpoints. Confounding was a critical domain for all, except for those in tier 1, and attrition was a critical domain in all except Mr and Ms OS. The heat map for the RoB assessment is in **Appendix L**, **Table L.1a**.

The Panel notes that the available studies are heterogeneous in relation to the analytical strategies applied to investigate the relationship between added sugars, free sugars or sucrose and measures of BW and WC, i.e. baseline intake vs. change in intake analyses, and models used to account for TEI. Also, the heterogeneity of the studies with respect to the exposure–endpoint relationships investigated precludes the calculation of pooled mean effect estimates across studies, as evidence is sparse by type of relationship. Such relationships were mostly negative or null, regardless of the RoB tier, particularly in PCs using adequate statistical models to account for TEI. Therefore, the Panel considers that the available BoE does not suggest a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and risk of obesity. **No comprehensive UA is performed**.

LoE3. Complementary: Body fat, abdominal fat. PCs. Of the above-mentioned studies, four had either %BF (DONALD and KoCAS; RoB tier 3), BF in kg (QUALITY, RoB tier 1), abdominal fat (kg) or a combination of these (Mr and Ms OS, RoB tier 2), as endpoints. The results for BF and abdominal fat were generally consistent with those for body weight/BMI and WC, respectively, within each study, except in KoCAS. Studies on BF (%) are plotted in **Appendix K, Figure K.1b**.

The Panel notes the heterogeneity of these studies with respect to the exposure–endpoint relationships investigated, that no clear pattern is observed with respect to the direction of the association and that changes in %BF were consistent with measures of body weight except in KoCAS (RoB tier 3).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and body fat.

Conclusion sQ2.1. PCs. The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and risk of obesity.

8.2.2.3. Overall conclusion on sQ2.1

There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and risk of obesity (**moderate** level of certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

8.2.3. Fructose

sQ3.1. Fructose and risk of obesity			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**2**	**2**
LoE3. Complementary	Body fat, abdominal fat	1	1

8.2.3.1. Intervention studies

LoE2. Standalone (surrogate). Body weight/BMI, waist circumference. RCTs. Two RCTs (Stanhope et al., 2009; Angelopoulos et al., 2015) assessed the effects of fructose and glucose in beverages at doses of 9 and 25E% in the respective studies. The studies were conducted ad libitum in overweight and obese males and females and lasted 10 and 8 weeks, respectively.

Preliminary UA. The consumption of fructose and glucose as beverages increased body weight significantly (all study arms combined) regardless of the type of sugar administered during the intervention with no differences between fructose and glucose in any of the two RCTs, which were at moderate RoB (tier 2). The pooled mean effect estimate is 0.02 kg (95% CI = −2.26, 2.29). The results of the individual studies are in **Appendix F**. Similar results were obtained for WC and BMI (Stanhope et al., 2009; Angelopoulos et al., 2015).

The Panel notes the limited number of studies available and that effect of fructose vs. glucose on body weight and WC was null. The Panel considers that the BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity. **No comprehensive UA is performed**.

LoE3. Complementary: Body fat, abdominal fat. RCTs. Results for %BF were consistent with those for body weight in the only study which reported on this outcome (Stanhope et al., 2009).

The Panel considers that the available BoE does not suggest a positive relationship between the intake fructose in isocaloric exchange with glucose and %BF.

Conclusion sQ3.1. RCTs. The Panel considers that the available BoE from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity.

8.2.3.2. Observational studies

The relationship between the intake of fructose and changes in WC during follow-up was investigated in two prospective cohorts (SCES, (Gopinath et al., 2013); TLGS, (Bahadoran et al., 2017)), one of which (SCES) also assessed changes in BMI and %BF. These studies used either the nutrient residuals model (SCES) or the multivariable nutrient density model (TLGS) to account for TEI in the analyses, and thus aimed at investigating the relationship between fructose and the endpoints while keeping TEI constant. Evidence tables are in **Annex J**.

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. PCs. In the SCES cohort of children (RoB tier 2), separate analyses are given for males and females. For males, results refer to fructose at baseline by tertiles of intake, whereas for females, results refer to changes in fructose intake over the follow-up as continuous variable. Reasons for the different analysis by sex are unclear. The relationship between fructose intake and changes in BMI and WC over the 5-year follow-up was positive but non-significant in both sexes. In the TLGS cohort of adult males and females (RoB tier 2), the relationship between fructose intake at baseline and change in WC over the mean follow-up of 6.7 years was positive and statistically significant. The only variable considered for adjustment in the model was age.

Preliminary UA. The Panel notes that only two PCs are available and that, although both report a positive association between the intake of fructose and WC (significant in one), both studies are at moderate RoB (tier 2) for that endpoints. Critical domains were confounding and exposure (TLGS), and selective reporting (other sources of bias) and attrition (SCES).

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of obesity. **No comprehensive UA is performed**.

LoE3. Complementary: Body fat, abdominal fat. PCs. Only the SCES cohort (RoB tier 2) investigated the relationship between fructose intake (at baseline for males, as changes in intake over follow-up for females) and changes in %BF over the 5-year follow-up (positive, non-significant in both sexes).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and %BF.

Conclusion sQ3.1. PCs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of obesity.

8.2.3.3. Overall conclusion on sQ3.1

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fructose in isocaloric exchange with glucose or other macronutrients and risk of obesity. Fructose was not investigated under other dietary conditions (e.g. not keeping TEI constant).

8.2.4. Sugar-sweetened beverages

sQ4.1. SSBs and risk of obesity

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**10**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**6(+2)**	**21**
LoE3. Complementary	Body fat, abdominal fat	4	6

8.2.4.1. Intervention studies

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. RCTs. Among the RCTs which investigated the effect of high vs. low sugars intake ad libitum on body weight (discussed in Section 8.2.2.1), six assessed the consumption of SSBs vs. a sugar-free alternative. The between-group target difference in sugars intake from beverages was between 6 and 20E%. Studies lasted between 12 and 72 weeks and most (n = 5) were conducted in overweight/obese individuals (**Appendix F**).

Preliminary UA

At the end of the intervention, body weight was higher in the SSBs group relative to the sugar-free alternative in all studies. The effect was statistically significant in two studies. Three studies were at low RoB (tier 1) and three at moderate RoB (tier 2). The mean pooled effect (95% CI) is 0.82 kg (0.36, 1.29; I^2 = 0%) **(Appendix G, Figure G.1a)**.

Results for BMI in the four studies reporting on this outcome were in the same direction. Mean pooled effect (95% CI) is 0.29 kg/m^2 (0.06, 0.51, I^2 = 0%) **(Appendix G, Figure G.1b)**. Results for WC were as for added sugars (Section 8.2.2.1) because all four studies reporting on this outcome were conducted with beverages **(Appendix G, Figure G.1c)**.

The Panel considers that the available BoE suggest a positive relationship between the intake of SSBs as compared to a sugar-free alternative and risk of obesity.

Comprehensive UA

Selection of the endpoint. Owing to the low number of studies having WC as an endpoint and the lower reliability of this measurement as compared to body weight, the Panel selected body weight as the key endpoint for the comprehensive UA in relation to sQ4.1 for RCTs (**Table 14**).

Dose-response relationship. Dose-response relationships were not investigated in individual studies or by meta-regression analysis across studies, and there was no indication of a dose-response relationship by visual examination of the forest plot.

LoE3. Complementary: Body fat, abdominal fat. RCTs. Four studies assessed changes in % BF, of which two at neutral energy balance and two ad libitum **(Appendix G, Figure G.1d)**. In all studies except one, %BF was higher with high vs. low consumption of SSBs at the end of the intervention relative to baseline. Changes in %BF were generally consistent with changes in body weight within each study conducted ad libitum, and consistent with changes in WC within each study conducted under neutral energy balance.

Consistency across LoEs. The Panel notes that changes in body weight were generally consistent with changes in WC and % BF, but few RCTs investigated these endpoints.

Table 14: Q4.1. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **SSBs** *ad libitum* and the risk of obesity at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint: body weight** **6 RCTs, 1,036 participants.** Pooled mean effect estimate (95%CI) = 0.82 kg (0.36, 1.29) assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be > 0.82. **(Appendix G, Figure G.1a)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	3 studies in tier 1; 3 studies tier 2 (**Appendix I, Table I.1**) Between low and moderate Key questions: • Randomisation: low • Exposure assessment: generally low • Outcome assessment: mixed low and probably high Probably high for allocation concealment and blinding	Serious
Unexplained inconsistency	Low statistical heterogeneity (I^2 = 0% for the pooled mean effect). Mean effect estimates are similar across studies and 95%CI largely overlap.	Not serious
Indirectness	Surrogate endpoint.	Serious
Imprecision	Low. It could be even lower because the correlation coefficient for this endpoint is expected to be > 0.82 **(Appendix G, Figure G1.a)**.	Not serious
Publication bias	Funnel plot suggests low risk of publication bias (**Appendix H, Figure H.1**). Public (n = 2), private (n = 2) and mixed (n = 2) funding.	Undetected
Upgrading factors	None identified	None
Final certainty	Started high, downgraded one level for indirectness. RoB was not considered sufficiently serious to downgrade because it was between low and moderate, and generally low for 2 out of the 3 key questions.	**Moderate (> 50–75% probability)**

Conclusion sQ4.1. RCTs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of obesity is **moderate** (rationale in **Table 14**). The studies were conducted ad libitum using sugar-free alternatives as control. Between-arm differences in sugars intake from beverages were between 6 and 20 E%. Most RCTs were in overweight/obese subjects, and two were in children and adolescents.

8.2.4.2. Observational studies

LoE1. Standalone (main): Incidence of obesity, incidence of abdominal obesity. PCs

Incidence of obesity

Six PCs investigated the relationship between the intake of SSBs and incidence of overweight and/or obesity in non-overweight/obese individuals. Of these, four were in infants, toddlers and young children (DDHP (Lim et al., 2009); Amsterdam (Weijs et al., 2011); Generation R (Leermakers et al., 2015); ELEMENT (Cantoral et al., 2015)) and one in young adolescents of both sexes (PHI, (Ludwig et al., 2001)), whereas one was in adult black females (BWHS, (Boggs et al., 2013)). One study also investigated the association between the intake of ASBs and incidence of obesity (PHI). The evidence table is in **Annex J**.

Among the three PCs that analysed the exposure by categories of intake, BWHS did not adjust for TEI and ELEMENT adjusted for non-SSBs energy, and thus did not keep TEI constant. The exception was the Generation R, which standardised the exposure using the nutrient residuals model and included TEI as covariate. The remaining PCs performed continuous analyses using the standard multivariable model (DDHP, PHI) or the multivariable nutrient density model not including TEI as covariate (Amsterdam). All PCs adjust for baseline BMI except the three studies conducted in infants, which use either infant body weight (Amsterdam, Generation R) or maternal obesity at 12 months post-partum (ELEMENT) as a proxy.

Five PCs report a positive association between the intake of SSBs at baseline (BWHS, RoB tier 1; PHI and DDHP, RoB tier 2; Amsterdam, RoB tier 3) or the cumulative intake between 1 and 5 years of age (ELEMENT, RoB tier 3) and incidence of overweight and/or obesity (significant in 3 out of 5), whereas in one PC (Generation R, RoB tier 2), the association was positive in females and negative in males **(Appendix K, Figure K.2a)**. In the PHI, a significant positive association was reported for changes in intake of SSSDs over follow-up and incidence of obesity, whereas the association was negative for ASBs. The heat map for RoB assessment is in **Appendix L, Table L.2**.

Incidence of abdominal obesity

The relationship between the intake of SSBs and incidence of abdominal obesity was investigated in five PCs, one in infants (ELEMENT, (Cantoral et al., 2015)), one in children and adolescents (TLGS, (Mirmiran et al., 2015)) and three in adults of both sexes (Girona, (Funtikova et al., 2015); KoGES, (Kang and Kim, 2017); CARDIA, (Duffey et al., 2010)). Evidence table is in **Annex J**.

Four PCs analyse the intake of SSBs as categorial variable using the standard multivariable model and including either TEI (Girona, TLGS, KoGES) or non-SSBs energy (ELEMENT) as covariate, whereas one analysed the exposure as a continuous variable adjusting for non-SSBs energy (CARDIA). All studies adjust for either WC, BMI, body weight at baseline or maternal obesity at 12 months post-partum as a proxy (ELEMENT).

All PCs report a positive relationship (significant in 4 out of 5) between the intake of SSBs at baseline or the cumulative intake of SSBs over 4 years and incidence of abdominal obesity at the end of follow-up **(Appendix K, Figure K.2b)**. Two PCs were in RoB tier 1 (CARDIA, Girona), one in tier 2 (KoGES) and two in tier 3 (ELEMENT, TLGS). Heat map for RoB assessment is in **Appendix L, Table L.3**.

Preliminary UA

The Panel notes that all PCs report positive associations between the intake of SSBs and incidence of obesity and/or abdominal obesity (n = 10). The association was statistically significant in six out of the seven PCs which did not keep TEI constant in the analysis, and in one out of the three PCs which kept TEI constant in the analysis. Five PCs were in RoB tier 1, two in tier 2 and three in tier 3. Critical domains were confounding, exposure assessment and attrition.

The Panel considers that the available BoE from PCs suggests a positive relationship between the consumption of SSBs and risk of obesity, particularly when TEI is not kept constant in the analysis.

Comprehensive UA

Selection of the endpoint. The Panel notes that the overlap between the PCs that investigated incidence of obesity and incidence of abdominal obesity is limited to one study (ELEMENT). The Panel also notes that incidence of (whole body) obesity and abdominal obesity are closely related measures at a population level and show a similar relationship with disease risk. Therefore, the Panel considers that the evidence on both endpoints can be combined and addressed in the comprehensive UA. Pooled mean effect estimates, however, were not calculated because, out of the 10 PCs available, three PCs did not report the number of cases across categories of intake (Girona, TLGS, Generation R), one did not report the exposure as used for data analysis (CARDIA) and one assessed cumulative exposure over 4 years (ELEMENT) (**Appendix K, Figure K.3**).

Dose-response relationship. Linear dose-response relationships across categories of SSBs intake were explored in six PCs. Significant positive linear dose-response relationships were reported in three PCs (ELEMENT, TLGS, GIRONA). In the BWHS cohort the relationship was borderline significant, whereas no evidence for a dose-response relationship was reported in the Generation R and KoGES cohorts. The Panel notes that two out of the three PCs reporting a significant positive linear dose-response were at high RoB (tier 3). Dose-response relationships were not investigated by meta-regression analysis because the data required (e.g. number of cases, exposure) were not available for most PCs.

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. PCs. A total of 21 PCs investigated the relationship between the intake of SSBs and measures of body weight or BMI, five of which also report on measures of WC, whereas one cohort reports only on WC (EPIC-Diogenes). Evidence tables are in **Annex J**.

Ten PCs investigated the relationship between the intake of SSBs at baseline and measures of body weight or BMI, four of which were in adults and six in children and/or adolescents. Of these, eight analysed the exposure as continuous variable using the standard multivariable model (n = 6) or the

nutrient residuals model (n = 1), thus keeping TEI constant. One PC (CoSCIS) did not adjust for TEI **(Appendix K, Figure K.4a)**. The two PCs which analysed the exposure as categorical variable (not included in the forest plot) used the multivariable nutrient density model not including TEI as covariate (MIT-GDS) or the standard multivariable model (Framingham-3Gen), and thus did not keep TEI constant in the analysis.

Seven PCs (DCH, (Olsen et al., 2016); MONICA, (Olsen et al., 2016); AGAHLS, (Stoof et al., 2013); DONALD, (Libuda et al., 2008); HSS-DK, (Zheng et al., 2015); MIT-GDS, (Phillips et al., 2004); GUTS, (Berkey et al., 2004)) report positive associations (statistically significant in DCH and MIT-GDS) between the intake of SSBs and measures of body weight or BMI, whereas three report non-significant negative associations (Inter99, (Olsen et al., 2016); CoSCIS, (Jensen et al., 2013); Framingham-3Gen, (Ma et al., 2016b)). In the PCs which provide models with and without TEI as covariate (n = 7, **Appendix K**, **Figure K.4a**), the introduction of this factor in the model did not substantially change the estimates of the association.

Thirteen PCs investigated the relationship between change in SSBs intake and measures of body weight or BMI **(Appendix K, Figure K.4b)**. Seven were in children and/or adolescents (GUTS, (Berkey et al., 2004); GUTS II, (Field et al., 2014); NGHS, (Striegel-Moore et al., 2006); ALSPAC, (Bigornia et al., 2015); MOVE, (Carlson et al., 2012); DONALD, (Libuda et al., 2008); WAPCS, (Ambrosini et al., 2013)) and six in adults (MTC, (Stern et al., 2017); HPFS, NHS and NHS II (Pan et al., 2013); SUN, (Barrio-Lopez et al., 2013); WHI; (Auerbach et al., 2018)). Eleven PCs analysed change in SSBs intake as a continuous variable. Of these, four used the standard multivariable model (GUTS, NGHS), the nutrient residuals model (WHI) or the multivariable nutrient density model (DONALD) and thus kept TEI constant in the analysis, whereas seven did not adjust for TEI. The two PCs analysing change in SSBs intake as categorical variable used either the standard multivariable model (SUN) or did not adjust for TEI (WAPCS), and thus did not keep TEI constant.

All 13 PCs report positive relationships between changes in intake of SSBs and measures of body weight or BMI, and these were statistically significant in eight studies (WAPCS only in females), seven of which did not keep TEI constant and six of which adjusted for measures of BMI at baseline. Among the five PCs in which the relationship was not significant, three kept TEI constant and one adjusted for measures of BMI at baseline.

A total of nine PCs also addressed the relationship between the intake of ASBs and measures of body weight or BMI. Only in two studies such relationship was positive (GUTS, GUTSII), whereas the remaining seven PCs report either null or negative associations. In six out of these seven PCs, the relationship between intake of SSBs and measures of body weight or BMI was positive and statistically significant (HPFS, NHS, NHSII, HSS-DK, NGHS, MTC).

In the three PCs which investigated the intake of SSBs at baseline in relation to measures of WC (DCH and Inter 99 (Olsen et al., 2016); EPIC-DiOGenes (Romaguera et al., 2011)), the direction of the association was inconsistent **(Appendix K, Figure K.4c)**. TEI was kept constant in all studies and one PC adjusted for BMI. Conversely, the three PCs which assessed changes in SSBs intake (MTC, (Stern et al., 2017); ALSPAC, (Johnson et al., 2007); WAPCS, (Ambrosini et al., 2013)) report significant positive associations (WAPCS only in males) between the exposure and measures of WC **(Appendix K, Figure K.4d)**. None of these kept TEI constant and two adjusted for BMI. Measures of WC were generally consistent with measures of BMI within each study.

Of the 21 PCs considered in this LoE, nine were in RoB tier 1, six in tier 2 and seven in tier 3 for measures of body weight/BMI. The WAPCS was in RoB tier 1 for BMI and in RoB tier 2 for WC. The heat map for the RoB assessment is in **Appendix L**, **Table L.4a**.

The Panel notes that the analytical strategy undertaken to investigate the association between the intake of SSBs and measures of body weight, BMI and WC differs among the PCs available. Most PCs report positive (and significant) associations between the intake of SSBs at baseline or changes in SSBs consumption and the endpoints particularly when TEI was not kept constant in the analysis, and thus allowing for the contribution of SSBs to excess energy intake. In contrast, the relationship is non-significant, null or even negative when TEI is kept constant (i.e. when SSBs are investigated in isocaloric exchange with other dietary sources of energy).

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and measures of body weight, BMI and WC when TEI is not kept constant in the analysis.

LoE3. Complementary: Body fat, abdominal fat. PCs. Only four of the above-mentioned PCs investigated measures of BF in relation to baseline intake of SSBs and the results were mixed. The relationship was negative (non-significant) in CoSCIS, DONALD (males) and AGAHLS (females), positive (non-significant) in females (MIT-GDS and DONALD) and positive and significant in the

AGAHLS cohort for males. Measures of BF were consistent with measures of BMI in the four cohorts (DONALD, CoSCIS and MIT-GDS, RoB tier 2; AGAHLS, RoB tier 3) which measured both endpoints, except for females in the AGAHLS and for males in DONALD (**Appendix K**, **Figure K.4a**). Conversely, the three PCs which assessed changes in SSBs consumption in relation to measures of BF report a positive association, which was statistically significant in two PCs (MOVE, RoB tier 3; ALSPAC, RoB tier 1). Measures of BF were consistent with measures of BMI in the three cohorts (**Appendix K**, **Figure K.4b**). In a separate publication reporting on the ALSPAC cohort (Johnson et al., 2007), there was a negative (non-significant) association between the intake of SSBs at baseline and body fat at end of follow-up.

Abdominal fat was only investigated in one PC (AGAHLS, **Appendix K**, **Figure K.4c**), and only in relation to baseline intake of SSBs, the results of which are mixed (positive and significant relationship for males, negative and non-significant relationship for females).

The Panel notes the limited data available on the association between the consumption of SSBs and measures of BF. The Panel also notes that measures of BF were generally consistent with measures of BMI in the few studies which assessed both endpoints.

Consistency across LoEs. The Panel notes that a large BoE suggests a positive relationship between the intake of SSBs and measures of body weight, BMI and WC when TEI is not kept constant in the analysis. Measures of BF were generally consistent with measures of BMI in the few studies which assessed both endpoints.

Table 15: sQ4.1. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **SSBs** and the risk of obesity at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoints:** incidence of obesity and incidence of abdominal obesity **10 PCs, 32,282 participants.** Pooled mean effect estimates could not be calculated because the minimum dataset needed to calculate RRs per unit of intake was not available for about half of the PCs (**Appendix K**, **Figure K.3**)	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	Three PCs in tier 1; 4 PCs in tier 2, 4 PCs in tier 3 (**Appendix L**, **Tables L.2 and L.3**) Generally moderate Key questions: • Confounding: mixed probably low and probably high • Exposure assessment: most probably high • Outcome assessment: most probably low Most probably high for attrition	Serious
Unexplained inconsistency	All PCs (n = 10) report positive relationships between the intake of SSBs and incidence of obesity and/or abdominal obesity.	Not serious
Indirectness	Direct endpoint	Not serious
Imprecision	Low in most studies	Not serious
Publication bias	Few studies available. RRs per unit of change in the exposure cannot be estimated for about half of the PCs. Risk of publication bias cannot be assessed. Public (n = 7) and mixed (n = 3) funding.	Undetected (cannot be assessed)
Upgrading factors	Consistency: a large BoE suggests a positive relationship between the intake of SSBs not keeping TEI constant in the analysis and measures of body weight, BMI and WC, whereas the relationship was null or negative for ASB in most of the PCs which also assessed this exposure (LoE2). Measures of BF where generally consistent with measures of BMI in the few studies which assessed both endpoints (LoE3).	Yes (consistency across LoEs)
Final certainty	Started moderate, decreased one level for RoB, increased one level for consistency across LoE	**Moderate (> 50–75% probability)**

Conclusion sQ4.1. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of obesity is **moderate** (rationale in **Table 15**). The relationship was observed

not keeping TEI constant in the analysis, and thus allowing for the contribution of SSBs to excess energy intake.

8.2.4.3. Overall conclusion on sQ4.1

There is evidence from RCTs for a positive and causal relationship between the intake of SSBs ad libitum and risk of obesity (**moderate** certainty). The Panel considers that the available BoE from PCs (**moderate** certainty) can be used to upgrade this level of certainty to **high** (> 75–100% probability), considering that the main uncertainty in the BoE from RCTs was indirectness (downgrading factor).

8.2.5. Fruit juices

sQ5.1. FJs and risk of obesity

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**2**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**10**
LoE3. Complementary	Body fat, abdominal fat	0	3

8.2.5.1. Observational studies

LoE1. Standalone (main): Incidence of obesity, incidence of abdominal obesity. PCs. Among the 5 PCs which assessed SSBs in relation to the incidence of abdominal obesity, two (CARDIA, (Duffey et al., 2010); Girona, (Funtikova et al., 2015)) also investigated FJs. No PCs on FJs had incidence of obesity as endpoint. The evidence table is in **Annex J**.

Preliminary UA

Both cohorts report non-significant negative associations between the intake of FJs and incidence of abdominal obesity after adjustment for relevant covariates, including baseline BMI or WC, respectively (**Appendix K, Figure K.2b**). As for SSBs, FJs was analysed as categorial variable using the standard multivariable model to adjust for TEI (Girona) or as continuous variable adjusting for non-FJs energy intake (CARDIA). In both cases, TEI is not kept constant.

The Panel notes that the two studies available are at low RoB (tier 1) and report a non-significant negative relationship between the intake of FJs and incidence of abdominal obesity.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of FJs and risk of obesity. **No comprehensive UA is performed on this LoE**.

LoE2. Standalone (surrogate): Body weight/BMI, waist circumference. **PCs**. Ten PCs investigated the association between the intake of FJs and body weight or BMI-related endpoints. Five cohorts included adults, three of which only females (WHI, (Auerbach et al., 2018); NHS and NHS II, (Pan et al., 2013)), one only males (HPFS, (Pan et al., 2013)) and one males and females combined (EPIC-DiOGenes, (Romaguera et al., 2011)). The remaining PCs were in children and/or adolescents, (GUTS, (Field et al., 2003); NGHS, (Striegel-Moore et al., 2006); MOVE, (Carlson et al., 2012); Project Viva, (Sonneville et al., 2015); DONALD, (Libuda et al., 2008)). All were US cohorts, except two (DONALD, Germany; EPIC-Diogenes, five European countries). Evidence tables are in **Annex J**.

Preliminary UA

Eight PCs (all except Project Viva and EPIC-DiOGenes) investigated changes in the exposure vs. concurrent changes in the endpoints as continuous variables. Of these, three adjusted for TEI using the standard multivariable model (GUTS, NGHS) or the nutrient residuals model (WHI), and thus kept TEI constant, whereas five did not adjust for TEI (HPFS, NHS, NHS II, MOVE) or adjusted for energy intake from other sources using an energy partition model (DONALD), not keeping TEI constant. Only the five PCs in adults and two PCs in children (GUTS, DONALD) adjusted for baseline BMI-related endpoints.

The four PCs in adults report statistically significant positive associations between changes in the intake of FJs and changes in body weight (HPFS, NHS, NHS II, WHI; RoB tier 1) **(Appendix K, Figure K.5)**. In two PCs in children, the association between changes in FJs intake and changes in BMI z-scores (MOVE) or BMI (NGHS) was not statistically significant (negative in MOVE and positive in NGHS; RoB tier 2). The Panel notes that these PCs did not adjust for baseline measures of BMI. In the

remaining two PCs in children, the association was positive and statistically significant for females (GUTS, RoB tier 2; DONALD, RoB tier 1). For males, the association was positive in GUTS and negative in DONALD (both non-significant). In GUTS and WHI, which introduced TEI stepwise in the multivariable models, adjustment for TEI did not substantially change the estimates of the association.

Three PCs (Project viva, DONALD, EPIC-DiOGenes) assessed FJs at baseline in relation to BMI z-scores or WC regressed to BMI. In the Project viva (RoB tier 3), which analysed categories of exposure using the standard multivariable model vs. BMI z-scores at the end of follow-up, the relationship was positive and statistically significant in the least adjusted model and after adjustment for BMI z-scores at baseline, but became non-significant when TEI was included in the model as covariate. Non-significant (negative in females, positive in males) associations were reported in DONALD (RoB tier 1) between baseline intake of FJs and change in BMI z-scores over follow-up. Similarly, a non-significant negative association was reported between the intake of FJs at baseline and annual changes in WC regressed to BMI in the EPIC-DiOGenes (RoB tier 3). These three PCs were at probably high RoB for confounding owing to the lack of adjustment for diet quality and physical activity.

The heat map for the RoB assessment can be found in **Appendix L**, **Table L.5**.

The Panel notes that seven out the eight PCs reported positive associations between changes in the intake of FJ and concurrent changes in body weight or BMI z-scores. The relationship was statistically significant in the four studies conducted in adults (3 cohorts in females, one cohort in males) and in two of the four studies conducted in children in females only. Conversely, non-significant positive and negative associations were reported in three PCs which addressed intakes of FJs at baseline and changes in BMI z-scores or WC regressed to BMI.

The Panel considers that the available BoE suggests a positive relationship between the intake of FJs and risk of obesity.

Comprehensive UA

Selection of the exposure and selection of the endpoint. The Panel decided to conduct the comprehensive UA on changes in FJs intake vs. concurrent changes in body weight (adults) and BMI z-scores (children) because of the higher number of studies available (vs FJs intake at baseline, vs. measures of WC) and owing to the consistency of the results across studies.

The Panel notes that the PCs investigated different exposure–endpoint relationships which were very heterogeneous both in terms of unit of change in exposure and definition of the endpoint. This precludes the calculation of pooled mean effect estimates across studies **(Appendix K**, **Figure K.5)**.

Dose-response relationship. Dose-response relationships across categories of intake were not investigated in any study. Dose-response relationships were not investigated by meta-regression analyses owing to the heterogeneity of the exposure–endpoints investigated.

LoE3. Complementary: Body fat, abdominal fat. **PCs**. Three PCs (all in children) investigated the association between the intake of FJs and BF. Two analysed intakes of FJs at baseline vs. body fat (kg) at the end of follow-up (ALSPAC, (Johnson et al., 2007); RoB tier 1) or vs. change in body fat (%) over follow-up (DONALD, (Libuda et al., 2008)) and two analysed changes in FJs intake vs. changes in body fat (%) over follow-up (DONALD, RoB tier 2; MOVE, (Carlson et al., 2012), RoB tier 3). All studies report negative (non-significant) relationships between the intake of FJs and the endpoints except the DONALD cohort for females only, where the relationship between changes in FJs intake and change in % body fat was positive (non-significant).

The Panel notes the limited data available on the relationship between the consumption of FJs and measures of BF. The Panel also notes that measures of body fat where generally consistent with measures of BMI in the only two studies which assessed both endpoints.

Consistency across LoEs. The Panel notes that changes in measures of body weight and BMI were consistent with measures of body fat (**LoE3**) but inconsistent with incidence of abdominal obesity in the few PCs which assessed these endpoints (**LoE1**).

Table 16: sQ5.1. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **FJs** and the risk of obesity at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoints: changes in body weight and BMI z-scores** **8 PCs, 191,881 participants.** Pooled mean effect estimates across studies cannot be calculated because of the heterogeneity of the exposure–endpoint relationships investigated **(Appendix K, Figure K.5)**. Most PCs found positive relationships between the intake of FJs and changes in the endpoints except for two children cohorts (MOVE, both sexes combined; DONALD, males only).	**Initial certainty: Low (> 15–50% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	Five PCs in tier 1; 3 PCs in tier 2 (**Appendix L, Table L.5**) Between low and moderate Key questions: • Confounding: mixed probably low and probably high • Exposure assessment: probably low • Outcome assessment: probably low Confounding was a critical domain in studies conducted in children, mostly because the lack of control for physical activity and the quality of the diet	Serious
Unexplained inconsistency	Inconsistency in the results of the two PCs in children (MOVE, DONALD) could be explained by differences in age, the type of analysis performed (e.g. by sex), sample size or by a combination of these factors.	Not serious
Indirectness	Surrogate endpoint	Serious
Imprecision	Low in most studies	Not serious
Publication bias	Few studies available, also heterogeneous. It cannot be assessed. Public (n = 6), mixed (n = 1) and unclear (n = 1) funding	Undetected (cannot be assessed)
Upgrading factors	None identified	None
Final certainty	Started low, downgraded for indirectness (one level). RoB was not considered sufficiently serious to downgrade because it was between low and moderate, and probably low for 2 out of the 3 key questions.	**Very low (0–15% probability)**

Conclusion sQ5.1. PCs. The level of certainty in a positive and causal relationship between the intake of FJs and risk of obesity is **very low** (rationale in **Table 16**).

8.2.5.2. Overall conclusion on sQ5.1

There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of obesity (**very low** level of certainty).

8.3. Risk of NAFLD/NASH

Standalone LoEs for the risk of NAFLD/NASH include studies reporting on the incidence of NAFLD/NASH (main LoE) and studies reporting changes in liver fat (surrogate LoE). The Panel decided to consider changes in skeletal muscle fat and visceral adipose tissue (VAT) in a complementary LoE because these two variables are reported in studies which investigate the effect of sugars on liver fat.

Ectopic fat deposition was an eligible endpoint in RCTs conducted ad libitum and in studies conducted in isocaloric conditions lasting at least 2 weeks if assessed by computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) or in biopsies.

For plotting, standardised mean differences were calculated for liver fat and VAT, owing to the different units of measurement in which these endpoints were reported in the RCTs and the lack of conversion factors. Data on skeletal muscle fat are not plotted due to lack of comparability across studies (i.e. biopsies were obtained from different muscles depending on the study).

8.3.1. Total sugars

sQ1.2. Total sugars and risk of NAFLD/NASH			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	**1**
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Changes in skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity	sQ1.1	sQ1.1

8.3.1.1. Observational studies

LoE1. Standalone (main): Incidence of NAFLD/NASH. PCs. One PC investigated the relationship between the intake of total sugars and incidence of NAFLD/NASH. Evidence table is in **Annex J**.

Preliminary UA

In the ALSPAC cohort (Anderson et al., 2015), energy-adjusted total sugars intake (nutrient residuals model) at 3, 7 and 10 years of age was positively but not significantly associated with the risk of NAFLD at 17–18 years of age or with liver stiffness as a surrogate marker for NASH, either in the crude model or after adjustment for relevant confounders. Results were similar in sensitivity analyses restricting the sample to plausible reporters of dietary intake or to participants with a complete data set for all variables. The only dietary variable consistently and significantly positively correlated with these endpoints was total energy intake, and the association appeared to be mediated by total body fat at the time of the endpoint assessment. The study was at low RoB (tier 1) for both endpoints.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of NAFLD/NASH. **No comprehensive UA is performed**.

8.3.1.2. Overall conclusion on sQ1.2

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of NAFLD/NASH. Total sugars were not investigated under other dietary conditions (e.g. not keeping TEI constant in the analysis).

8.3.2. Added and free sugars

sQ2.2. Added and free sugars and risk of NAFLD/NASH			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**4**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/3	0
LoE4. Complementary	Risk of obesity	sQ2.1	sQ2.1

8.3.2.1. Intervention studies

The effect of high vs. low added sugar intakes on liver fat was assessed in four intervention studies (5 study groups), three of which (4 study groups) also investigated VAT and two of which also report on skeletal muscle fat (Maersk et al., 2012; Lowndes et al., 2014b) **(Appendix F)**.

LoE2. Standalone (surrogate): Liver fat. RCTs

Preliminary UA

Liver fat accrual was higher in the high sugar arm relative to the low sugar arm in all the studies which investigated this endpoint, three of which recruited exclusively overweight/obese individuals **(Appendix G, Figure G.2a)**. Between-arm differences in added and free sugar intakes ranged from

18 to 22 E%, and study duration between 10 and 24 weeks. Three studies used beverages and one foods and beverages. The increase in liver fat was similar among overweight subjects with and without NAFLD (Umpleby et al., 2017). The pooled standardised mean effect estimate (95%CI) was 0.66 (0.45, 0.86). The mean difference in body weight change between the high and the low sugar arms ranged from 0.85 to 2.3 kg regardless of whether the study aimed at neutral energy balance (i.e. and thus investigated added or free sugars in isocaloric exchange with other macronutrients, n = 2) or was conducted ad libitum (n = 2). In one study (Maersk et al., 2012) changes in liver fat were already adjusted for changes in body weight, suggesting an effect of added and free sugars on liver fat beyond any effect on body weight. Studies were at low to moderate RoB (1 in tier 1; 3 in tier 2).

The Panel considers that the available BoE from RCTs suggests a positive relationship between the intake of added and free sugars ad libitum and in isocaloric exchange with other macronutrients and risk of NALFLD/NASH.

Comprehensive UA

Selection of the endpoint. The only endpoint in this standalone LoEs is liver fat.

Dose-response relationship. No dose-response relationship between the intake of added sugars and liver fat was reported in one study which tested three sugar doses (8, 18 and 30E%) (Lowndes et al., 2014b). Dose-response was not investigated by meta-regression analysis owing to the low number of studies available. Visual inspection of the forest plot **(Appendix G, Figure G.2a)** does not suggest a dose-response relationship. The sugars dose range investigated (between-arm difference) is narrow (18–22E%).

LoE3. Complementary: Skeletal muscle fat and visceral adipose tissue. RCTs. Changes in Skm followed the same trend as liver fat in the two studies which assessed this variable (Maersk et al., 2012; Lowndes et al., 2014b). Changes in VAT followed the same trend as liver fat in overweight subjects without NAFLD, but no differences in VAT were observed between the high and the low sugar arms in subjects with NAFLD (Umpleby et al., 2017) **(Appendix G, Figure G.2b)**.

LoE4 (sQ2.1). **Complementary: risk of obesity. RCTs**. There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and an increased risk of obesity (**moderate** level of certainty).

Consistency across LoEs. The Panel notes that changes in skeletal muscle fat and VAT were consistent with changes in LF except for changes in VAT in subjects with NAFLD, but few RCTs investigated these endpoints. Consistent with an increased risk of obesity.

Table 17: sQ2.2. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty that the intake of **added and free sugars** is positively and causally associated with the risk of NAFLD/NASH at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint: liver fat** **4 RCTs, 87 participants**. Pooled standardised mean effect estimate (95% CI) = 0.66 (0.45, 0.86) assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be < 0.82. **(Appendix G, Figure G.2a)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	1 study in tier 1; 3 studies tier 2 (**Appendix I, Figure I.2**) Generally moderate. Key questions: • Randomisation: low • Exposure assessment: generally low • Outcome assessment: generally low Probably high for allocation concealment, blinding and attrition	Serious
Unexplained inconsistency	Substantial statistical heterogeneity (I^2 = 67% for the pooled standardised mean effect). However, the number of studies is small, mean effect estimates are similar across studies and 95% CI largely overlap	Not serious

Indirectness	Surrogate endpoint for risk of NAFLD. Indirectness is bigger for risk of NASH.	Serious
Imprecision	Low. It could be higher because the expected correlation coefficient for this endpoint is < 0.82, but still low **(Appendix G, Figure G.2a)**.	Not serious
Publication bias	The few (n = 4) studies available are small (n = 7–13 subjects per arm) possibly due to the nature of the endpoint measured and all show significant effects, as illustrated in the funnel plot **(Appendix H, Figure H.2)**. It is unclear whether this is due to publication bias. Public (n = 1), private (n = 1) and mixed (n = 2) funding.	Undetected (it cannot be assessed)
Upgrading factors	None identified	None
Final certainty	Started high, downgraded one level for risk of bias and one level for indirectness	**Low (> 15–50% probability)**

Conclusion sQ2.2. RCTs. The level of certainty in a positive and causal relationship between the intake of added and free sugars and risk of NAFLD/NASH is **low** (rationale in **Table 17**). RCTs were in adults, mostly overweight/obese. Between-arm differences in added and free sugars were between 18 and 22E%, consumed *ad libitum* or in isocaloric exchange with other macronutrients.

8.3.2.2. Observational studies

There are no eligible PCs for standalone LoEs in relation to this sQ and there is no supportive evidence from complementary LoEs (sQ2.1, Section 8.3.1.2).

8.3.2.3. Overall conclusion on sQ.2.2

There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars *ad libitum* or in isocaloric exchange with other macronutrients and risk of NAFLD/NASH (**low** level of certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

8.3.3. Fructose

sQ3.2. Fructose and risk of NAFLD/NASH

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/2	0
LoE4. Complementary	Risk of obesity	sQ3.1	sQ3.1

8.3.3.1. Intervention studies

LoE2. Standalone (surrogate): Liver fat. RCTs. Three RCTs (4 study groups) assessed the effects of fructose vs. glucose provided as beverages at doses from 22 to 25 E% on liver fat. The interventions lasted between 2 and 4 weeks (**Appendix F**).

Preliminary UA

The three studies showed lower liver fat accrual with fructose vs. glucose when fructose and glucose were consumed either ad libitum (Jin et al., 2014) or in positive energy balance (Silbernagel et al., 2011; Johnston et al., 2013). The opposite was observed in the study by (Johnston et al., 2013) under neutral energy balance. The effect was not statistically significant in any of the studies, which were at low to moderate RoB (2 in tier 1; 1 in tier 2) **(Appendix G, Figure G.3a)**. The pooled mean effect (standardised effect estimate) is −0.4 (95% CI = −0.20, 0.12). The Panel notes that the BoE is limited to three RCTs conducted under three different dietary conditions.

The Panel considers that the available BoE from RCTs does not suggest a positive relationship between fructose in isocaloric exchange with glucose and risk of NAFLD/NASH. **No comprehensive UA is performed**.

LoE3. Complementary: Skeletal muscle fat and visceral adipose tissue. RCTs. Similar results to liver fat were obtained for skeletal muscle fat (Silbernagel et al., 2011; Johnston et al., 2013). In relation

to VAT (2 studies), one (Stanhope et al., 2009) showed an increase in VAT with fructose relative to glucose in men only (sensitivity analysis by sex, **Appendix F**), whereas the second (Silbernagel et al., 2011) showed no difference between these two sugars **(Appendix G, Figure G.3b)**.

In the study by Johnston et al. (2013), conducted in males with abdominal obesity, both glucose and fructose (providing 25E% as beverages) increased liver fat and skeletal muscle fat when subjects were on positive energy balance, but not when these sugars were consumed under neutral energy balance. In the study by Silbernagel et al. (2011), no changes in liver fat or skeletal muscle fat were observed with either fructose or glucose on positive energy balance. The Panel notes that the BoE is limited to two RCTs, which show conflicting results.

The Panel considers that the available BoE from RCTs does not suggest a positive relationship between fructose in isocaloric exchange with glucose and ectopic fat deposition.

LoE 4 (sQ3.1). Complementary: Risk of obesity. RCTs. The available BoE from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity.

Conclusion sQ3.2. RCTs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of NAFLD/NASH.

8.3.3.2. Observational studies

There are no eligible PCs for standalone LoEs in relation to this sQ3.2. and there is no supportive evidence from complementary LoEs (sQ3.1, Section 8.3.3.2).

8.3.3.3. Overall conclusion on sQ3.2

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fructose in isocaloric exchange with glucose or other macronutrients and risk of NAFLD/NASH.

8.3.4. Sugar-sweetened beverages

sQ4.2. SSBs and risk of NAFLD/NASH

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat/visceral adipose tissue	2/2	0/1
LoE4. Complementary	Risk of obesity	sQ4.1	sQ4.1

8.3.4.1. Intervention studies

LoE2. Standalone (surrogate): Liver fat. **RCTs**. Three out of the four RCTs which investigated the effect of high vs. low sugars intake on liver fat (Section 8.3.2.1) were conducted with beverages **(Appendix G, Figure G.2a)**. The between-arm target difference in sugars intake from beverages was between 18 and 22E% and study duration between 10 and 24 weeks.

Preliminary UA

Liver fat was significantly higher in the high vs. the low sugar arms in the three RCTs. One study was at low RoB (tier 1) and two at moderate RoB (tier 2). The pooled standardised mean effect estimate (95% CI) for these studies was 0.65 (0.31, 0.99, I^2 = 85%).

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and risk of NAFLD/NASH.

Comprehensive UA

Selection of the endpoint. The only endpoint in this standalone LoE is liver fat.

Dose-response relationship. No dose-response relationship between the intake of sugars in beverages and liver fat was reported in one study using sucrose and HFCS in beverages at doses of 8, 18 and 30E% (Lowndes et al., 2014b). Dose-response was not investigated by meta-regression analysis owing to the low number of studies available. Visual inspection of the forest plot

(Appendix G, Figure G.2a) does not suggest a dose-response relationship, but the number of studies is small and the dose range investigated is narrow (18–22E%).

LoE3. Complementary: Skeletal muscle fat/visceral adipose tissue. RCTs. The two RCTs which investigated the effect of high vs. low sugars intake on skeletal muscle and two out of the three which reported on VAT (Section 8.3.2.1) were conducted with beverages **(Appendix G, Figure G.2b)**. In these studies, skeletal muscle fat and VAT were significantly higher in the high vs. the low sugar arm.

LoE4 (sQ4.1). **Complementary: Risk of obesity. RCTs**. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate** certainty).

Consistency across LoE. The Panel notes that changes in skeletal muscle fat and VAT were consistent with changes in LF except for changes in VAT in subjects with NAFLD, but few RCTs investigated these endpoints. Consistent with an increased risk of obesity.

Table 18: sQ4.2. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty that the intake of **SSBs** is positively and causally associated with the risk of NAFLD/NASH at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint: liver fat** **3 RCTs, 70 participants**. Pooled standardised mean effect estimate (95% CI) = 0.65 (0.31, 0.99) assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be < 0.82 **(Appendix G, Figure G.2a)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	1 study in tier 1; 2 studies tier 2 (**Appendix I, Figure I.2**) Generally moderate. Key questions: • Randomisation: low • Exposure assessment: low • Outcome assessment: generally low Probably high for allocation concealment, blinding and attrition	Serious
Unexplained inconsistency	Substantial statistical heterogeneity (I^2 = 83% for the pooled standardised mean effect). However, the number of studies is small, mean effect estimates are similar across studies and 95% CI largely overlap.	Not serious
Indirectness	Surrogate endpoint for risk of NAFLD. Indirectness is bigger for risk of NASH	Serious
Imprecision	Low. It could be higher because the expected correlation coefficient for this endpoint is < 0.82, but still low.	Not serious
Publication bias	The few (n = 3) studies available are small (n = 7–13 subjects per arm) possibly due to the nature of the endpoint measured and all show significant effects, as illustrated in the funnel plot **(Appendix H, Figure H.2)**. It is unclear whether this is due to publication bias. Private (n = 1) and mixed (n = 2) funding.	Undetected (cannot be assessed)
Upgrading factors	None identified	None
Final certainty	Started high, downgraded one level for RoB and one level for indirectness	**Low (> 15–50% probability)**

Conclusion sQ4.2. RCTs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of NAFLD/NASH is **low** (rationale in **Table 18**). Most RCTs were conducted in overweight/obese subjects. Beverages were consumed ad libitum or under neutral energy balance and between arm differences in sugars from beverages were between 18 and 20E%.

8.3.4.2. Observational studies

No PCs were eligible for standalone LoEs in relation to sQ4.2.

LoE3. Complementary: Skeletal muscle fat/visceral adipose tissue. PCs. One PC (Framingham-3Gen, (Ma et al., 2016b)) investigated the relationship between the intake of SSBs at baseline and changes in VAT and VAT:SAAT ratio over the 6-year follow-up in adult males and females.

SSBs were analysed as categorical variable using the standard multivariable model for energy adjustment, thus not keeping TEI constant. The evidence table is in **Annex J**.

A significant positive linear dose-response relationship between the intake of SSBs and changes in VAT and the VAT:SAAT ratio was reported after adjusting for confounders, including changes in body weight, whereas no relationship was found with the intake of ASBs. The study was a low RoB (tier 1), the critical domain being the exposure assessment.

Although this study suggests a positive relationship between the consumption of SSBs not keeping TEI constant and ectopic fat deposition in VAT, the Panel notes that only one PC is available on this endpoint.

LoE4 (sQ4.1). **Complementary: Risk of obesity. PCs**. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate** certainty).

Conclusion sQ4.2. PCs. Although there is some evidence from PCs in complementary LoE that SSBs could increase the risk of obesity (**moderate** certainty, **LoE4 (sQ4.1)**) and ectopic fat deposition in VAT (**LoE3**), no PCs were eligible for standalone LoEs in relation to this sQ. Thus, the Panel considers that the available BoE does not suggest a positive relationship between the consumption of SSBs and risk of NAFLD/NASH.

8.3.4.3. Overall conclusion on sQ4.2

There is evidence from RCTs for a positive and causal relationship between the intake of SSBs ad libitum or under neutral energy balance and risk of NAFLD/NASH (**low** level of certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

8.3.5. Fruit juices

sQ5.2. FJs and risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1

8.3.5.1. Observational studies

No PCs were eligible for standalone LoEs in relation to sQ5.2.

LoE4 (sQ5.1). Complementary: Risk of obesity. PCs. There is evidence for a positive relationship between the intake of FJs and risk of obesity (**very low** certainty).

Conclusion sQ5.2. **PCs**. The Panel considers that the available BoE does not suggest a positive relationship between the intake of FJs and risk of NAFLD/NASH.

8.3.5.2. Overall conclusion on sQ5.2

Since no studies were available for standalone LoEs in relation to this sQ, the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of FJs and risk of NAFLD/NASH.

8.4. Risk of type 2 diabetes mellitus

8.4.1. Total sugars

sQ1.3. Total sugars and risk of type 2 diabetes mellitus (T2DM)			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence of T2DM	0	4*
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	1
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity	sQ1.1	sQ1.1

*: Of which one was a PCC.

8.4.1.1. Observational studies

LoE1. Standalone (main): Incidence of T2DM. PCs. Three PCs (FMCHES, (Montonen et al., 2007); WHS, (Janket et al., 2003); WHI, (Tasevska et al., 2018)) and one PCC (EPIC-Interact, (Sluijs et al., 2013)) investigated the relationship between total sugars and incidence of T2DM. The evidence table is in **Annex J**. Three studies analysed total sugars as categorical variable (EPIC-Interact, FMCHES, WHS) and one as continuous variable (WHI). Mean/median intakes of total sugars were 24.8 E% in the WHI and ranged between 65 g/day and 134–137 g/day in the EPIC-Interact and WHS, and between 92 and 171 g/day in the FMCHES (all energy-adjusted values) across categories of intake.

The multivariable nutrient density model (WHI) or the nutrient residuals model with (EPIC-Interact, FMCHES) or without (WHS) further adjustment for TEI were used to investigate total sugars while keeping TEI constant. In the WHI, energy partition models were also built to assess the full effect of total sugars intake on T2DM risk (i.e. the energy and non-energy contribution of the nutrient while keeping energy intake from other nutrients constant).

Preliminary UA

Three studies (EPIC-Interact, WHI, WHS) report significant negative associations between total sugars intake and incidence of T2DM in energy substitution models **(Appendix K, Figure K.6)**. The associations were attenuated in all cohorts after adjustments for relevant covariates, including baseline BMI and/or TEI, and remained statistically significant in the WHI only. Similar results were obtained using energy partition models in the WHI cohort (results not plotted). In contrast, the FMCHES reports a non-significant positive association between the intake of total sugars and incidence of T2DM, with a relative risk of 1.42 (95% CI = 0.90, 2.24) for the highest vs. the lowest quartile of energy-adjusted total sugars intake. The relationship was observed at higher levels of total sugars intake as compared to the other PCs.

Similar results were found in the four studies described above when cases of T2DM diagnosed in the first 2–4 years of follow-up and/or cases of hypertension, dyslipidaemia and/or CVD at baseline were excluded in sensitivity analyses to address reverse causality.

Two studies were at low RoB (tier 1; FMCHES, WHS) and two were at moderate RoB (tier 2; EPIC-Interact, WHI), critical domains being outcome assessment (n = 3), attrition (n = 2) and confounding (n = 1). The heat map for the RoB assessment is in **Appendix L, Table L.6**.

The Panel notes that three out the four studies available report a negative relationship between the intake of total sugars in isocaloric exchange with other macronutrients and incidence of T2DM. In one study, negative relationships were also reported when the full effect (the energy and non-energy components) of total sugars was assessed (energy partition models).

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of total sugars and incidence of T2DM. **No comprehensive UA is performed on this LoE**.

LoE2. Standalone (surrogate): Measures of glucose tolerance. PCs. Only one PC investigated the relationship between the intake of total sugars and measures of glucose tolerance (Feskens et al., 1995). The evidence table is in **Annex J**.

Preliminary UA

In a 20-year follow-up of a random sample from the Seven Countries cohort (Feskens et al., 1995) including 338 males from the Netherlands and Finland, a non-significant negative relationship was reported between the intake of total sugars at baseline and blood glucose concentrations at 2 h during an OGTT at the end of follow-up. A non-significant positive association was observed when change in total sugar intake over follow-up was used as the exposure variable. The multivariable nutrient density model was used to adjust for TEI. The study was at moderate RoB (tier 2), critical domains being confounding and attrition.

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and adverse effects on measures of glucose tolerance. **No comprehensive UA is performed**.

LoE5 (sQ1.1). Complementary: Risk of obesity. PCs. The available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity.

8.4.1.2. Overall conclusion on sQ1.3

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars (as net intake or in isocaloric exchange with other macronutrients) and risk of T2DM.

8.4.2. Added and free sugars

sQ2.3. Added and free sugars and risk of Type 2 diabetes mellitus

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of T2DM	0	**4***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**17**	**2**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	5	2
LoE4. Complementary	Measures of insulin sensitivity	7	0
LoE5. Complementary	Risk of obesity	sQ2.1	sQ2.1

*: Of which one was a PCC.

8.4.2.1. Intervention studies

LoE2. Standalone (surrogate): Measures of glucose tolerance. RCTs. Ten RCTs assessed the effect of high vs. low intakes of added sugars on blood glucose at 120′ during an OGTT, eight of which were conducted in isocaloric exchange with starch under neutral energy balance and two were ad libitum **(Appendix G, Figure G.4a)**. The same studies except Huttunen et al. (1976) also measured insulin at 120′ **(Appendix G, Figure G.4b)**. Between-arm differences in added sugar intakes ranged from 10 to 54 E%, and study duration between 1 and 56 weeks. Six RCTs were in healthy subjects, two were in overweight/obese individuals and two included individuals with hyperinsulinaemia **(Appendix F)**.

Seventeen studies (19 groups) assessed the effect of high vs. low added and free sugars intake (8–43E%) on fasting glucose, of which nine were conducted in isocaloric exchange with starch under neutral energy balance and eight were ad libitum **(Appendix G, Figure G.4c)**. Most of these also measured fasting insulin **(Appendix G, Figure G.4d)**. Study duration ranged from 4 to 36 weeks. Eight RCTs were in overweight/obese individuals and two RCTs included subjects with hyperinsulinaemia.

Preliminary UA

Results for blood glucose and insulin at 120′ during an OGTT were mixed and apparently unrelated to the difference in added sugars intake between the study arms **(Appendix G, Figures G.4a and G.4b)**. An additional study (Lewis et al., 2013) not included in the forest plots (values for glucose and insulin at 120′ not shown in the publication) reported no significant differences in the iAUC for glucose ad insulin during the OGTT between the high and the low sugar arms (18 E% difference). The only two studies showing a significant effect of added sugars on glucose at 120′ were restricted to subjects with hyperinsulinaemia (Israel et al., 1983) or included a group of subjects with hyperinsulinaemia (Hallfrisch et al., 1983a). The only RCTs showing a significant effect of added sugars on insulin at 120′ was restricted to overweight/obese individuals. These RCTs used either fructose (Hallfrisch et al., 1983a) or sucrose (Israel et al., 1983; Lewis et al., 2013) in isocaloric exchange with starch. In the study by Israel et al. (1983), conducted in men and women with hyperinsulinaemia, glucose and insulin responses during the OGTT significantly increased with increasing doses of sucrose (2E%, 15E % and 30E% in isocaloric exchange with starch) in a dose-response manner (Appendix F). The Panel notes that these individuals were at high risk for developing T2DM. Five RCTs were in RoB tier 1 and five in tier 2. Critical domains were randomisation, allocation concealment and blinding. The Panel notes that these individuals were at high risk for developing T2DM. Five RCTs were in RoB tier 1 and five in tier 2. Critical domains were randomisation, allocation concealment and blinding.

Fasting glucose was higher in the high sugar arm relative to the low sugar arm in 11 of the 17 studies, whereas the effect of the intervention was null in three studies and negative in the remaining three studies **(Appendix G, Figure G.4c)**. The mean pooled effect (95% CI) is 1.94 mg/dL (0.23, 3.66; I^2 = 87%). The mean pooled effect (95% CI) for studies in isocaloric exchange with other macronutrients (starch in most studies) at neutral energy balance is 3.01 mg/dL (0.41, 5.60; I^2 = 89%), and for studies conducted ad libitum is 0.48 mg/dL (−1.48, 2.44; I^2 = 79%).

Similar results were obtained for fasting insulin **(Appendix G, Figure G.4d)**. The mean pooled effect (95% CI) is 16.21 ρmol/L (3.91, 28.50; I^2 = 93%). The mean pooled effect (95% CI) for studies in isocaloric exchange with starch at neutral energy balance is 19.99 ρmol/L (0.67, 39.31; I^2 = 93%), and 7.58 ρmol/L (1.04, 14.12; I^2 = 34%) for studies ad libitum.

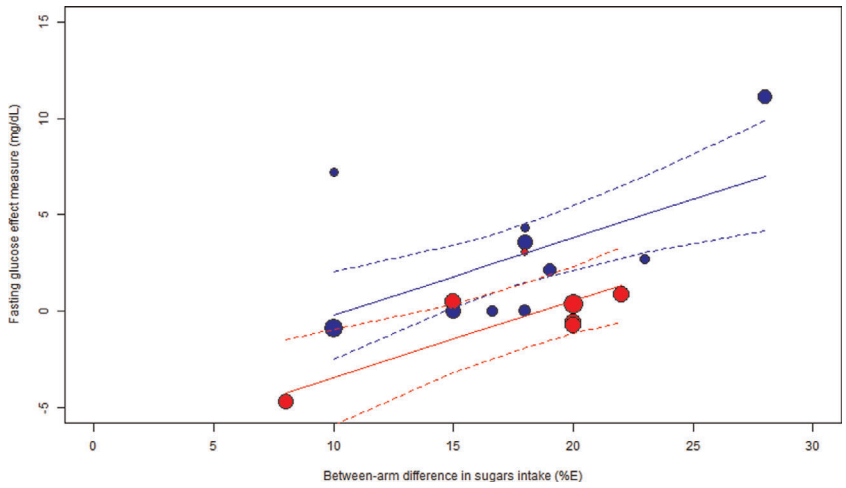
The Panel considers that the available BoE suggest a positive relationship between the intake of added and free sugars and risk of T2DM.

Comprehensive UA

Selection of the endpoint. Within this LoE2, which includes two surrogate endpoints for the risk of T2DM (fasting glucose and glucose at 120' during an OGTT), the Panel decided to perform a comprehensive UA on fasting blood glucose owing to: (a) the higher number of studies available, particularly in ad libitum conditions; (b) the consistency of the results across studies; and c) to the higher reliability of the measurement, as the type of sugar used in the OGTT challenge (sucrose vs. glucose) and the amount of sugar given (fixed vs. relative amounts depending on body weight) varied across studies **(see Appendix F)**.

Dose-response relationship. A linear dose-response relationship was observed between the intake of sucrose at doses 2, 15 and 30 E% in isocaloric exchange with starch and fasting glucose and insulin levels in the RCT by Israel et al. (1983) conducted in men and women with hyperinsulinaemia.

A meta-regression linear dose-response analysis was performed to investigate the association between the difference in sugars intake between arms (dose range 6–43%) and the corresponding difference in fasting glucose. A total of 19 observations from 18 RCTs were eligible for the analysis. Potential effect-modifiers were identified using a graphical display of the stratified dose-response curves. These include main characteristics of the exposure (i.e. sugars source and type, dietary conditions) and methodological aspects related to study design and duration, run-in and RoB. The only adjusting factor retained in the final model was RoB, owing to the best fit performance (AIC = 75) and the statistical significance of the parameters. Residual heterogeneity remains high (Cochran Q-test = 43.26) and statistically significant ($p < 0.0001$) for the best fitting model, suggesting that other factors not identified in the BoE, or for which it was not possible to adjust due to the low number of studies, might play a role in explaining differences across studies. Several diagnostics, the Hat indicator, the Cook distance and the influence analysis (One-At-a-Time leave out analysis), identified one study (Moser et al., 1986), conducted on the subgroup of young women taking contraceptives, as highly influential because of the high sugars dose and the particularly small size of the effect. Since the results of the study-subgroup were counter-conservative (i.e. very low responses at high doses), and their impact was to flatten the dose-response, it was decided to exclude the observation from the dose-response analysis. Despite not being influential and showing a pattern fitting well the model, also the other sub-group (women not taking contraceptives) from the same study was dropped from the analysis because randomisation was performed for the two sub-groups combined. Therefore, the final dose-response model was set up on 17 observations from 17 RCTs (**Figure 12**). The difference in sugars intake between arms in the final model was between 6 and 30 E%. The model indicates an expected increase of around 4 mg/dL (95% CI: 1.7–6.3, $p < 0.01$) of blood fasting glucose levels per each increase of 10E% intake from sugar. Adjusting for RoB leads to higher absolute fasting glucose mean expected levels for the same dose of sugars intake when considering RCTs at low RoB (tier 1; intercept = −4.2mg/dL, 95% CI = −8.4, 0.03) as compared to RCTs at moderate RoB (tier 2; intercept = −7.4, 95% CI = −13.91, −0.95). Between-arm differences in sugars intake (E%) and RoB only accounted for 25.6% of the variability across studies, thus leaving most of the heterogeneity unexplained. In this context, the Panel considers that this analysis can be used to conclude on the direction of the linear dose-response relationship, but not to make a quantitative prediction of the effect of added or free sugars on fasting glucose levels. A meta-regressive non-linear dose-response relationship was also investigated using a cubic spline function with three knots. Non-linearity was supported by the model. The shape of the non-linear dose-response was monotonically positive. However, the AIC showed a slightly better fit for the linear model, which was retained.



Blue = RoB Tier 1; Red = RoB Tier 2.

Figure 12: Meta-regressive dose-response linear model between the intake of added and free sugars (E%) and fasting glucose

A series of linear and non-linear dose-response models were explored for assessing the relationship between the difference in sugars intake between arms and the corresponding difference in fasting insulin changes during the intervention. All the models were highly sensitive to one study and to other methodological choices (i.e. hypothesised level of the correlation between observations at beginning and end of the intervention). Therefore, none of them was considered sufficiently robust to be used for drawing conclusions on the shape and strength of the dose-response relationship.

The full report of the dose-response analyses can be found in **Annex L**.

LoE3. Complementary: Indices of insulin sensitivity/beta-cell function. RCTs. Among the above-mentioned studies reporting on fasting glucose and insulin and/or glucose and insulin during an OGTT, five (Raben et al., 2002; Maersk et al., 2012; Campos et al., 2015; Lowndes et al., 2015; Umpleby et al., 2017) also report on indices of insulin sensitivity/insulin resistance (HOMA-IR, n = 5; ISI indices during an OGTT, n = 2) and/or indices of beta-cell function (HOMA-β, n = 1) **(Appendix F)**.

No significant differences were observed in any of these indices between the high and the low sugar arms in any study. The Panel notes that changes in glucose and insulin (fasting conditions or during an OGTT) were also not significantly different between the high and low sugar arms in these studies. Three studies were in RoB tier 1 and two were in tier 2. Critical domains were allocation concealment and blinding.

LoE4. Complementary: Measures of insulin sensitivity. RCTs. A total of seven RCTs investigated the effect of high vs. low added sugars intake on measures of insulin sensitivity **(Appendix F)**. In five studies, an euglycaemic hyperinsulinaemic clamp was performed to assess insulin sensitivity in steady-state conditions (Black et al., 2006; Le et al., 2009; Aeberli et al., 2013; Lewis et al., 2013; Schwarz et al., 2015), whereas two studies were conducted in non-steady state conditions using an IVITT (Beck-Nielsen et al., 1978) or a stable labelled intravenous glucose tolerance test (SLIVGTT, (Sunehag et al., 2008)). The testing conditions (e.g. one vs. two or three-step clamps, insulin infusion rates), the endpoint variables used to assess insulin sensitivity, the dietary conditions (i.e. isocaloric with neutral or positive energy balance, hypercaloric, ad lib*itum) and* the type of sugar assessed (e.g. sucrose, fructose) varied from study to study. All RCTs were in young or middle age adults (4 in males and 3 in males and females) and had a duration between 1 and 6 weeks.

Higher intakes of sucrose in mixed diets (25 E% vs. 10 E% and 15 E% vs. 5 E%) had no effect on whole-body insulin sensitivity (glucose disposal) or hepatic insulin sensitivity (suppression of endogenous glucose production) in steady-state conditions (euglycaemic hyperinsulinaemic clamp) and neutral energy balance (Black et al., 2006; Lewis et al., 2013), whereas sucrose (32 E%) decreased whole-body insulin sensitivity in non-steady state conditions (IVITT) and positive energy balance as compared to fat (Beck-Nielsen et al., 1978).

Fructose given as beverages significantly decreased hepatic insulin sensitivity (euglycaemic hyperinsulinaemic clamp) at intakes of 20 E% in isocaloric exchange with starch on neutral energy

balance in non-obese males (Schwarz et al., 2015), at intakes of 35E% in hypercaloric conditions in subjects with and without family history of type 2 diabetes (Le et al., 2009) and at intakes of 16 E% when consumed ad libitum as compared to sucrose or glucose given in the same amounts or to fructose given at 8E% in normal weight males (Aeberli et al., 2013). In these studies, whole body glucose disposal was generally not affected. No significant differences were observed in whole body insulin sensitivity (SLIVGTT) or indices of insulin secretion between high (24E%) and low (6E%) intakes of fructose in mixed diets on neutral energy balance in the only study performed in adolescents (Sunehag et al., 2008).

Five studies were at low RoB (tier 1: Black et al. (2006); Sunehag et al. (2008); Le et al. (2009); Aeberli et al. (2013); Lewis et al. (2013)) and two were at moderate RoB (tier 2: Beck-Nielsen et al. (1978); Schwarz et al. (2015)). Critical domains were allocation concealment and blinding.

The Panel considers that the available BoE suggests an adverse effect of fructose given as beverages for short periods of time (1–6 weeks) on hepatic insulin sensitivity in isocaloric exchange with other carbohydrates (glucose, starch) regardless the dietary conditions in which fructose is consumed. This effect is generally not observed on measures of whole-body insulin sensitivity or with comparable amounts of sucrose. The Panel notes that, whereas the effect is observed at intakes of 16 E% and above (lowest dose tested), the available RCTs do not allow identifying a level of fructose intake, either alone or in combination with glucose, at which the risk is not increased.

LoE5 (sQ2.1). **Complementary: Risk of obesity. RCTs**. There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and an increased risk of obesity (**moderate** level of certainty).

Consistency across LoEs. The Panel notes that changes in fasting glucose were consistent with changes in fasting insulin but less consistent with other measures of glucose tolerance and with measures of insulin sensitivity/resistance in the few and heterogeneous RCTs available on these endpoints. Consistent with an increased risk of obesity.

Table 19: sQ2.3. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **added and free** sugars and the risk of T2DM at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?

BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint: fasting glucose 17 RCTs, 935 participants.** Pooled mean effect estimate (95% CI) = 1.94 mg/dL (0.23, 3.66); assuming a within-subject correlation coefficient of 0.82. Considering that blood glucose levels are under homeostatic control in non-diabetic subjects, the correlation coefficient for this endpoint is expected to be > 0.82. **(Appendix G, Figure G.4c)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	11 studies in tier 1; 6 studies in tier 2 (**Appendix I, Figure I.3**) Generally low Key questions: • Randomisation: low • Exposure assessment: generally low • Outcome assessment: generally low Probably high for allocation concealment and blinding	Not serious
Unexplained inconsistency	High heterogeneity (I^2 = 87%) for the pooled mean effect estimate. Point estimates vary widely, and 95% CI show minimal overlap. Residual heterogeneity in dose-response analysis remained high and statistically significant. Between-arm difference in sugars intake (E%) plus RoB only accounted for 34.4% of the variability across studies.	Very serious
Indirectness	Surrogate endpoint	Serious
Imprecision	Low. It could be even lower because the correlation coefficient for this endpoint is expected to be > 0.82	Not serious

Publication bias	Funnel plot shows a slight association between the magnitude of the effect and the SE, and Egger's test was significant (p = 0.004), suggesting a small risk of publication bias (**Appendix H**, **Figure H.3**). However, there is some indication for true heterogeneity in small studies. Public (n = 3), private (n = 6), mixed (n = 4) and NR (n = 4) funding.	Undetected
Upgrading factors	Dose-response: The dose-response meta-regression analysis conducted by EFSA showed that an increase of at least 11E% from sugar is needed to predict a positive effect on fasting glucose. Any further increase of 10E% from sugar leads to an increase of 4 mg/dL in fasting glucose (linear dose-response).	Yes (dose-response)
Final certainty	Downgraded two levels for unexplained inconsistency and one level for indirectness. Upgraded one level for dose-response.	**Low (> 15–50% probability)**

Conclusion sQ2.3. RCTs. The level of certainty in a positive and causal relationship between the intake of added and free sugars and risk of T2DM is **low** (rationale in **Table 19**). RCTs included only adults. About half of the RCTs were in overweight/obese subjects and two were limited to (or included a group of) hyperinsulinaemic individuals. Added and free sugars were consumed ad libitum or in isocaloric exchange with other macronutrients and between-arm differences in added and free sugars intake were between 8 and 43 E%.

8.4.2.2. Observational studies

LoE1. Standalone (main): Incidence of T2DM. PCs. The relationship between sucrose and incidence of T2DM was investigated in four PCs (EPIC-Norfolk, (Ahmadi-Abhari et al., 2014); FMCHES, (Montonen et al., 2007); MDCS, (Sonestedt et al., 2012); WHS, (Janket et al., 2003)). The MDCS cohort also reports on added sugars from all sources. Three PCs analysed sucrose as categorical variable (FMCHES, MDCS, WHS) and one both as categorical and continuous variable (EPIC-Norfolk). The multivariable nutrient density model (EPIC-Norfolk, MDCS) or the nutrient residuals model with (FMCHES) and without (WHS) further adjustment for TEI were used to investigate sucrose while keeping TEI constant. In the EPIC-Norfolk cohort, energy partition models were also built to assess the full effect of sucrose on T2DM risk (i.e. keeping energy intake from other nutrients constant). The evidence table is in **Annex J**.

Preliminary UA

Three PCs report either a non-significant negative (EPIC-Norfolk, WHS) or no (MDCS) association between sucrose intake while keeping TEI constant and incidence of T2DM **(Appendix K, Figure K.7)**. Similar results were obtained using energy partition models in the EPIC-Norfolk cohort (results not plotted). In contrast, the FMCHES cohort reports a non-significant positive association between the intake of sucrose and incidence of T2DM, with a relative risk of 1.22 (95% CI = 0.77, 1.92) for the highest vs. the lowest quartile of energy-adjusted sucrose intake (most adjusted model), with no apparent dose-response relationship. Similar results were found in EPIC-Norfolk, WHS and FMCHES when cases of T2DM diagnosed in the first 2–4 years of follow-up and/or cases of hypertension, dyslipidaemia and/or CVD at baseline were excluded in sensitivity analyses to address reverse causality. In the MDCS cohort, a significant negative relationship between the intake of added sugars and incidence of T2DM became non-significant when BMI was included in the model as covariate (**Annex J)**.

Three PCs were at low RoB (Tier 1; Epic-Norfolk, FMCHES, WHS) and one at moderate RoB (Tier 2; MDCS). The heat map for the RoB assessment is in **Appendix L**, **Table L.7**.

The Panel notes that these studies were inconsistent in the direction of the association and that in three out of the four PCs the relationship was null or negative. The Panel considers that the available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and incidence of T2DM. **No comprehensive UA is performed on this LoE**.

LoE2. Standalone (surrogate): Changes in glucose tolerance. PCs. Two PCs assessed the relationship between the intake of added sugars (QUALITY, (Wang et al., 2014)), or sucrose (CARDIA, (Folsom et al., 1996)), and changes in glucose tolerance. The QUALITY study investigated the relationship between the baseline intake of added sugars from solids and from liquids and changes in fasting glucose and insulin over a follow-up of 2 years in children 8–10 years of age. Results for added

sugars from all sources are not reported. The CARDIA cohort of young adults investigated the relationship between changes in sucrose intake and concurrent changes in fasting insulin over the 7-year follow-up.

In the QUALITY cohort, added sugars from solids and from liquids were analysed as continuous variables using the standard multivariable model to adjust for TEI. In the CARDIA cohort, sucrose was analysed as a continuous variable using repeated measures analysis, without adjustment for TEI. The evidence table is in **Annex J**.

Preliminary UA

Baseline intake of added sugars from solid foods was not associated with changes in fasting glucose or fasting insulin over follow-up in the QUALITY cohort. A significant positive relationship was found, however, between the intake of added sugars from liquid sources at baseline and changes in fasting glucose and insulin over follow-up. For each 10 g/day increase in added sugars from liquids, mean fasting glucose increased by 0.039 mmol/L (95% CI: 0.015, 0.063, $p < 0.01$) and mean fasting insulin by 2.261 ρmol/L (95% CI: 0.676, 3.845, $p < 0.01$).

In the CARDIA cohort, changes in sucrose were not associated with changes in fasting insulin over the follow-up, with the exception of white females, where a significantly inverse association was found; for each 6E% from sucrose there was a fasting insulin decrease of 0.7 μU/mL (spread values not reported) over the follow-up.

Both studies were at moderate RoB (Tier 2), critical domains being attrition (QUALITY only) and other sources of bias (selective reporting). Confounding was a critical domain in the CARDIA only (**Annex K**).

The Panel notes that added sugars from all sources were not investigated in the QUALITY cohort. The Panel considers that the available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and measures of glucose tolerance. **No comprehensive UA is performed on this LoE**.

LoE3. Complementary: Changes in indices of insulin sensitivity/beta-cell function. PCs. In the QUALITY cohort (Wang et al., 2014), baseline intake of added sugars from solid foods was not associated with changes in the HOMA-IR[15] index or the Matsuda-IS index[16] over follow-up. A significant positive relationship was found, however, between the intake of added sugars from liquid sources at baseline and changes in the HOMA-IR index and the Matsuda-ISI. For each 10 g/day increase in added sugars from liquids at baseline, mean HOMA-IR was +0.091 (95% CI: 0.034, 0.149, $p < 0.01$) and mean Matsuda-IS index was −0.356 (95% CI: −0.628, −0.084, $p < 0.01$), suggesting an increase in hepatic and whole-body insulin resistance (RoB tier 2). Conversely, in the DONALD cohort of adolescents followed up for 12.6 years (Goletzke et al., 2013b), baseline intake of free sugars from all sources or from liquid sources only was not associated with HOMA-IR or HOMA-β at the end of follow-up (RoB tier 1).

The Panel notes from the limited number of studies available that the direction of the relationship is inconsistent across studies for added and free sugars from liquids, and that free sugars from all sources were not associated with adverse effects on indices of insulin sensitivity/resistance or beta-cell function. The Panel considers that the available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and indices of insulin sensitivity/resistance or beta-cell function.

LoE5 (sQ2.1) Complementary: Risk of obesity. PCs. The available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of obesity.

Conclusion sQ2.3. PCs. The available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of T2DM.

8.4.2.3. Overall conclusion on sQ2.3

There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars and risk of T2DM (**low** certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

[15] Fasting plasma glucose (mmol/L) x fasting plasma insulin (pmol/L)/22.5.
[16] 10,000/square root [(fasting plasma glucose x fasting plasma insulin) x (mean OGTT glucose 3 mean OGTTinsulin)].

8.4.3. Fructose

sQ3.3. Fructose and risk of Type 2 diabetes mellitus

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of T2DM	0	**3***
LoE2. Standalone (surrogate)	Changes in glucose tolerance	**10**	0
LoE3. Complementary	Changes in indices of insulin sensitivity/beta-cell function	5	1
LoE4. Complementary	Changes in insulin sensitivity	6	0
LoE5. Complementary	Risk of obesity	sQ3.1	sQ3.1

*: Of which one was a PCC.

8.4.3.1. Intervention studies

LoE2. Standalone (surrogate): Changes in glucose tolerance. RCTs. The effect of fructose vs. glucose on fasting glucose was investigated in eight RCTs (of which seven also measured fasting insulin) under different dietary conditions (neutral energy balance, positive energy balance, ad libitum) and in different population groups (with NGT or IGT, with NAFLD, overweight/obese, with BMI $< 35 kg/m^2$, healthy subjects) at doses between 9 and 42.5 E% **(Appendix G, Figures G.5a and G.5b)**. Two additional studies (Hallfrisch et al., 1983a; Swanson et al., 1992) assessed the effect of different doses of fructose in isocaloric exchange with starch on fasting glucose, one of which (Hallfrisch et al., 1983a) also reported on fasting insulin **(Appendix G, Figures G.4c and G.4d)**. Finally, the effect of fructose vs. glucose on glucose and insulin at 120′ during an OGTT was investigated at doses of 15E% in mixed diets under neutral energy balance (Koh et al., 1988) and at doses of 25E% given as beverages ad libitum (Stanhope et al., 2009) (**Appendix F**).

Preliminary UA

The results of RCTs comparing fructose in isocaloric exchange with glucose were mixed. Overall fasting glucose was lower in three studies (4 arms) and higher in five studies with fructose than with glucose. The pooled mean effect estimate (95% CI) was −2.67 mg/dL (−6.46, 1.11). Results for fasting insulin followed a similar pattern (pooled mean effect estimate and 95% CI = −0.77 ρmol/L and −20.07, 18.53) except in the study by Jin et al. (2014) in adolescents with NAFLD, where fructose intake (20E%) significantly increased fasting insulin and decreased fasting glucose as compared to glucose when consumed ad libitum in beverages.

The study by Hallfrisch et al. (1983a) showed no effect of fructose in solid foods at 15 E% as compared to starch on fasting glucose and no difference between hyper- and normo-insulinaemic subjects. Fasting insulin, however, was significantly higher with fructose vs. starch though only in hyperinsulinaemic individuals. No significant differences in fasting glucose were noted between fructose at similar levels of intake (16.6 E%) and starch in the study by Swanson et al. (1992) conducted in healthy subjects.

No effect of fructose vs. glucose was reported on glucose or insulin at 120′ during an OGTT at doses of 15 and 25 E% in the two studies that assessed this endpoint (Koh et al., 1988; Stanhope et al., 2009).

The Panel considers that the available BoE does not suggest an adverse effect of fructose on measures of glucose tolerance when consumed in isocaloric exchange with other carbohydrates (glucose, starch). **No comprehensive UA is performed**.

LoE3. Complementary: Changes in indices of insulin sensitivity/beta-cell function. RCTs. A total of five RCTs investigated the effects of fructose vs. glucose from beverages at doses from 9 to 25 E% on indices of insulin sensitivity/resistance (**Appendix F**). Changes in the HOMA-IR did not differ significantly between the fructose and glucose arms in the five studies which assessed this endpoint (Stanhope et al., 2009; Silbernagel et al., 2011; Jin et al., 2014; Mark et al., 2014; Lowndes et al., 2015). The Matsuda ISI, calculated from glucose and insulin values during an OGTT, significantly decreased in both arms with no differences between fructose and glucose in positive energy balance (Silbernagel et al., 2011), but decreased significantly more in the fructose arm when both sugars in beverages were provided ad libitum (Stanhope et al., 2009). In the latter RCTs, the increase in body weight was similar in the glucose and fructose arms, whereas the increase in total fat and VAT was significantly higher in the fructose vs. the glucose arm.

The Panel considers that the available BoE does not suggest an adverse effect of fructose on indices of insulin sensitivity/resistance when consumed in isocaloric exchange with glucose under controlled energy conditions.

LoE4. Complementary: Changes in insulin sensitivity. **RCTs**. Three studies investigated the effect of fructose vs. glucose given as beverages on measures of insulin sensitivity, two in steady-state conditions using the euglycaemic hyperinsulinaemic clamp (Aeberli et al., 2013; Johnston et al., 2013) and one in non-steady state conditions using an IVITT (Beck-Nielsen et al., 1980) (Appendix F). The effect of fructose was also investigated in studies providing different amounts of fructose *ad libitum* (Aeberli et al., 2013), in isocaloric exchange with starch (Sunehag et al., 2008; Schwarz et al., 2015), in hypercaloric conditions (Le et al., 2009) and in isocaloric exchange with sucrose (Aeberli et al., 2013). The results of these studies are discussed in Section 8.4.2.1 under LoE 4 for added and (free) sugars.

The Panel considers that the available BoE suggests an adverse effect of fructose given as beverages for short periods of time (1–6 weeks) on hepatic insulin sensitivity in isocaloric exchange with other carbohydrates (glucose, starch) regardless the dietary conditions in which fructose is consumed. This effect is generally not observed on measures of whole-body insulin sensitivity. The Panel notes that, whereas the effect is observed at intakes of 16 E% and above, the available RCTs do not allow identifying a level of fructose intake at which the risk is not increased.

LoE5. Complementary: risk of obesity. RCTs. The available BoE from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity.

Conclusion sQ3.3. RCTs. Whereas there is some evidence for an adverse effect of fructose on hepatic insulin sensitivity when consumed in isocaloric exchange with other carbohydrates (glucose, starch), which could eventually lead to hyperinsulinaemia and in the long term to the development of T2DM, the RCTs available do not suggest an adverse effect of fructose on measures of glucose tolerance. Therefore, the Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (glucose, starch) and risk of T2DM.

8.4.3.2. Observational studies

LoE1. Standalone (main): Incidence of T2DM. **PCs**. The relationship between the intake of free fructose and free glucose (as mono-saccharides) and incidence of T2DM was investigated in three cohorts, one of females (WHS, (Janket et al., 2003)) and two of males and females combined (EPIC-Norfolk, (Ahmadi-Abhari et al., 2014)); FMCHES, (Montonen et al., 2007)). The Epic-Norfolk was a PCC. Free fructose and free glucose were analysed as categorical variables in all the studies. The dose ranges covered were similar across the PCs, with intakes of free fructose being slightly higher than those of free glucose in all the studies. The multivariable nutrient density model (Epic-Norfolk) or the nutrient residuals model with (FMCHES) and without (WHS) further adjustment for TEI were used to investigate free fructose and glucose while keeping TEI constant. The evidence table is in **Annex J**.

Preliminary UA

The results of these studies were mixed. In the most adjusted models including TEI and baseline BMI, the incidence of T2DM significantly increased across categories of free fructose intake (from lowest to highest) in the FMCHES cohort and significantly decreased in the EPIC-Norfolk cohort. No association between free fructose intake and incidence of T2DM was observed in the WHS **(Appendix K**, **Figure K.8)**. Similar results were obtained for free glucose, although the negative relationship reported in the EPIC-Norfolk cohort was not statistically significant for this exposure **(Appendix K**, **Figure K.9)**. The three PCs were at low RoB (tier 1).

In the EPIC-Norfolk cohort, free fructose and free glucose were also analysed using the nutrient residuals and the standard multivariable models for energy adjustment, obtaining similar results. Using the multivariable nutrient density model and modelling specific substitution patterns, replacement of free fructose with other carbohydrates did not affect the risk of T2DM, whereas replacement of saturated fatty acids and protein with an isocaloric amount of fructose significantly decreased the risk of T2DM. This was also the case when the energy partition model was used, where higher intakes of free fructose and free glucose were negatively associated with T2DM risk while keeping energy intake from other macronutrients constant.

The Panel notes the low number of PCs available and the inconsistency of the results across studies. The Panel considers that the available BoE from PCs does not suggest a positive relationship

between the intake of fructose in isocaloric exchange with glucose or other macronutrients and incidence of T2DM.

LoE3. Complementary: Changes in indices of insulin sensitivity/beta-cell function. PCs. The relationship between the intake of fructose and indices of insulin resistance was investigated only in the TLGS cohort of males and females in Iran (Bahadoran et al., 2017). Fructose intake at baseline (E%, continuous analysis) was positively associated with an increase in fasting insulin and HOMA-IR over follow-up. This study was at high RoB (tier 3). The only covariate included in the model for data analysis was age.

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and adverse effects on indices of insulin resistance.

Conclusion sQ3.3. PCs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose or other macronutrients and risk of T2DM.

8.4.3.3. Overall conclusion on sQ3.3

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fructose in isocaloric exchange with other carbohydrates (glucose, starch) or other macronutrients and risk of T2DM.

8.4.4. Sugar-sweetened beverages

sQ4.3. SSBs and risk of Type 2 diabetes mellitus

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of T2DM	0	**14***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**7**	**1**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	3	2
LoE4. Complementary	Measures of insulin sensitivity	3	0
LoE5. Complementary	Risk of obesity	sQ4.1	sQ4.1

*: Of which one was a PCC.

8.4.4.1. Intervention studies

LoE2. Standalone (surrogate): Measures of glucose tolerance. RCTs. Out of the 17 RCTs which investigated the effect of high vs. low added and free sugars intake on fasting glucose (see Section 8.4.2.1), seven were conducted with beverages **(Appendix G, Figure G.4c2)**. Pooled mean effect estimates (95% CI) for sugars from different sources were 0.82 mg/dL (−1.46, 3.10) for beverages (n = 7, dose range = 8–22E%), 0.67 mg/dL (−0.77, 2.12) for mixtures of food and beverages (n = 7, 8 study groups, dose range = 10–23E%) and 6.63 mg/dL (0.52, 12.75) for solid foods (n = 3, 4 study groups, dose range = 15–43E%). The Panel notes that, although the pooled effect estimates vary across food sources, the 95% CI overlap. The Panel also notes that the sugar doses investigated were different across food sources, and that the study by Moser et al. (1986) using 43 E% in solid foods was dropped from the dose-response meta-regression analysis (leverage point).

In the dose-response meta-regression analysis conducted by EFSA (technical report in **Annex L**), the sugar source was not found to be a significant modifying factor of the dose-response relationship, although the BoE had obvious limitations to test this hypothesis owing to the low number of studies which used solid foods only. The Panel also notes that the conclusions on complementary LoEs 3 and 4 for added and free sugars were mainly driven by studies conducted with beverages.

Based on the available BoE from RCTs, the Panel has the same level of certainty on a positive and causal relationship between the intake of SSBs and risk of T2DM as for added and free sugars (**low** certainty).

Conclusion sQ4.3. RCTs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of T2DM is **low**.

8.4.4.2. Observational studies

LoE1. Standalone (main): Incidence of T2DM. PCs. The relationship between the intake of SSBs and incidence of T2DM was investigated in 14 studies, of which 13 were PCs and one was a PCC

study (EPIC-InterAct; InterAct consortium, 2013). These include three PCs in which the endpoint was high fasting glucose (> 100 or 110 mg/dL, depending on the study) or the use of hypoglycaemic medications (CARDIA, KoGES, TLGS) and one PC which investigated incidence of pre-diabetes and incidence of T2DM as a composite endpoint (Framingham Offspring).

Three PCs included only females (BWHS, (Palmer et al., 2008); NHS II, (Schulze et al., 2004); WHI, (Huang et al., 2017)); two included only males (HPFS (de Koning et al., 2011); Toyama (Sakurai et al., 2014)); in three PCs, males and females were analysed separately (KoGES, (Kang and Kim, 2017); JPHC (Eshak et al., 2013); ARIC (Paynter et al., 2006)) and the remaining studies were on males and females combined (FMCHES, (Montonen et al., 2007); CARDIA, (Duffey et al., 2010); EPIC-InterAct (InterAct consortium, 2013); Framingham Offspring, (Ma et al., 2016a); MDCS, (Ericson et al., 2018); TLGS, (Mirmiran et al., 2015)). All the studies were in adults, except for the TLGS (children and adolescents 6–18 years of age). Six of these studies (Framingham Offspring, HPFS, NHS II, Toyama, WHI, EPIC-InterAct) also investigated the association between the intake of ASBs and incidence of T2DM.

All studies analyse the intake of SSBs as categorial variable using the standard multivariable model to adjust for energy except CARDIA, which analyses the exposure as a continuous variable adjusting for non-SSBs energy. In both cases, the analysis allows for TEI to change as a function of SSBs consumption. The EPIC-InterAct also analyses the exposure as a continuous variable adjusting for TEI. All studies include BMI (or body weight in CARDIA) as covariate in the most adjusted models. The evidence table is in **Annex J**.

Preliminary UA

A positive relationship between the consumption of SSBs and incidence of T2DM was observed in 13 out of the 14 studies considered (ARIC, BWHS, FMCHES, KoGES, MDCS, TLGS, Toyama; statistically significant in EPIC-InterAct, Framingham Offspring, HPFS, NHS II, WHI and JPHC in females only), whereas the relationship was null in the CARDIA and in the JPHC for males. The forest plot for the 13 studies in adults can be found in **Appendix K**, **Figure K.10**. The TLGS cohort in children and adolescents is not included (number of cases was not reported).

The association between the consumption of SSBs and incidence of T2DM was attenuated when BMI was included in the model as an additional variable after adjusting for relevant covariates in four (BWHS, EPIC-InterAct, MDCS, NHSII) out of the eight studies which tested this hypothesis (exceptions were Framingham-Offspring, Toyama, HPFS and TLGS), suggesting that the relationship may be in part mediated by BMI.

Out of the six studies which addressed the relationship between ASBs and incidence of T2DM, the association was weaker than for SSBs in five (Framingham Offspring, HPFS, NHS II, WHI, EPIC-InterAct) and non-significant in four (EPIC-InterAct, Framingham Offspring, HPFS, NHS II), whereas one PC reported a stronger and statistically significant association as compared to SSBs (Toyama). The Panel notes that the relationship between ASBs and incidence of T2DM in these studies is inconsistent and generally weaker than for SSBs.

Five studies were in RoB tier 1 (ARIC, BWHS, Framingham Offspring, HPFS, Toyama), six were in tier 2 (CARDIA, EPIC-InterAct, FMCHES, JPHC, NSH II, TLGS) and three were in tier 3 (KoGES, MDCS, WHI). The heat map can be found in **Appendix L**, **Table L.8**.

The Panel considers that the available BoE suggests a positive relationship between the consumption of SSBs and risk of T2DM.

Comprehensive UA

Selection of the endpoint. The only eligible endpoint in this LoE1 is incidence of T2DM. As anticipated in the protocol for this scientific opinion, the definition of T2DM and the methods used for the identification of cases varied from study to study. True incidence of T2DM may have been underestimated in some studies (e.g. when cases were identified through drug reimbursement records only) and overestimated in others (e.g. when high fasting glucose below the diagnostic threshold for diabetes and diagnosis or treatment of diabetes were combined in composite endpoints).

Dose-response relationship. A significant linear dose-response relationship across categories of SSBs intake was originally reported in eight (BWHS, FMCHES, EPIC-InterAct, Framingham Offspring, HPFS, NHS II, JPHC in women only, WHI) of the 13 studies which performed a categorical analysis. Upon request for additional data from the study authors of EPIC-InterAct, individual country-specific cohort risk estimates were included in the dose-response analysis.

In the dose-response meta-analysis conducted by EFSA, parametric dose-response models were estimated based on summarised data. Both linear and non-linear (restricted cubic splines) dose-response relationships were investigated. Random-effects models were fitted on risk ratios from most adjusted multivariable models via restricted maximum likelihood using a one-stage and a two-stage approach (to estimate individual studies pooled effects across exposure categories). The reference dose chosen was zero mL/day. The between-study heterogeneity was investigated with Cochran's Q test and the I^2 statistic; to explore possible sources of heterogeneity, adjusted study-specific RRs per 250 mL/day increase in intake were stratified by age, sex, study location, categorisation of exposure, follow-up time and tier of reliability. Sensitivity analyses were run to address the uncertainty in the exposure characterisation, in the choice of splines knots and in the internal validity of the individual studies. Publication bias was assessed using Egger's test and funnel plot on the same study-specific RRs used in the subgroup analyses.

Fifty-five non-referent RRs from 19 study-specific analyses were included (I^2 = 51%; p = 0.001) in the dose-response analysis. The TLGS (number of cases not reported), BWHS (model diagnostics) and CARDIA (RR already provided per unit increase) cohorts were excluded. The predicted pooled relative risk of T2DM was 1.13 (95% CI: 1.07, 1.20) for an increase in SSBs intake of 250 mL/day in the linear model (p for linear trend < 0.0001) and 1.13 (95% CI: 1.07, 1.20) at 250 mL/day in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50% and 90%, of the distribution; p for non-linearity = 0.816) (**Figure 13**). The subgroup analyses did not identify clear sources of heterogeneity: there was a suggestion that the risk was higher in subjects younger than 55 years old; in Asian populations; in cohorts with longer follow-up; in RoB tier 2 studies. A sensitivity analysis excluding RoB tier 3 studies confirmed no evidence of departure from linearity (p = 0.295) and showed higher RRs estimates (1.15 (95% CI: 1.06, 1.24); 1.19 (95% CI: 1.09, 1.29)), narrower exposure range and improved fitting. The funnel plot and related Egger's regression suggested the possibility of a 'small-study effect' (larger effects in PCs where RRs are more imprecise). This can be interpreted as publication bias (e.g. study results not published or not located) or can be explained by actual heterogeneity (e.g. differences in the underlying risk across populations), outcome reporting or poor quality of small studies. In this case, the Panel considers that the 'small-study effect' can be explained by true heterogeneity. The PC driving the asymmetry of the funnel plot was a cohort of Finnish males and females (FMCHES) with very low incidence of T2DM. The technical report and all related references are in **Annex J**.

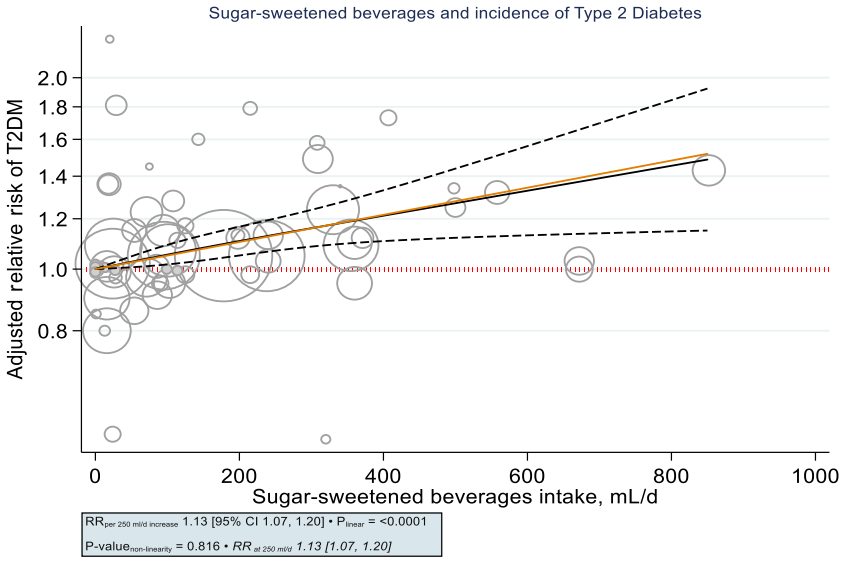


Figure 13: Dose-response meta-analysis on the relationship between the intake of sugar-sweetened beverages and incidence of type 2 diabetes mellitus (T2DM)

LoE2. Standalone (surrogate): Measures of glucose tolerance. PCs. One PC (WAPCS, (Ambrosini et al., 2013)), investigated the relationship between changes in SSBs intake and concurrent changes in fasting glucose and fasting insulin over the 3-year follow-up. Change in SSBs intake was analysed as a categorical variable and TEI was not adjusted for (WAPCS). The evidence table is in **Annex J**.

Non-significant negative associations were reported for changes in fasting glucose and fasting insulin in the highest vs. lowest tertile of increase in SSBs intake in males and females after adjusting for BMI and major dietary patterns.

The study was at low RoB (tier 1), the critical domain being attrition (**Annex K**).

The Panel notes the limited evidence available from PCs. The Panel considers that the available BoE does not suggest a positive relationship between intake of SSBs and measures of glucose tolerance.

LoE3. Complementary: Indices of insulin sensitivity/resistance or beta-cell function. **PCs**. The Framingham-Offspring (Ma et al., 2016a) investigated the relationship between the cumulative intake of SSBs and HOMA-IR at end of follow-up, while the WAPCS (Ambrosini et al., 2013) investigated changes SSBs intake and concurrent changes in HOMA-IR over the follow-up (**Annex J**). The Framingham-Offspring reports a positive and significant relationship between SSBs intake and insulin resistance, whereas the WAPCS reports a negative non-significant association for changes in HOMA-IR across tertiles of increase in SSBs intake over the follow-up. In the Framingham-Offspring, no relationship was observed between the intake of ASBs and HOMA-IR. Both PCs were at low RoB (tier 1), the critical domains being attrition (WAPCS) and confounding (Framingham-Offspring) (**Annex K**).

The Panel notes from the limited number of studies available that the direction of the relationship is inconsistent across studies. The Panel considers that the available BoE does not suggest a positive relationship between the intake of SSBs and indices of insulin resistance.

LoE5 (sQ4.1). **Complementary: Risk of obesity. PCs**. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate** certainty).

Consistency across LoE. The Panel notes an increased incidence of T2DM is consistent with an increased risk of obesity. However, few PCs assessed endpoints for other LoEs specific to this sQ (e.g. measures of glucose tolerance, indices of insulin sensitivity/resistance or beta-cell function).

Table 20: sQ4.3. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **SSBs** and the risk of T2DM at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint:** incidence of T2DM **13 PCs and 1 PCC, 338,007 participants.** 19 study-specific analyses from 11 PCs were included in the dose-response analysis. (**Appendix K**, **Figure K.10**)	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	Five PCs in tier 1; 6 PCs in tier 2, 3 PCs in tier 3 (**Appendix L**, **Table L.8**) Generally moderate Key questions: • Confounding: most probably low • Exposure assessment: mixed probably low and probably high • Outcome assessment: mixed low and probably high Mixed probably low and probably high for attrition	Serious
Unexplained inconsistency	Moderate heterogeneity (I^2 = 51%) for the pooled mean effect estimate of study-specific RRs per unit increase of intake. RRs are similar across large studies; small studies show higher effects, but confidence intervals overlap. No clear sources of heterogeneity identified.	Not serious
Indirectness	Direct endpoint in most studies	Not serious
Imprecision	Low	Not serious
Publication bias	Funnel plot showed asymmetry and Egger's test was significant (p = 0.021), suggesting a possible small-study effect **(Annex M)**. However, the number of studies available is small, and there is some indication for true heterogeneity of small (vs large) studies. Public (n = 13) and mixed (n = 1) funding.	Undetected

Upgrading factors	Dose-response: A significant linear dose-response relationship across categories of SSBs intake was reported in eight of the 13 PCs which performed a categorical analysis. The dose-response meta-analysis conducted by EFSA showed a significant linear positive dose relationship (linear pooled mean effect estimate (95% CI) = 1.13 (1.07, 1.20) for 250 mL/d increase with no support for non-linearity (p = 0.816). In sensitivity analysis, exclusion of PCs at high RoB (tier 3) had a negligible impact on the dose-response relationship (**Annex M**).	Yes (dose-response)
Final certainty	Started moderate, upgraded one level for dose-response. Not downgraded for RoB because PCs at high RoB (tier 3) had a negligible impact on the dose-response relationship.	**High (> 75–100% probability)**

Conclusion sQ4.3. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk T2DM is **high** (rationale in **Table 20**). The relationship was mostly observed for SSBs not keeping TEI constant.

8.4.4.3. Overall conclusion on sQ4.3

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of T2DM (**high** certainty). Evidence from RCTs (**low** certainty) supports the relationship.

8.4.5. Fruit juices

sQ5.3. FJs and risk of Type 2 diabetes mellitus

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of T2DM	0	**9***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	0
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity	sQ5.1	sQ5.1

*: Of which one was a PCC.

8.4.5.1. Observational studies

LoE1. Standalone (main): Incidence of T2DM. PCs. The relationship between the intake of FJs and incidence of T2DM was investigated in nine studies, of which eight were PCs and one was a PCC (EPIC-InterAct; InterAct consortium, 2013). In the CARDIA cohort the endpoint was high fasting glucose (> 110 mg/dL) or the use of hypoglycaemic medications.

Four PCs included only females (BWHS (Palmer et al., 2008); NHS and NHS II (Muraki et al., 2013); WHI (Auerbach et al., 2017)); one included only males (HPFS, (Muraki et al., 2013)); in one, males and females were analysed separately (JPHC, (Eshak et al., 2013)); and the remaining were on males and females combined (CARDIA, (Duffey et al., 2010); EPIC-InterAct, (InterAct consortium, 2013); SUN, (Fresan et al., 2017)). All the studies were in adults.

All studies analysed the intake of FJs as categorial variable using the standard multivariable model to adjust for energy except WHI, which used the residuals (energy-adjusted) model, the CARDIA, which analysed the exposure as a continuous variable adjusting for non-SSBs energy, and the BWHS, which did not adjust for TEI. In all cases except for the WHI, the analysis allows for TEI to change as a function of FJs consumption. All studies except the BWHS include BMI (or body weight in CARDIA) as covariate in the most adjusted models. EPIC-InterAct, NHS, NHSII and HPFS also report results for FJs analysed as a continuous variable, and thus in isocaloric exchange with other food sources. The evidence table is in **Annex J**.

Preliminary UA

A positive relationship between the consumption of FJs and incidence of T2DM was observed in six studies (EPIC-InterAct, BWHS, JPHC and statistically significant in HPFS, NHS and NHS II), whereas it was null in one (CARDIA) and negative (non-significant) in two (SUN and WHI). The forest plot can be found in **Appendix K**, **Figure K.11**. The Panel notes that, in the WHI cohort, TEI was kept constant in the analysis. Results in the EPIC-InterAct, NHS, NHSII and HPFS cohorts were similar when FJs were

analysed as a continuous variable using the standard multivariable model to adjust for TEI, and thus in isocaloric exchange with other food sources.

Three PCs are in RoB tier 1 (BWHS, HPFS, WHI), five in tier 2 (CARDIA, EPIC-InterAct, NHS, NSH II, SUN) and one in tier 3 (JPHC). The heat map can be found in **Appendix L**, **Table L.9**.

The Panel considers that the available BoE suggests a positive relationship between the consumption of FJs and risk of T2DM.

Comprehensive UA

Selection of the endpoint. The only eligible endpoint in this LoE is incidence of T2DM.

Dose-response relationship. A significant linear dose-response relationship across categories of FJs intake was reported in three (HPFS, NHS, NHS II) of the eight PCs which performed a categorical analysis. Upon request for additional data from the study authors of EPIC-InterAct, individual country-specific cohort risk estimates were included in the dose-response analysis.

In the dose-response meta-analysis conducted by EFSA, parametric dose-response models were estimated based on summarised data. Both linear and non-linear (restricted cubic splines) dose-response relationships were investigated. The methodological approach applied was the same as for the dose-response meta-analyses of SSBs intake and incidence of T2DM (**Annex M**).

Forty-two non-referent RRs from 13 study-specific analyses were included in the dose-response meta-analysis (I^2 = 3%; p = 0.414). The BWHS (RRs not adjusted for BMI and EI), CARDIA (RR already provided per unit increase), SUN and WHI (model diagnostics) cohorts were excluded. The predicted pooled relative risk of T2DM was 1.16 (95% CI: 1.09, 1.24) for an increase in FJs intake of 250 mL/day in the linear model (p for linear trend < 0.0001) and 1.19 (95% CI: 1.11, 1.28) at 250 mL/day in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50% and 90%, of the distribution; p for non-linearity = 0.372) (**Figure 14**). The subgroup analyses did not identify clear sources of heterogeneity, also given the overall heterogeneity quantified as 3%. A sensitivity analysis excluding RoB tier 3 studies confirmed no evidence of departure from linearity (p = 0.704) and showed similar RRs estimates (1.17 (95% CI: 1.09, 1.25); 1.18 (95% CI: 1.10, 1.27)) and improved fitting. The funnel plot and related Egger regression did not support a possible small-study effect.

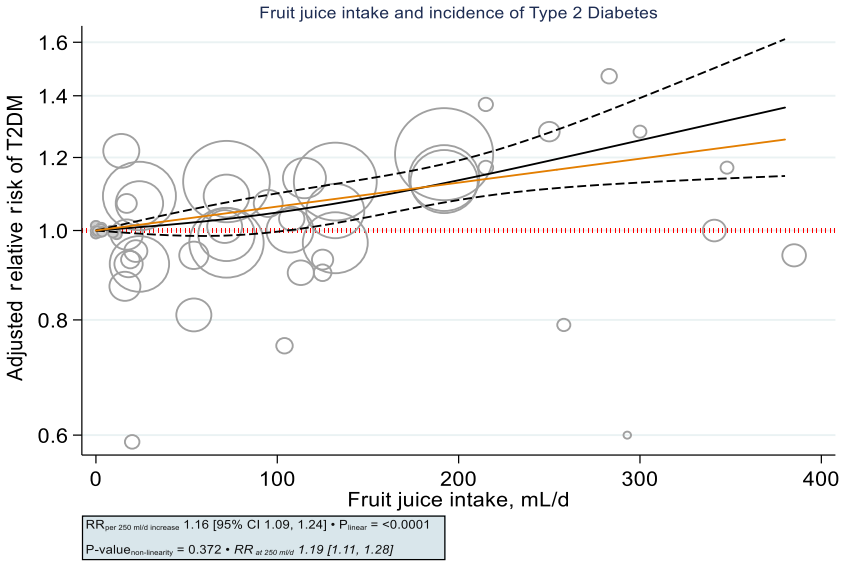


Figure 14: Dose-response meta-analysis on the relationship between the intake of fruit juices and incidence of Type 2 diabetes mellitus (T2DM)

LoE5. Complementary: Risk of obesity. PCs. There is evidence for a positive and causal relationship between the intake of FJs and risk of obesity (**very low** level of certainty).

Consistency across LoEs. The Panel notes and an increased incidence of T2DM is consistent with an increased risk of obesity. However, no PCs are available from other standalone or complementary LoEs which are specific to this sQ.

Table 21: sQ5.3. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of **FJs** and risk of T2DM at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint: incidence of T2DM 8 PCs and 1 PCC, 419,152 participants.** 13 study-specific analyses from 5 PCs were included in the dose-response analysis.	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	Three PCs in tier 1; 5 PCs in tier 2, 1 in tier 3 (**Appendix L**, **Table L.9**) Generally moderate Key questions: • Confounding: probably low • Exposure assessment: mixed probably low and probably high • Outcome assessment: most probably high Mixed low and probably high for attrition	Serious
Unexplained inconsistency	No heterogeneity detected (I^2 = 3%) for the pooled mean effect estimate of study-specific RRs per unit increase of intake. RRs are similar across studies and confidence intervals overlap.	Not serious
Indirectness	Direct endpoint in most studies.	Not serious
Imprecision	Low	Not serious
Publication bias	No evidence of asymmetry in funnel plot and Egger test was not significant (p = 0.703). Limited number of studies (**Annex M**). Public funding (n = 9).	Undetected
Upgrading factors	Dose-response: A significant linear dose-response relationship across categories of FJs intake was reported in 3 (HPFS, NHS, NHS II) of the 8 PCs which performed a categorical analysis. The dose-response meta-analysis conducted by EFSA showed a significant linear positive relationship (linear pooled mean effect estimate (95% CI) = 1.16 (1.09, 1.24; I^2 = 3%) for 250 mL/d increase with weak support for non-linearity (p = 0.372) (**Annex M**).	Yes (dose-response)
Final certainty	Started moderate, downgraded one level for RoB, upgraded one level for dose-response.	**Moderate (> 50–75% probability)**

Conclusion sQ5.3. PCs. The level of certainty in a positive and causal relationship between the intake of FJs and risk T2DM is **moderate** (rationale in **Table 21**). The relationship was observed for FJs both keeping and not keeping TEI constant in the analysis.

8.4.5.2. Overall conclusion on sQ5.3

There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of T2DM (**moderate** level of certainty).

8.5. Risk of dyslipidaemia

8.5.1. Total sugars

sQ1.4. Total sugars and risk of dyslipidaemia

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c	0	0
LoE2. Standalone (surrogate)	Changes in total-c, LDL-c, TG, HDL-c or derived indices	0	**2**
LoE3. Complementary	Risk of obesity	sQ1.1	sQ1.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus	sQ1.3	sQ1.3

8.5.1.1. Observational studies

LoE2. Standalone: Total-c, LDL-c, TG, HDL-c or derived indices. PCs. Two PCs investigated the relationship between total sugars intake and blood lipid levels, one in the older adults (BMES, (Goletzke et al., 2013a)) and one in toddlers (ALSPAC, (Cowin and Emmett, 2001)) of both sexes. Total sugars were analysed as continuous variable using either the nutrient residuals (energy adjusted) model (ALSPAC) or the nutrient density (energy adjusted) model (BMES), and thus in isocaloric exchange with other macronutrients. The evidence table is in **Annex J**.

Preliminary UA

The BMES found no association between changes in total sugars intake and concurrent changes in TG and HDL-c over the 5-year follow-up. In the ALSPAC, a non-significant positive correlation was found between energy-adjusted total sugar intakes at baseline and blood lipid levels (total cholesterol, HDL-c and LDL-c) at the end of the 13-month follow-up. In a backward stepwise regression analysis that excluded the least significant variables until all were $p < 0.1$, total sugars intake was retained in the model only for the T-c:HDL-c ratio and only for females, showing a positive association ($p = 0.052$).

Both PCs were at moderate RoB (tier 2), with critical domains being confounding and attrition (**Annex K**).

The Panel notes that the two PCs available were heterogeneous regarding the population studied and the exposure–endpoint combinations assessed (total sugars intake at baseline vs. blood lipid levels at the end of follow-up; changes in total sugars intake vs. concurrent changes in blood lipids) and that total sugars intake was largely unrelated to blood lipid levels in both studies after adjusting for relevant covariates, including dietary fat.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and adverse effects on blood lipids. **No comprehensive UA is performed**.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. **PCs**. The available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ1.1, Section 8.2.1.1) or risk of T2DM (sQ1.3, Section 8.4.1.1).

Conclusion sQ1.4. PCs. The available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of dyslipidaemia.

8.5.1.2. Overall conclusion on sQ1.4

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of dyslipidaemia. Total sugars were not investigated under other dietary conditions (e.g. not keeping TEI constant).

8.5.2. Added and free sugars

sQ2.4. Added and free sugars and risk of dyslipidaemia

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c	0	0
LoE2. Standalone (surrogate)	Changes in total-c, LDL-c, TG, HDL-c or derived indices	**24**	**3**
LoE3. Complementary	Risk of obesity	sQ2.1	sQ2.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus	sQ2.3	sQ2.3

8.5.2.1. Intervention studies

LoE2. Standalone (surrogate): Changes in total-c, LDL-c, TG, HDL-c or derived indices. RCTs. Twenty-four RCTs (29 study groups) investigated the effect of high vs. low sugar intakes on changes in total cholesterol **(Appendix G, Figure G.6a1)**, of which 17 (21 study groups) also assessed changes in LDL-cholesterol **(Appendix G, Figure G.6b1)**, 20 (24 study groups) report on changes in HDL-cholesterol **(Appendix G, Figure G.6c1)** and 23 (29 study groups) on fasting triglycerides (TG) **(Appendix G, Figure G.6d1)**. Differences in sugar intakes in the high vs. the low sugar arms ranged from 6 to 43 E% and study duration from 4 to 72 weeks. Six RCTs were conducted

with solid foods, seven with beverages and 11 with mixtures of solid foods and beverages (**Appendix F**). All the studies were in adults: six were in healthy subjects and the remaining in selected population subgroups (e.g. overweight/obese, BMI < 35 kg/m^2, individuals with gallstones, hypertriglyceridaemia, hyperinsulinaemia, etc.).

Added and free sugars were provided under neutral energy balance in isocaloric exchange with other macronutrients (mostly starch) (13 studies) or ad libitum (11 studies). In 10 studies conducted under neutral energy balance, the macronutrient composition of the background diet was known and controlled by the investigators. Of these, eight RCTs also controlled for the polyunsaturated/saturated (P/S) fatty acid ratio (**Appendix F**).

Preliminary UA

Total-c and fasting TG were higher in the high vs. the low sugar arm in 20 and 19 out of the 29 study groups, respectively. Pooled mean effect estimates (95%CI) are 8.71 mg/dL (2.86, 14.56; I^2 = 87%) for total-c **(Appendix G, Figure G.6a1)** and 14.59 mg/dL (7.16, 22.02; I^2 = 81%) for fasting TG **(Appendix G, Figure G.6d1)**. LDL-c was also higher in the high vs. the low sugar arm in 16 out of the 21 study groups. The pooled mean effect estimate (95%CI) is 4.50 mg/dL (−0.88, 9.87; I^2 = 90%) **(Appendix G, Figure G.6b1)**. Conversely, HDL-c was minimally affected by the intervention (pooled mean effect estimate (95% CI) = 0.83 mg/dL (−0.25, 1.91; I^2 =77%) **(Appendix G, Figure G.6c1)**. Heterogeneity across studies was high and statistically significant.

The effect of high vs. low sugars intake was of bigger magnitude and statistically significant for all blood lipid variables when the analysis was restricted to studies conducted under neutral energy balance in isocaloric exchange with starch, of which most controlled for the macronutrient composition of the diet and the P/S ratio. Pooled mean effect estimates (95%CI) are 13.40 mg/dL (6.63, 20.16, I^2 = 75%) for total-c **(Appendix G, Figure G.6a1)**, 7.88 mg/dL (1.82, 13.94; I^2 = 75%) for LDL-c, 1.98 mg/dL (0.96, 2.99; I^2 = 32%) for HDL-c and 17.24 mg/dL (7.67, 26.81; I^2 = 79%) for fasting TG **(Appendix G, Figures G.6b1, G.6c1 and G.6d1)**.

In studies conducted ad libitum, the effect of high vs. low sugars intake on fasting TG was consistent with that observed in studies under neutral energy balance, although not statistically significant (pooled effect estimate and 95% CI = 10.32 mg/dL, −2.04 to 22.68; I^2 = 85%) (**Appendix G, Figure G.6d1**), whereas the effect on total-c, LDL-c and HDL-c was negligible (**Appendix G, Figures G.6a1, G.6b1 and G.6c1**).

Twelve RCTs were at low RoB (tier 1) and 12 at moderate RoB (tier 2). The heat map is in **Appendix I, Figure I.4**.

The Panel considers that the available BoE suggests a positive relationship between the intake of added and free sugars and risk of dyslipidaemia.

Comprehensive UA

Selection of the endpoint. The Panel decided to conduct the comprehensive UA on fasting TG for the following reasons: (a) the effect of the intervention on fasting TG was higher than on any other blood lipid fraction; (b) dietary lipids, which can affect total-c and LDL-c, were not controlled for in studies ad libitum; (c) TG are more likely to be affected by dietary sugars (particularly fructose) than any other blood lipid fraction (see Section 3.6.1.3).

Dose-response relationship. A dose-response relationship between the intake of sucrose (doses 2, 15 and 30E%) in isocaloric exchange with starch and fasting TGs was observed in the RCT by Israel et al. (1983) conducted in individuals with hyperinsulinaemia (men only). A dose-response relationship between the intake of fructose (doses 0, 7.5 and 15 E%) in isocaloric exchange with starch and fasting TGs was also reported in the RCT by Hallfrisch et al. (1983a)* conducted in men with hyperinsulinaemia.

A meta-regression linear dose-response analysis was performed by EFSA to investigate the association between the difference in sugars intake and the difference in fasting TG between study arms. A total of 29 observations were eligible for the analysis. Potential effect-modifiers were identified using graphical displays of the stratified dose-response curves. These variables included main characteristics of the exposure (i.e. sugars source and type, dietary conditions), methodological aspects related to study design (parallel or cross-over, with and without wash-out) and RoB. The final model was chosen considering goodness of fit, significance of the parameters, explained heterogeneity and robustness in response to the inclusion/exclusion of individual studies. Although various models with adjustment factors were able to improve the model fit, the estimates of the related parameters were not statistically significant and the explained heterogeneity was lower than in the final model

(24%). Therefore, no adjusting factors have been retained in the final dose-response model. Residual heterogeneity remained high (Cochran Q-test = 66.39) and statistically significant ($p < 0.0001$), indicating that other factors not identified in the BoE, or for which it was not possible to adjust due to the low number of studies available, play a role in explaining differences across studies.

Several diagnostics, the Hat indicator, the Cook distance and the influence analysis (One-at-a-Time leave out analysis), identified one study (Moser et al., 1986), conducted on two subgroups of young women taking/not taking contraceptives, as highly influential because of the high sugars dose and the particularly small size of the effect. Since the results of the study were counterconservative (i.e. very low responses at high sugar doses), and their impact was to flatten the dose-response, it was decided to exclude the two observations from the dose-response analysis. The final model was set up on 27 observations with sugars E% intake ranging between 6% and 30%). It indicates an expected increase in fasting TG of around 17 mg/dL (95% CI: 8.9, 25.8, $p < 0.01$) per each increase of 10E% intake from sugar with a negative estimate of the intercept (−16.70 mg/dL, 95% CI: −32.88, −0.53, $p = 0.04$). A meta-regressive non-linear dose-response relationship was also investigated using a restricted cubic spline (RCS) with three knots. The linear model was retained as the parameter entailing the quadratic component of the model was not statistically significant (**Figure 15**). In the final linear model, between-arm differences in sugars intake (E%) only accounted for around 20% of the variability across studies thus leaving most of the heterogeneity unexplained. In this context, the Panel considers that this analysis can be used to conclude on the shape and direction of the dose-response relationship, but not to make a quantitative prediction of the effect of added or free sugars on fasting levels of triglycerides. The Panel notes that RCTs showing the highest absolute difference in fasting triglycerides between arms for the same difference in sugars intake were conducted in subjects with obesity, hypertriglyceridaemia or hyperinsulinaemia. These are represented by points outside the upper bound of the 95% CI in **Figure 15**. The technical report can be found in **Annex L**.

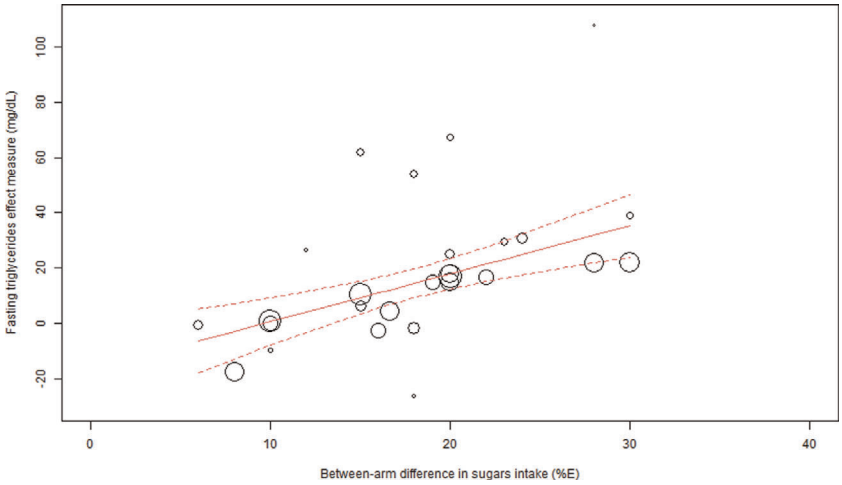


Figure 15: Meta-regressive dose-response linear model between the intake of added and free sugars (E%) and fasting triglycerides

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. RCTs. There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and risk of obesity (moderate certainty, sQ2.1, Section 8.2.2.1) and for a positive and causal relationship between the intake of added and free sugars *ad libitum* or in isocaloric exchange with other macronutrients and risk of T2DM (low certainty, sQ2.3, Section 8.4.2.1).

Consistency across LoE. The effect on total TG was consistent with the effect on total-c and LDL-c, particularly in RCTs conducted under neutral energy balance in isocaloric exchange with starch, where the macronutrient composition and P/S ratio were controlled for, whereas HDL-c was minimally affected (LoE2). It is also consistent with an increased risk of obesity (LoE3) and T2DM (LoE4).

Table 22: sQ2.4. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty that the intake of **added and free sugars** is positively and causally associated with the risk of dyslipidaemia at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?

BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint:** fasting TG **23 RCTs (29 study groups), 1,086 participants**. Pooled mean effect estimate (95% CI) = 14.59 mg/dL (7.16, 22.02) for all studies combined, assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be lower. **(Appendix G, Figure G.6d1)**.	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	12 studies in tier 1; 11 studies tier 2 (**Appendix I, Figure I.4**) Between low and moderate. Key questions: • Randomisation: low • Exposure assessment: low • Outcome assessment: low Probably high for allocation concealment and blinding	Serious
Unexplained inconsistency	High heterogeneity. I^2 = 81% (p < 0.01) for the pooled mean effect. Point estimates vary widely, and 95% CI show minimal overlap. Residual heterogeneity in dose-response analysis is high (Cochran Q-test=66.39) and statistically significant. Between-arm difference in sugars intake (E%) only accounted for 24% of the variability across studies.	Very serious
Indirectness	Surrogate endpoint	Serious
Imprecision	Low. It could be higher because the expected correlation coefficient for this endpoint is < 0.82, but still low **(Appendix G, Figure G.6d1)**.	Not serious
Publication bias	Funnel plot shows a slight association between the magnitude of the effect and the SE, and Egger's test was significant (p = 0.004), suggesting a risk of publication bias (**Appendix H, Figure H.4**). However, there is some indication for true heterogeneity in small studies. Public (n = 5), private (n = 5), mixed (n = 5) and NR (n = 8) funding.	Undetected
Upgrading factors	Dose-response: two RCTs reported linear dose-response relationships for fructose (doses between 0 and 15E%) and sucrose (doses between 2 and 30E%) in men with hyperinsulinaemia. In the meta-regression dose-response analysis, a between-arm difference in added sugars intake of at least 9.6E% is needed to predict a positive effect on fasting TG. Any further increase of 10E% in the between-arm difference in added sugars intake leads to an increase in fasting TG of 17mg/dL (linear dose-response). Consistency: The effect on TG is consistent with the effect on total-c and LDL-c, particularly in RCTs conducted under neutral energy balance in isocaloric exchange with starch, where the macronutrient composition and P/S ratio were controlled for. It is also consistent with a positive and causal relationship between the intake of added and free sugars ad libitum and risk of obesity (LoE3; **moderate** certainty) and with a positive and causal relationship between the intake of added and free sugars ad libitum or in isocaloric exchange with other macronutrients risk of T2DM (LoE4; **low** certainty).	Yes (dose-response and consistency)
Final certainty	Started high, downgraded two levels for heterogeneity and one level for indirectness, upgraded one level for dose-response and one level for consistency. RoB was not considered sufficiently serious to downgrade because it was between low and moderate but low for the three key questions.	**Moderate (> 50–75% probability)**

Conclusions sQ2.4. RCTs. The level of certainty in a positive and causal relationship between the intake of added and free sugars and risk of dyslipidaemia is **moderate** (rationale in **Table 22**). The effect is particularly observed under neutral energy balance in isocaloric exchange with starch while controlling for the macronutrient composition and P/S ratio of the diet. RCTs included only adults. About half of the RCTs were in overweight/obese subjects and three included a group of hyperinsulinaemic individuals. Between-arm differences in added and free sugars intake were between 6 and 43E%.

8.5.2.2. Observational studies

LoE2. Standalone (surrogate): Changes in total-c, LDL-c, TG, HDL-c or derived indices. PCs. Three PCs studies on the relationship between the intake of added sugars (NGHS, (Lee et al., 2014)) or sucrose (CARDIA, (Archer et al., 1998); NSHDS, (Winkvist et al., 2017)) and blood lipids were available. Two report on changes in HDL-c and one on changes in total cholesterol and fasting TG. All PCs analysed the exposure as a continuous variable and used the nutrient density model for energy adjustment, but only the NGHS included TEI in the models as a covariate. Evidence table is in **Annex J**.

Preliminary UA

In the NGHS cohort of black and Caucasian female adolescents, HDL-c was significantly higher by 0.26 mg/dL per year (95% CI: 0.04, 0.48; p = 0.02) in the group consuming < 10E% as added sugars vs. the group consuming > 10E% over the 10-year follow-up (RoB tier 1). This was mostly due to an increase in HDL-c in the first group, whereas HDL-c concentrations in the second group were virtually unchanged. Similar results were obtained for sucrose in the CARDIA cohort of young black and white males and females. A negative association was observed between the intake of sucrose and HDL-c concentrations in both ethnicities and sexes over the 7-year follow-up. The relationship was statistically significant in all groups except black males. Per each 10E% increase in sucrose intake, mean reductions in HDL-c ranged between 0.3 and 0.04 mmol/L (SE between 0.01 and 0.02) (RoB tier 2). Sucrose intake was not significantly associated with changes in total cholesterol (positive) or fasting TG (negative) in the large NSHDS cohort of middle age Swedish males and females followed-up for 10 years (RoB tier 2).

Critical domains across studies in the RoB assessment were confounding and attrition (**Annex K**).

The Panel notes the small number of PCs available and the different blood lipid fractions assessed. Whereas added sugars and sucrose were negatively associated with HDL-c in the NGHS and CARDIA cohorts, both studies were at probably high risk of bias for confounding. The Panel considers the available BoE from PCs does not suggest a positive relationship between the intake of added and free sugars and adverse effects on blood lipids. **No comprehensive UA is performed**.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. PCs. The available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ2.1, Section 8.2.2.2) or risk of T2DM (sQ1.3, Section 8.4.2.2).

sQ2.4. PCs. The available BoE does not suggest a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and risk of dyslipidaemia.

8.5.2.3. Overall conclusion on sQ2.4

There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars and risk of dyslipidaemia (**moderate** level of certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

8.5.3. Fructose

sQ3.4. Fructose and risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Changes in total-c, LDL-c, TG, HDL-c or derived indices	**10**	**1**
LoE3. Complementary	Risk of obesity	sQ3.1	sQ3.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus	sQ3.3	sQ3.3

8.5.3.1. Intervention studies

LoE2. Standalone (surrogate): Changes in total-c, LDL-c, TG, HDL-c or derived indices RCTs. A total of seven RCTs (9 study groups) assessed the effect of fructose vs. glucose on fasting TG under different dietary conditions (under neutral or positive energy balance, ad libitum), of which six also reported on total-c, LDL-c and HDL-c **(Appendix G, Figures G.7a–G.7d)**. Doses of fructose and glucose ranged from 9 to 25 E% and study duration between 4 and 10 weeks. All RCTs were in adults selected based on BMI (overweight obese, BMI < 32 or 35 kg/m^2), glucose tolerance status (NGT, IGT) or liver fat (NAFLD).

Three additional RCTs investigated the effect of doses of fructose between 15 and 20E% in isocaloric exchange with starch under neutral energy balance **(Appendix G, Figures G.6a–G.6d)**. Study duration was between 4 and 5 weeks. One study (Swanson et al., 1992) was in healthy males and females, whereas two RCTs were in males and included one group with normoinsulinaemia and one group with hyperinsulinaemia (Hallfrisch et al., 1983a; Reiser et al., 1989a).

Preliminary UA

The results of the RCTs assessing the effect of fructose vs. glucose were mixed (**Appendix F**). Pooled effect estimates (95%CI) were 1.5mg/dL (−2.97, 6.10) for total-c **(Appendix G, Figure G.7a)**, −0.03 mg/dL (−1.64, 1.59) for LDL-c **(Appendix G, Figure G.7b)**, −0.29 mg/dL (−1.25, 0.68) for HDL-c **(Appendix G, Figure G.7c)** and 4.25 mg/dL (−7.68, 16.17) for fasting TG **(Appendix G, Figure G.7d)**. The only RCT which showed a consistent significant effect of fructose vs. glucose across the blood lipid profile was conducted at doses of 22 E% with beverages in positive energy balance (Silbernagel et al., 2011). RoB was low for five studies (tier 1) and moderate for two (tier 2). Overall, these studies do not suggest a positive relationship between fructose in isocaloric exchange with glucose and adverse effects on blood lipids.

Conversely, fructose consistently increased total-c, LDL-c, HDL-c and fasting TG when consumed in isocaloric exchange with starch under neutral energy balance in the three RCTs which investigated this relationship (Reiser et al., 1989a)*(Hallfrisch et al., 1983a; Swanson et al., 1992)*. The effect on fasting TG was particularly marked in men with hyperinsulinaemia (Reiser et al., 1989a)*(Hallfrisch et al., 1983a)*; **Appendix G, Figure G.6d**), which are at higher risk for developing T2DM. A positive dose-response relationship between the intake of fructose (at doses of 0, 7.5 and 15 E%) in isocaloric exchange with starch and fasting TGs was reported by (Hallfrisch et al., 1983a)* in this population subgroup.

The Panel notes that RCTs investigating the effect of fructose in isocaloric exchange with starch were part of the BoE used to reach conclusions on a positive and causal relationship between the intake of added (and free sugars) and risk of dyslipidaemia and considers that the same conclusions apply, since the type of sugar used in the studies (fructose, mixtures of fructose and glucose) was not a significant modifying factor (see Section 8.5.2.1). The Panel also considers that the available BoE from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of dyslipidaemia. **No comprehensive UA is performed**.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. RCTs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity (sQ3.1, Section 8.2.3.1) or T2DM (sQ3.3, Section 8.4.3.1).

Conclusion sQ3.4. RCTs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of dyslipidaemia. The Panel considers, however, that the conclusions for a positive and causal relationship between the intake of added and free sugars and risk of dyslipidaemia also apply to fructose in isocaloric exchange with starch (**moderate** certainty).

8.5.3.2. Observational studies

LoE2. Standalone (surrogate): Total-c, LDL-c, TG, HDL-c or derived indices. PCs. Only one PC investigated the relationship between fructose intake and changes in blood lipids (fasting TG and HDL-c). In the TLGS cohort of males and females (Bahadoran et al., 2017) each 1E% from fructose was associated with non-significant mean increase in fasting TG of 0.310 mg/dL (95% CI: −0.521, 1.145) and with a significant mean decrease in HDL-c of −0.297 mg/dL (95% CI: −0.410, −0.184). This study, however, was at high RoB (tier 3) and at definitively high RoB for confounding (i.e. the only variable included in the model was age).

The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and adverse effects on blood lipids.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. PCs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of obesity (sQ3.1, Section 8.2.3.2) or risk of T2DM (sQ3.3, Section 8.4.3.2).

Conclusion sQ3.4. PCs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of dyslipidaemia.

8.5.3.3. Overall conclusion on sQ3.4

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fructose in isocaloric exchange with glucose or other macronutrients and risk of dyslipidaemia. The Panel considers, however, that the conclusions for a positive and causal relationship between the intake of added and free sugars and risk of dyslipidaemia also apply to fructose in isocaloric exchange with starch (**moderate** certainty).

8.5.4. Sugar-sweetened beverages

sQ4.4. SSBs and risk of dyslipidaemia

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**5**
LoE2. Standalone (surrogate)	Changes in total-c, LDL-c, TG, HDL-c or derived indices	**7**	**4**
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3

8.5.4.1. Intervention studies

LoE2. Standalone (surrogate): Changes in total-c, LDL-c, TG, HDL-c or derived indices. RCTs. Of the 24 RCTs which investigated the effect of high vs. low added and free sugars intake on changes in total cholesterol (see Section 8.5.2.1), seven were conducted with beverages. The same studies also investigated changes in LDL-cholesterol, HDL-cholesterol and fasting TG, except for Campos et al., 2015, which did not report on LDL-cholesterol. The between-group target difference in sugars intake from beverages was between 8 and 22 E% and study duration from 4 to 36 weeks. Two studies were under neutral energy balance and the other five were conducted ad libitum. Six RCTs were in adults selected based on BMI (overweight, obese and BMI < 35 kg/m^2) and one in healthy subjects (**Appendix F**).

Preliminary UA

The results of RCTs comparing a high sugar dose from SSBs to a lower one, or to a sugar-free alternative, were mixed for all blood lipids. At the end of the intervention, total cholesterol was higher in the high sugar arm relative to the low sugar arm in two studies, lower in three and null in the other two. The pooled mean effect estimate (95%CI) for these studies was −0.30 mg/dL (−14.02, 13.41; I^2 = 90%) (**Appendix G**, **Figure G.6a2**). The results on LDL-c, HDL-c and fasting TG followed a similar pattern. The pooled mean effect estimates (95%CI) are −2.50 mg/dL (−13.52, 8.52; I^2 = 87%) (**Appendix G**, **Figure G.6b2**), 0.16 mg/dL (−1.69, 2.01; I^2 = 78%) (**Appendix G**, **Figure G.6c2**) and 6.10 mg/dL (−12.43, 24.64; I^2 = 88%) (**Appendix G**, **Figure G.6d2**), respectively. There was high heterogeneity across the studies. Three RCTs were at low RoB (tier 1) and four at moderate RoB (tier 2) (**Appendix I, Table I.4**).

The Panel considers that the available BoE from RCTs does not suggest a positive relationship between consumption of SSBs and adverse effects on blood lipids. The Panel notes, however, that most studies were conducted ad libitum and thus did not control for the lipid profile of the diet. This is consistent with the fact that the strongest relationship between the intake of added and free sugars and adverse effects on blood lipids was observed in RCTs conducted at neutral energy balance in isocaloric exchange with starch while controlling for the macronutrient composition and P/S ratio of the diet (see Section 8.5.2.1). **No comprehensive UA is performed**.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM. RCTs. There is evidence from RCTs for a positive and causal relationship between the intake of SSBs and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.1) and T2DM (low certainty, sQ4.3, Section 8.4.4.1).

Conclusions sQ4.4. RCTs. While there is evidence for a positive and causal relationship between consumption of SSBs and risk of obesity and T2DM, the available BoE does not suggest a positive relationship between the intake of SSBs and risk of dyslipidaemia. The Panel notes, however, that most RCTs were conducted ad libitum and thus did not control for the lipid profile of the diet.

8.5.4.2. Observational studies

LoE1. Standalone (main): Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs). **PCs**. Five PCs, four of which were in adults (KoGES, (Kang and Kim, 2017); CARDIA, (Duffey et al., 2010); Framingham-3Gen and Framingham Offspring, (Haslam et al., 2020)) and one in children and adolescents (TLGS), investigated the relationship between the intake of SSBs and incidence of high triglycerides and low HDL-cholesterol. The CARDIA, Framingham-3Gen and Framingham Offspring cohorts also investigated the relationship with incidence of high LDL-cholesterol (≥ 4.1 mmol/L). Cut-off values for high triglycerides were ≥ 1.7 mmol/L except for Framingham-3Gen and Framingham Offspring (≥ 2.0 mmol/L). Cut-off values for low HDL-cholesterol were < 1.04 mmol/L for men and < 1.3 mmol/L for women in all cohorts. The use of cholesterol-lowering medication was also considered part of the incidence case criteria in the CARDIA cohort and for subjects age > 18 years in the TLGS cohort. Evidence table can be found in **Annex J**.

The TLGS, KoGES, Framingham-3Gen and Framingham Offspring cohorts analysed SSBs as a categorical variable using the standard multivariable model for energy adjustment and the CARDIA cohort analysed the exposure as a continuous variable adjusting for non-SSBs energy intake. In both cases, TEI was not kept constant.

Preliminary UA

All PCs report positive relationships between the intake of SSBs and incidence of high TG. The positive relationship was statistically significant in the Framingham Offspring cohort. The KoGES, CARDIA, Framingham-3Gen and Framingham Offspring cohorts report a positive relationship between the intake of SSBs and incidence of low HDL-c, significant only in the CARDIA cohort. Contrariwise, in the TLGS cohort the association was negative (non-significant). In the CARDIA, Framingham-3Gen and Framingham Offspring cohorts, the relationship between the intake of SSBs and incidence of high LDL-c was positive, but statistically significant only in CARDIA.

One study was at low RoB (tier 1; Framingham Offspring), three at moderate RoB (tier 2; CARDIA, TLGS and Framingham-3Gen) and one at high RoB (tier 3; KoGES), critical domains being confounding, exposure and attrition (**Appendix L**, **Table L.10**).

The Panel notes that most PCs available report positive and non-significant relationships between the intake of SSBs and incidence of high-TG, low-HDL-c and high-LDL-c. The direction of the relationship was negative (non-significant) for low-HDL-c in the TLGS cohort of children and adolescents. The Panel considers that the available BoE supports a positive relationship between the consumption of SSBs and risk of dyslipidaemia.

Comprehensive UA

Selection of the endpoint. The Panel decided to conduct the comprehensive UA on the incidence of high fasting TG because of the higher number of studies, the consistency of the relationship, and because TG are more likely to be affected by dietary sugars (particularly fructose) than any other blood lipid fraction (see Section 3.6.1.3) **(Appendix K**, **Figure K.12)**. Pooled mean effect estimates, however, were not calculated because, out of the five PCs available, one did not report the number of cases across categories of intake (TLGS), one did not report the exposure as used for data analysis (CARDIA) and one assessed cumulative mean intakes up to diagnosis for cases and over the entire follow-up for non-cases (Framingham Offspring).

Dose-response relationship. Linear dose-response relationships across categories of SSBs intake were explored in four PCs. Significant positive linear dose-response relationships were reported only in one PC (Framingham Offspring). Dose-response relationships were not investigated by meta-regression analysis because the data required (e.g. number of cases, exposure) were not available for most PCs.

LoE2. Standalone (surrogate): Changes in total-c, LDL-c, TG, HDL-c or derived indices. PCs

Two cohorts of children (Daily-D (Van Rompay et al., 2015); WAPCS (Ambrosini et al., 2013)) and two cohorts of adults (Framingham-3Gen and Framingham Offspring, (Haslam et al., 2020)) investigated the relationship between intake of SSBs and changes in blood lipids over the follow-up. The Daily-D cohort investigated the relationship between SSBs intake at baseline, as well changes in SSBs intake and changes in TG and HDL-cholesterol over the one-year follow-up. The WAPCS cohort investigated changes in SSBs intake and concurrent changes in TG, HDL-c and LDL-c over the 3-year follow-up. The Framingham-3Gen and Framingham Offspring cohorts assessed average intakes of SSBs over a 4-year period and concurrent changes in TG, HDL-c and LDL-c. The evidence table is in **Annex J**.

The Daily-D, Framingham-3Gen and Framingham Offspring cohorts analysed SSBs as a categorical variable using the standard multivariable model for energy adjustment. Although the WAPCS cohort had not adjusted for energy intake in the multivariable models for which results were presented, associations were reported to be unchanged after additional adjustment for TEI in separate models (data not shown).

The four PCs reported positive relationships between the intake of SSBs and changes in fasting TG over follow-up, which remained statistically significant in the Framingham-3Gen and Framingham Offspring cohorts after adjusting for relevant confounders. Similarly, the relationship between SSBs intake and changes in HDL-c was negative in all PCs and statistically significant in all but for females in the WAPCS. The results for LDL-c were mixed in the three PCs which assessed this endpoint (Framingham-3Gen, Framingham Offspring, WAPCS).

The WAPCS, Framingham-3Gen and Framingham Offspring cohorts were at low RoB (tier 1) and the Daily-D cohort at moderate RoB (tier 2), critical domains being exposure and attrition (**Annex K**).

The Panel notes the consistency of the results across PCs regarding the positive and negative relationships between the intake of SSBs and changes in fasting TG and HDL-c, respectively, and that most studies were at low RoB (tier 1). The Panel considers that the available BoE from PCs suggests a positive relationship between the intake SSBs and adverse effects on blood lipids.

Complementary LoE3: Risk of obesity and LoE4: Risk of T2DM (sQ4.1). PCs. There is evidence from PCs for a positive and causal relationship between the intake of SSBs ad libitum and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.2) and T2DM (moderate certainty, sQ4.3, Section 8.4.4.2).

Consistency across LoE. An increased incidence of high-TG with higher intakes of SSBs is consistent with an increased incidence of low HDL-c, with changes in TG and HDL-c as continuous variables in the same direction, respectively, and with an increased risk of obesity and T2DM. This lipid profile (high TG, low HDL-c) is characteristic of the metabolic syndrome, a risk factor for the development of T2DM, possibly mediated by insulin resistance. Changes in LDL-c were less consistent.

Table 23: sQ4.4. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty that the intake of SSBs is positively and causally associated with the risk of dyslipidaemia at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint:** incidence of high TG **5 PCs, 12,660 participants**. Pooled mean effect estimates were not calculated because the data required were not available from the individual PCs.	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	1 PC in tier 1; 3 PCs in tier 2, 1 PC in tier 3 **(Appendix L, Table L.10)** Generally moderate. Key questions: • Exposure assessment: between low and probably high • Outcome assessment: low • Confounding: between low and probably high Probably high for attrition	Serious

Unexplained inconsistency	All PCs report positive relationships between the intake of SSBs and incidence of high TG.	Not serious
Indirectness	Direct endpoint	Not serious
Imprecision	High in most studies	Serious
Publication bias	Few studies available, also heterogeneous. It cannot be assessed. Public (n = 4) and mixed (n = 1) funding.	Undetected (cannot be assessed)
Upgrading factors	Consistency: An increased incidence of high TG with higher intakes of SSBs is consistent with an increased incidence of low HDL-c, with changes in TG and HDL-c as continuous variables in the same direction, respectively, and with an increased risk of obesity and T2DM. This lipid profile (high TG, low HDL-c) is characteristic of the metabolic syndrome, a risk factor for the development of T2DM, possibly mediated by insulin resistance. Changes in LDL-c were less consistent.	Yes (consistency)
Final certainty	Started moderate, downgraded for RoB (one level) and imprecision (one level), upgraded for consistency (one level).	**Low (> 15–50% probability)**

Conclusions sQ4.4. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of dyslipidaemia is **low** (rationale in **Table 23**).

8.5.4.3. Overall conclusion on sQ4.4

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of dyslipidaemia (**low** level of certainty). The available BoE from RCTs cannot be used to modify the level of certainty in this conclusion.

8.5.5. Fruit juices

sQ5.4. FJs and risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**1**
LoE2. Standalone (surrogate)	Changes in total-c, LDL-c, TG, HDL-c or derived indices	0	0
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3

8.5.5.1. Intervention studies

No RCTs were eligible for sQ5.4.

8.5.5.2. Observational studies

LoE1. Standalone (main): Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs). PCs

Only one PC investigated the relationship between FJs intake and incidence of high triglycerides, high LDL-cholesterol and low HDL-cholesterol (CARDIA, (Duffey et al., 2010)). The evidence table is in **Annex J**.

Preliminary UA

No significant relationships were observed between the intake of FJs at baseline and incidence of high TG (negative), high LDL-c (positive) or low HDL-c (null) at the end of the 20-year follow-up. The study was at moderate RoB (tier 2), critical domains being confounding and attrition (**Annex K**).

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of FJs and incidence of high TG, high LDL-c or low HDL-c. **No comprehensive UA is performed**.

Complementary LoE3: Risk of obesity and LoE 4: T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of obesity (very low certainty sQ5.1, Section 8.2.5.1) and T2DM (moderate certainty, sQ5.3, Section 8.4.5.1).

Conclusions sQ5.4. PCs. While there is evidence for a positive and causal relationship between consumption of FJs and risk of obesity and T2DM, the available BoE does not suggest a positive relationship between the intake of FJs and risk of dyslipidaemia.

8.5.5.3. Overall conclusion on sQ5.4

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of FJs and risk of dyslipidaemia.

8.6. Risk of hypertension

8.6.1. Total sugars

sQ1.5. Total sugars and risk of hypertension

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	Changes in SBP and/or DBP	0	**1**
LoE3. Complementary	Incidence of hyperuricaemia/changes in uric acid	0	0
LoE4. Complementary	Risk of obesity	sQ1.1	sQ1.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus	sQ1.3	sQ1.3

8.6.1.1. Intervention studies

No RCTs were eligible for sQ1.5.

8.6.1.2. Observational studies

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. PCs.

One PC (SCES, (Gopinath et al., 2012)) investigated the relationship between total sugars intake and BP in adolescents of both sexes. The evidence table is in **Annex J**.

Preliminary UA

The SCES cohort reports a positive association between changes in total sugar intake and concurrent changes in BP over the 5-year follow-up (statistically significant in females only), both in the crude model and after adjusting for relevant covariates, which included TEI and baseline BP. The study was at low RoB (tier 1), with attrition being the only critical domain. The Panel notes, however, that only one PC with about 500 participants is available.

The Panel considers that the available BoE does not suggest a positive association between the intake of total sugars in isocaloric exchange with other macronutrients and an increased risk of obesity.

LoE4 (sQ1.1). Complementary: Risk of obesity. PCs. The available evidence does not suggest a positive association between the intake of total sugars in isocaloric exchange with other macronutrients and an increased risk of obesity.

LoE5 (sQ1.3). Complementary: Risk of T2DM. PCs. The available evidence does not suggest a positive association between the intake of total sugars in isocaloric exchange with other macronutrients and an increased risk of type 2 diabetes mellitus.

sQ1.5. PCs. The Panel considers the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of hypertension.

8.6.1.3. Overall conclusion on sQ1.5

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of hypertension. Total sugars were not investigated under other dietary conditions (e.g. not keeping TEI constant).

8.6.2. Added and free sugars

sQ2.5. Added and free sugars and risk of hypertension

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	Changes in SBP and/or DBP	**10**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/ uric acid	0/7	0
LoE4. Complementary	Risk of obesity	sQ2.1	sQ2.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus	sQ2.3	sQ2.3

8.6.2.1. Intervention studies

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. RCTs. The effect of high vs. low added sugar intakes on changes in blood pressure was investigated in 10 intervention studies (11 study groups), four of which had the sugar source as beverages, two as solid foods and the remaining four as combinations of beverages and solid foods. Between-arm differences in added sugar intakes ranged from 10 to 28 E%, and study duration between 6 and 36 weeks (**Appendix F**). Five RCTs were ad libitum and five were conducted under neutral energy balance, most in isocaloric exchange with starch. Two RCTs selected subjects based on serum insulin concentrations (were on, or included one group of, hyperinsulinaemic individuals) and the remaining on the basis of BMI cut-offs (five were in overweight/obese individuals, one in non-obese and two in subjects with BMI < 35 kg/m^2).

Preliminary UA

Seven RCTs found SBP to be higher in the high vs. the low sugar arm, whereas three studies (four study groups) showed the opposite (**Appendix G**, **Figure G.8a1**). The pooled mean effect estimate (95% CI) for SBP is 1.47 mmHg (−0.75, 3.68, I^2 = 83%). The pooled mean effect estimate (95% CI) for studies under neutral energy balance in isocaloric exchange with starch is 0.47 mmHg (−2.60, 3.55, I^2 = 82%) and for RCTs conducted ad libitum is 2.77 mmHg (−0.72, 6.26, I^2 = 85%). A similar pattern was observed for DBP (**Appendix G**, **Figure G.8b1**), with the pooled mean effect estimate (95% CI) being 1.48 mmHg (−0.05, 3.00, I^2 = 73%). Three RCTs were at low RoB (tier 1) and seven at moderate RoB (tier 2).

The Panel considers that the available BoE suggests a positive relationship between the intake of added and free sugars and risk of hypertension.

Comprehensive UA

Selection of the endpoint. The Panel decided to conduct the comprehensive UA on SBP because SBP, rather than DBP, is used for CVD risk stratification owing to its higher predictive value (Graham et al., 2007).

Dose-response relationship. It was not investigated in individual RCTs. No meta-regression analysis could be performed owing to the small number of RCTs available. Visual inspection of the forest plots does not suggest a dose-response relationship.

LoE3. Complementary: Incidence of hyperuricaemia/uric acid. RCTs. A total of seven RCTs (8 study groups) investigated the effect of high vs. low sugar intake on uric acid, four of which also report on blood pressure (Israel et al., 1983; Maersk et al., 2012; Lowndes et al., 2014b; Campos et al., 2015) (Appendix F). Between-arm differences in added sugar intakes that ranged from 16 to 30E%. Except for Lowndes et al. (2014b) and Campos et al. (2015), which found no differences between the two sugar arms, uric acid levels were higher in the high sugar arm relative to low sugar arm. The pooled mean effect estimate (95% CI) is 0.39 mg/dL (0.14, 0.64, I^2 = 59%) (**Appendix G**, **Figure G.10a**). Pooled mean effect estimates (95%CI) are similar for studies conducted in isocaloric exchange with starch at neutral energy balance (0.35 mg/dL (0.03, 0.68), I^2 = 69%) and for studies conducted ad libitum (0.47 mg/dL (0.03, 0.91), I^2 = 41%). Mean differences in body weight change between the high and low sugar arms ranged between −4.1 and 2.3 kg when these were reported and were apparently unrelated to changes in uric acid (**Appendix G**, **Figure G.10a**).

The Panel considers that the available BoE suggests a positive relationship between the intake of added sugars at doses between 16 to 30E% and uric acid levels, both when consumed ad libitum and in isocaloric exchange with starch. The effect appears to be independent of changes in body weight.

Complementary LoE4: Risk of obesity and LoE5: Risk of T2DM. RCTs. The is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars and risk of obesity (moderate certainty, sQ2.1, Section 8.2.2.1) and T2DM (low certainty, sQ2.3, Section 8.4.2.1).

Consistency across LoE. Changes in SBP are consistent with changes in DBP, with changes in uric acid and consistent with an increased risk of obesity and T2DM.

Table 24: sQ2.5. RCTs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty that the intake of added and free sugars is positively and causally associated with the risk of hypertension at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE2. Standalone (surrogate). Endpoint:** SBP **10 RCTs (11 study groups), 568 participants**. Pooled mean effect estimate (95%CI) = 1.47 mmHg (−0.75, 3.68) assuming a within-subject correlation coefficient of 0.82. The correlation coefficient for this endpoint is expected to be close to that value. (**Appendix G**, **Figure G.8a1**)	**Initial certainty: High (> 75–100% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	3 studies in tier 1; 7 studies tier 2 (**Appendix I**, **Figure I.5**) Generally moderate. Key questions: • Randomisation: generally low • Exposure assessment: generally low • Outcome assessment: between low and probably high Probably high for allocation concealment and blinding	Serious
Unexplained inconsistency	High heterogeneity. I^2 = 83% for the pooled mean effect. Point estimates vary widely, and 95% CI show minimal overlap.	Very serious
Indirectness	Surrogate endpoint	Serious
Imprecision	High. The 95%CI includes 0 and thus the possibility of a beneficial (rather than adverse) effect. **(Appendix G**, **Figure G.8a1)**	Serious
Publication bias	Funnel plot does not suggest a high risk of publication bias and the Egger's test was not significant (p = 0.209) **(Appendix H**, **Figure H.5)** Private (n = 5), mixed (n = 2) and NR (n = 3) funding.	Undetected
Upgrading factors	Consistency: Changes in SBP are consistent with changes in DBP, with changes in uric acid and consistent with an increased risk of obesity and T2DM.	Yes (consistency)
Final certainty	Started high, downgraded one level for RoB, one level for heterogeneity, one level for indirectness and one level for imprecision; upgraded one level for consistency.	**Very low (0–15% probability)**

Conclusions sQ2.5. **RCTs**. The level of certainty in a positive and causal relationship between the intake of added and free sugars and risk of hypertension is **very low** (rationale in **Table 24**). RCTs included only adults. About half of the RCTs were in overweight/obese subjects and two were in (or included a group of) hyperinsulinaemic individuals. Added and free sugars were consumed ad libitum or in isocaloric exchange with starch and between-arm differences in added and free sugars intake ranged between 10 and 28 E%.

8.6.2.2. Observational studies

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. **PCs**. Two prospective cohorts investigated the relationship between change in intake of added sugars (SCES, (Gopinath et al., 2012) or sucrose (NSHDS, (Winkvist et al., 2017)) over follow-up and concurrent changes in blood pressure. The exposure was analysed as a continuous variable using either the nutrient residuals model (SCES) or the nutrient density model (NSHDS) for analysis, and thus aimed at maintaining TEI constant. The Panel notes, however, that TEI was not included as additional factor in the model in the NSHDS cohort. The evidence table is in **Annex J**.

Preliminary UA

In the SCES cohort of adolescent males and females, a positive relationship between changes in added sugars intake and changes in SBP and DBP was observed in females. The relationship was statistically significant only for changes in DBP. Each standard deviation (27.63 g/day) increase in added sugar intake during the 5-year follow-up was concurrently related to an increase in DBP of 1.31 mmHg (SE: 0.57, $p < 0.02$). Non-significant relationships between changes in added sugars intake and SBP (negative) or DBP (positive) were reported for males.

In the NSHDS cohort, female and male adults had a mean baseline consumption of sucrose of 6.5 and 6.6E%, respectively. Each 1E% increase in sucrose intake over follow-up was related to a decrease in SBP of 0.66 mmHg (SE: 0.38, $p = 0.08$) in females and with an increase of 0.38 mmHg (SE: 0.32, $p = 0.22$) in males during the 10-year follow-up. The study did not report results for DBP.

These studies were at RoB tier 1 (SCES) and tier 3 (NSHDS), critical domains being confounding, outcome assessment and attrition (**Annex K**).

The Panel notes the paucity of data available from PCs. The Panel also notes that in the PC at low RoB, changes in SBP were inconsistent between sexes and inconsistent with changes in DBP in males.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of added sugars in isocaloric exchange with other macronutrients and BP.

Complementary LoE4: Risk of obesity and LoE5: Risk of T2DM. PCs. The available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ2.1, Section 8.2.2.2) or T2DM (sQ2.3, Section 8.4.2.2).

sQ2.5. PCs. The available BoE does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of hypertension.

8.6.2.3. Overall conclusion on sQ2.5

There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and isocaloric exchange with starch and risk of hypertension (**very low** certainty). The available BoE from PCs cannot be used to modify the level of certainty in this conclusion.

8.6.3. Fructose

sQ3.5. Fructose and risk of hypertension

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of hypertension	0	**3**
LoE2. Standalone (surrogate)	Changes in SBP and/or DBP	**5**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/5	0
LoE4. Complementary	Risk of obesity	sQ3.1	sQ3.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus	sQ3.3	sQ3.3

8.6.3.1. Intervention studies

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. RCTs. Four RCTs investigated the effects of fructose in isocaloric exchange with glucose at doses between 9 and 25 E% on blood pressure. The results of the individual studies can be found in **Appendix F**.

Preliminary UA

All RCTs except Angelopoulos et al. (2015) show a decrease in SBP and DBP with fructose relative to glucose, with a pooled mean effect estimate (95% CI) of −1.61 (−4.61, 1.38, $I^2 = 57\%$) and −2.09 mmHg (−4.30, 0.13, $I^2 = 65\%$), respectively **(Appendix G, Figures G.9a,b)**.

All these studies were at moderate RoB (tier 2), the critical domains being randomisation, allocation concealment, blinding and endpoint assessment (**Appendix I**, **Figure I.6**).

One cross-over design study investigated the effect of varying levels of fructose (0, 7.5 and 15 E%) in isocaloric exchange with starch for 5 weeks (Hallfrisch et al., 1983a)*. SBP was significantly lower with diets providing 7.5 and 15 E% from fructose than with the diet providing 0 E% from fructose ($p < 0.015$).

The Panel considers that the available evidence from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose or starch and SBP or DBP. **No comprehensive UA is performed**.

LoE3. Complementary: Incidence of hyperuricaemia/uric acid. RCTs. The same four studies that reported on the effect of fructose vs. glucose on changes in BP also report on changes in fasting uric acid levels. Uric acid levels were higher in four out of the five study groups when fructose was consumed, the effect being statistically significant only in the study by Stanhope et al. (2009) conducted ad libitum (results in Cox et al. (2012)). The exception were subjects with IGT in the study by Koh et al. (1988), which showed lower uric acid levels with fructose compared to glucose. The pooled mean effect estimate (95% CI) is 0.12 (−0.16, 0.40, I^2 = 74%). Mean differences in body weight change between the fructose and glucose arms ranged between −1.5 and 0.1 kg when these were reported, suggesting that the effect is independent of changes in body weight (**Appendix G**, **Figure G.11**).

In another study by Reiser et al. (1989a), fructose intake at 20 E% in isocaloric exchange with starch significantly increased uric acid levels in normo- and hyperinsulinaemic individuals. The mean effect (95%CI) was 0.54 mg/dL (0.19, 0.89).

The Panel considers that there is some evidence from RCTs for a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (i.e. glucose, starch) at doses between 9 and 25E% and uric acid levels. The effect appears to be independent of changes in body weight.

Complementary LoE4: Risk of obesity and LoE5: risk of T2DM. RCTs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity (sQ3.1, Section 8.2.3.1) or T2DM (low certainty, sQ3.3, Section 8.4.3.1).

Conclusions sQ3.5. RCTs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of hypertension.

8.6.3.2. Observational studies

LoE1. Standalone (main): Incidence of hypertension. PCs. Three large independent PCs of male (HPFS) and female (NHS and NHS-II) health professionals in the USA reported in the same publication (Forman et al., 2009) investigated the relationship between fructose (E%, quintiles of intake) and incidence of hypertension. Models were adjusted for both baseline BMI and TEI. TEI was kept constant in the analyses. Evidence table is in **Annex J**.

Preliminary UA

No significant relationship was found between fructose and incidence of hypertension across quintiles of intake in any cohort (most adjusted models). Median intakes ranged from about 6 E% to about 14 E% across quintiles of fructose. Duration of follow-up ranged from 14 to 20 years (**Appendix K**, **Figure K.14**). The three PCs were at low RoB (tier 1) for this endpoint and no critical domains were identified.

The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and incidence of hypertension. **No comprehensive UA is performed on this LoE**.

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. PCs. Two PCs (SCES, (Gopinath et al., 2012); TLGS, (Bahadoran et al., 2017)) investigated associations between fructose intake and changes in SBP and DBP. The evidence table is in **Annex J**.

Preliminary UA

The SCES cohort reported a statistically significant association between fructose intake and BP in female adolescents, but no association was found among males (RoB tier 1). In females, each standard deviation increase in fructose intake over the 5-year follow-up (1 SD = 14.19 g/day) was concurrently related to an increase of 1.80 mmHg (SE = 0.82; p = 0.03) in SBP and of 1.67 mmHg (SE = 0.61; p = 0.01) in DBP. In the TLGS cohort of Iranian adults with a mean baseline fructose consumption of 6.4 E%, each 1 E% of fructose intake at baseline was related to an increase of 0.217 mmHg (95% CI: 0.063 to 0.371) in SBP and 0.267 mmHg (95% CI: 0.157, 0.376) in DBP during a mean follow-up of 6.7 year. The only adjustment made in the linear regression was age (RoB tier 3).

The Panel notes that the available BoE is limited to two PCs, one of which is at high RoB.

The Panel considers that the available BoE from PCs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and blood pressure.

No comprehensive UA is performed on this LoE.

Complementary LoE4: Risk of obesity and LoE5: risk of T2DM. PCs. The available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of obesity (sQ3.1, Section 8.2.3.2) or T2DM (sQ3.3, Section 8.4.3.2).

Conclusions sQ3.5. PCs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of hypertension.

8.6.3.3. Overall conclusion on sQ3.5

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fructose in isocaloric exchange with glucose or other macronutrients and risk of hypertension.

8.6.4. Sugar-sweetened beverages

sQ4.5. SSBs and risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**7**
LoE2. Standalone (surrogate)	SBP and/or DBP	**4**	**1**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/3	1/0
LoE4. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3

8.6.4.1. Intervention studies

LoE2. Standalone (surrogate): Changes in SBP and/or DBP. RCTs. Four of the 10 intervention studies that investigated the effect of high vs. low added sugar intakes on changes in BP (see Section 8.6.2.1) were on beverages.

For SBP (**Appendix G**, **Figure G.8a2**), the variable used for the comprehensive UA, pooled mean effect estimates (95%CI) for sugars from different sources were 3.05 mmHg (−0.96, 7.06, I^2 = 91%) for beverages (n = 4, dose range 18–22E%), 2.04 mmHg (−1.98, 6.07, I^2 = 77%) for mixtures of food and beverages (n = 4, dose range = 10–23E%) and −1.14 mmHg (−4.58, 2.30, I^2 = 63%) for solid foods (n = 2, 3 study groups, dose range = 15–28E%). A similar pattern was observed for DBP (**Appendix G**, **Figure G.8b2**), with the pooled mean effect estimate (95% CI) for beverages being 2.25 mmHg (−0.70, 5.21, I^2 = 75%).

LoE3. Complementary: Incidence of hyperuricaemia/uric acid. RCTs. Out of the seven RCTs that investigated the effect of high vs. low sugar intake on uric acid levels (see Section 8.6.2.1), three were conducted with beverages (**Appendix F**). Between-arm differences in energy derived from SSBs ranged from 18 to 22E%. Uric acid levels were significantly higher in the high vs. the low sugar arm in one study conducted ad libitum, whereas no difference was observed in another RCTs conducted *ad libitum*. In the study conducted at neutral energy balance, uric acid levels were lower in the high vs. the low sugar arms. The pooled mean effect estimate (95% CI) is 0.10 mg/dL (−0.42, 0.63, I^2 = 63%) (**Appendix G**, **Figure G.10b**). One of the studies was at low RoB (tier 1) and two were at moderate RoB (tier 2).

The Panel notes the low number of RCTs available on the effect of SSBs on uric acid levels and the inconsistency of the results across studies. The Panel considers that the available BoE does not suggest a positive relationship between the intake of SSBs and uric acid levels.

Complementary LoE4: Risk of obesity and LoE5: Risk of T2DM. RCTs. There is evidence from RCTs for a positive and causal relationship between the intake of SSBs and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.1) and T2DM (low certainty, sQ4.3, Section 8.4.4.1).

Based on the available BoE from RCTs, the Panel has the same level of certainty on a positive and causal relationship between the intake of SSBs and risk of hypertension as for added and free sugars (**very low** certainty).

Conclusion sQ4.5. RCTs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of hypertension is **very low**.

8.6.4.2. Observational studies

LoE1. Standalone (main): Incidence of hypertension. PCs. Seven PCs, six in adults and one in children and adolescents (TLGS), investigated the relationship between intake of SSBs and incidence of hypertension. In five PCs (KoGES, (Kwak et al., 2018); HPFS, NHSII and NHS, (Cohen et al., 2012); SUN, (Sayon-Orea et al., 2015)) hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg or use of antihypertensive medication, whereas lower thresholds of $\geq$ 130 mmHg and $\geq$ 85 mmHg, respectively, were used in TLGS (Mirmiran et al., 2015) and the CARDIA (Duffey et al., 2010) cohort of young adults.

Six cohorts analysed SSBs as a categorical variable using the standard multivariable model for energy adjustment and one cohort (CARDIA) analysed the exposure as a continuous variable adjusting for non-SSBs energy intake. In both cases, the analysis allows for TEI to change as a function of SSBs consumption. Three cohorts (NHS, NHSII, HPFS) also investigated the relationship between ASBs and incidence of hypertension. Evidence table is in **Annex J**.

Preliminary UA

All cohorts report a positive association between the intake of SSBs and incidence of hypertension and the associations were significant in four of the seven cohorts (KoGES, NHS, NHSII, SUN). The forest plot for the six PCs in adults can be found in **Appendix K**, **Figure K.14**. The TLGS cohort in children and adolescents is not included (number of cases was not reported).

The three cohorts that analysed consumption of ASBs showed similar, or even stronger (HPFS), associations with hypertension as for SSBs. The associations were positive and statistically significant in all three cohorts. Data from these cohorts were collected and analysed using the same methodology.

Five PCs were at low RoB (tier 1), one at moderate RoB (tier 2) and one at high RoB (tier 3) (**Appendix L**, **Table L.11**).

The Panel considers that the available BoE suggests a positive relationship between the consumption of SSBs and risk of hypertension.

Comprehensive UA

Selection of the endpoint. The only eligible endpoint in this LoE is incidence of hypertension. The definition of hypertension and the methods used for the identification of cases were similar for all cohorts, except for the CARDIA and TLGS cohorts which used lower SBP and DPB thresholds for defining hypertension.

Dose-response relationship. A significant linear dose-response relationship across categories of SSBs intake was reported in five (KoGES, NHS, NHSII, SUN, TLGS) of the six PCs which performed a categorical analysis.

In the dose-response meta-analysis conducted by EFSA, parametric dose-response models were estimated based on summarised data. Both linear and non-linear (restricted cubic splines) dose-response relationships were investigated. The methodological approach applied was the same as for the dose-response meta-analyses of SSBs intake and incidence T2DM (**Annex M**).

Fourteen non-referent RRs from five study-specific analyses were included in the dose-response meta-analysis (I^2 = 70.5%; p = 0.009). The TLGS (number of incident cases not reported) and CARDIA (RR already provided per unit increase) cohorts were excluded. The predicted pooled relative risk of HTN was 1.06 (95% CI: 1.04, 1.08) for an increase in SSBs intake of 250 mL/day in the linear model (p for linear trend < 0.0001) and 1.07 (95% CI: 1.04, 1.11) at 250 mL/day in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50% and 90%, of the distribution; p for non-linearity = 0.237) (**Figure 16**). The subgroup analyses did not identify clear sources of heterogeneity, also given the limited number of studies across strata. The funnel plot and related Egger regression were not carried out as the number of studies was very limited.

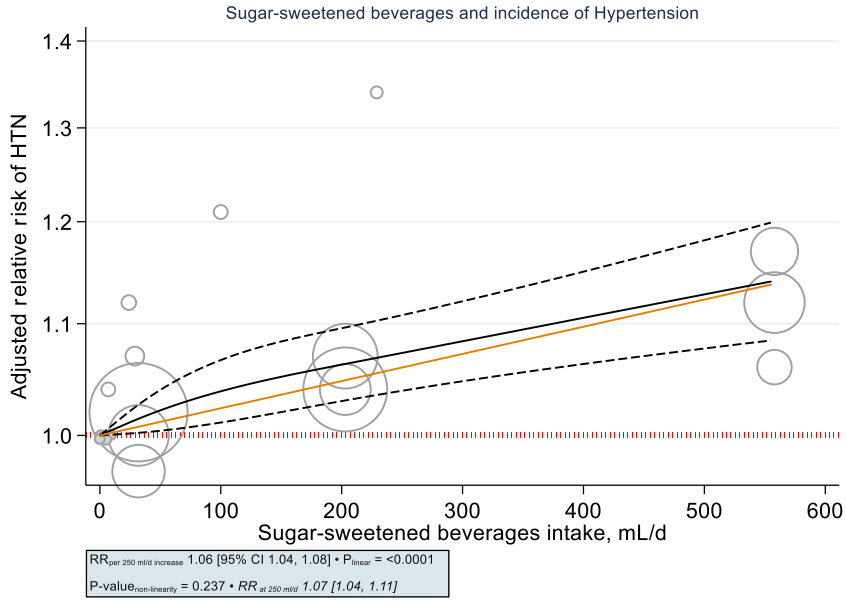


Figure 16: Dose-response meta-analysis on the relationship between the intake of sugar-sweetened beverages and incidence of hypertension (HTN)

LoE2. **Standalone (surrogate): Changes in SBP and/or DBP**. **PCs**. One PC (WAPCS, (Ambrosini et al., 2013)), investigated the relationship between changes in SSBs intake and concurrent changes in BP over the 3-year follow-up. Evidence table is in **Annex J**.

Non-significant positive (for SBP) and negative (for DBP) associations were reported for changes in BP across tertiles of increase in SSBs intake in males and females after adjusting for BMI and major dietary patterns. The authors state that these relationships were unchanged after additional adjustment for TEI in separate models (data not shown). The study was at low RoB (tier 1). The critical domain was attrition.

The Panel notes the limited evidence available from PCs. The Panel considers that the available BoE does not suggest a positive relationship between intake of SSBs and changes in BP.

LoE3. Complementary: Incidence of hyperuricaemia/uric acid. PCs. One PC (ARIC, (Bomback et al., 2010)) investigated the relationship between intake of SSBs and incidence of hyperuricaemia. SSBs were analysed as a categorical variable without adjustment for energy intake. Evidence table is in **Annex J**.

There was a positive (non-significant) association between consumption of SSBs and incidence of hyperuricaemia. In comparison to the referent category consuming less than one serving or 355 mL per day), those consuming more than one serving per day had an OR for incident hyperuricaemia of 1.17 (95% CI: 0.95, 1.43, $p = 0.1$). A negative (non-significant) relationship with incident hyperuricaemia (OR 0.97, 95% CI: 0.83, 1.14) was found for ASBs. The study was at low RoB (tier 1).

The Panel notes the paucity of data available and considers that the available BoE does not suggest a positive relationship between intake of SSBs and incidence of hyperuricaemia.

Table 25: sQ4.5. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of SSBs and the risk of hypertension at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint: incidence of hypertension** **7 PCs, 246,572 participants.** Five study-specific analyses from five PCs were included in the dose-response analysis.	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	Five PCs in tier 1; 1 PC in tier 2; 1 PC in tier 3 (**Appendix L**, **Table L.11**). Generally low Key questions: • Confounding: most probably low • Exposure assessment: most probably low • Outcome assessment: most probably low Mixed probably low and probably high for attrition The study at RoB tier 3 (TLGS) was not included in the dose-response analysis (number of cases not reported).	Not serious
Unexplained inconsistency	All PCs (n = 7) report positive relationships between the intake of SSBs and incidence of hypertension. Substantial heterogeneity (I^2 = 70.5%) for the pooled mean effect estimate of study-specific RRs per unit increase of intake. RRs are similar across large studies; small studies show higher effects, but confidence intervals overlap. No clear sources of heterogeneity identified beyond sample size.	Not serious
Indirectness	Direct endpoint	Not serious
Imprecision	Low	Not serious
Publication bias	Limited number of studies, it cannot be assessed. Public (n = 6) and mixed funding (n = 1).	Undetected (cannot be assessed)
Upgrading factors	Dose-response: A significant linear dose-response relationship across categories of SSBs intake was reported in 5 of the 6 PCs which performed a categorical analysis. The dose-response meta-analysis conducted by EFSA showed a significant linear positive dose relationship (linear pooled mean effect estimate (95%CI) = 1.06 (1.04, 1.08) for 250 mL/d increase with no support for non-linearity (p = 0.237).	Yes (dose-response)
Final certainty	Started moderate, upgraded one level for dose-response.	**High (> 75–100% probability)**

Complementary LoE4: Risk of obesity and LoE5: risk of T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.2) and T2DM (moderate certainty, sQ4.3, Section 8.4.4.2).

Consistency across LoEs. The Panel notes that an increased incidence of hypertension is consistent with an increased risk of obesity and T2DM, but very few PCs assessed endpoints for other LoEs specific to this sQ (e.g. changes in BP, incidence of hyperuricaemia).

Conclusion sQ4.5. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of hypertension is **high** (rationale in **Table 25**). The relationship was observed for SSBs not keeping TEI constant in the analysis.

8.6.4.3. Overall conclusion on sQ4.5

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of hypertension (**high** certainty). Evidence from RCTs (**very low** certainty) supports the relationship.

8.6.5. Fruit juices

sQ5.5. FJs and risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**2**
LoE2. Standalone (surrogate)	Changes in SBP and/or DBP	0	0
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3

8.6.5.1. Observational studies

LoE1. Standalone (main): Incidence of hypertension. PCs. Two PCs (CARDIA, (Duffey et al., 2010); WHI, (Auerbach et al., 2017)) investigated the relationship between FJs intake and incidence of hypertension. The CARDIA cohort analysed the exposure as a continuous variable adjusting for non-SSBs energy intake, thus not keeping TEI constant. Conversely, the WHI cohort analysed the exposure as a categorical variable using the nutrient residual (energy adjusted) model and thus kept TEI constant. In the WHI cohort, participants were considered to have incident hypertension if they initiated medication for treatment and in the CARDIA cohort either use of antihypertensive medication or BP $\geq$ 130 mmHg/$\geq$ 85 mmHg. Evidence table is in **Annex J**.

Preliminary UA

Both PCs found that the association between FJs intake and incidence of hypertension was null. The Panel notes that, in the WHI cohort, TEI was kept constant in the analysis. Both cohorts were at low RoB (tier 1).

The Panel notes the small number of studies available. The Panel considers that the available BoE does not suggest a positive relationship between intake of FJs and incidence of hypertension. **No comprehensive UA is performed**.

Complementary LoE4: Risk of obesity and LoE5: risk of T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of obesity (very low, sQ5.1, Section 8.2.5.1) and T2DM (moderate, sQ5.3, Section 8.4.5.1).

8.6.5.2. Overall conclusion on sQ5.5

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of FJs and risk of hypertension.

8.7. Risk of cardiovascular diseases

8.7.1. Total sugars

sQ1.6. Total sugars and risk of cardiovascular diseases (CVDs)			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint), CHD or stroke	0	**8**
LoE2. Complementary	Risk of obesity	sQ1.1	sQ1.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus	sQ1.3	sQ1.3
LoE4. Complementary	Risk of dyslipidaemia	sQ1.4	sQ1.4
LoE5. Complementary	Risk of hypertension	sQ1.5	sQ1.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ1.5	LoE3 for sQ1.5

8.7.1.1. Observational studies

LoE1. Standalone (main): Incidence and mortality: CVD (composite endpoint), CHD or stroke. PCs. Two publications report on the relationship between the intake of total sugars and incidence of CVDs using data from one PC (WHI) or several PCs (EPIC-Multicentre). The WHI cohort of post-menopausal women (Tasevska et al., 2018) provides results for incidence of CVD, CHD and stroke, whereas the EPIC-Multicentre study (Sieri et al., 2020) reports on incidence of CHD. For three centres included in that study (EPIC-Utrecht, EPIC-Morgen, EPICOR), results on incidence of CHD and stroke are reported in separate publications (EPIC-Utrecht: (Beulens et al., 2007), EPIC-Morgen: (Burger et al., 2011), EPICOR: (Sieri et al., 2010, 2013)). Results on incidence of CHD for these centres have not been considered in the final data set because of the overlap with the EPIC-Multicentre. The EPIC-Utrecht also reports on CVD incidence (Beulens et al., 2007).

In addition, three PCs provide results on the relationship between the intake of total sugars and mortality from CVDs, two on CVD mortality as a composite endpoint (NIH-AARP, (Tasevska et al., 2014b); Takayama, (Nagata et al., 2019)) and one on CHD mortality (SCHS, (Rebello et al., 2014)).

The cohorts involved Asian populations (Takayama, SCHS), US populations (WHI, NIH-AARP) and European populations (EPIC cohorts).

In these PCs, total sugars were analysed either as a continuous (WHI) variable, as categorical variable (all other cohorts) or both, using either the nutrient residuals (energy-adjusted) model or the nutrient density (energy-adjusted) model for energy adjustment, and thus, total sugars were investigated in isocaloric exchange with other macronutrients. The WHI also analysed the data applying energy partition models to investigate the full effect of total sugars intake on CVD risk (i.e. the energy and non-energy contribution of the nutrient while keeping energy intake from other nutrients constant). All PCs included BMI in most-adjusted models. The evidence table is in **Annex J**.

Preliminary UA

CVD (incidence and mortality). Results on the relationship between total sugars intake and CVD (composite endpoint) were mixed in the four PCs reporting on this endpoint. The relationship was positive and non-significant in the NIH-AARP (mortality) for males and females, positive and significant for males and null for females in the Takayama (mortality), null for the EPIC-Utrecht cohort of females and negative (non-significant) in the WHI cohort (incidence). These data are plotted in **Appendix K**, **Figure K.15a**.

CHD (incidence and mortality). A positive and significant relationship between total sugars intake and CHD (incidence) was observed in the EPIC-Multicentre study. Conversely, negative relationships were reported in the WHI (incidence) and the SCHS (mortality) cohorts. The negative relationship was statistically significant for males in the SCHS (**Appendix K**, **Figure K.15b**).

Stroke (incidence). The results on incidence of stroke in the three EPIC centres reporting on this endpoint were mixed. The relationship was positive and non-significant in EPICOR for males and females combined, null for males and negative, non-significant for females in EPIC-Morgen and null for the female-only cohort of EPIC-Utrecht. A negative (non-significant) association between the intake of total sugars and incidence of stroke was reported in the WHI cohort (**Appendix K**, **Figure K.15b**).

Six out of the eight PCs were at low risk of bias (tier 1; EPIC-Multicentre, EPIC-Utrecht, EPIC-Morgen, EPICOR, NIH-AARP, SCHS) and two at moderate RoB (tier 2; WHI and Takayama) for all the endpoints assessed in each study. Critical domains were exposure and outcome assessment (Takayama) and outcome assessment and attrition (WHI) (**Appendix L**, **Table L.12**).

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: risk of hypertension. PCs. The available BoE does not support a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ1.1, Section 8.2.1.1), T2DM (sQ1.3, Section 8.4.1.1), dyslipidaemia (sQ1.4, Section 8.5.1.1) or hypertension (sQ1.5, Section 8.6.1.2).

The Panel notes that most PCs report null or negative relationships between the intake of total sugars and incidence of stroke, and that these PCs were mostly at low RoB. The Panel also notes that, for CHD and CVD (composite endpoint), the results were mixed across cohorts.

For CHD, the Panel considers that the EPIC-Multicentre study is most relevant to the present assessment because it consists of a pooled analysis of data from 23 centres representing eight European countries, including males and females 35–70 years of age. RR (95%CI) for the highest vs. the lowest quartile of total sugars intake (energy-adjusted intakes using the residual method = ≤ 77.2 g/day and > 129.3 g/day, respectively) was 1.24 (1.09, 1.40). The RR per each 50 g/day

increase in total sugars was 1.09 (1.02, 1.17). When pooled effect estimates were calculated by country (continuous analysis), heterogeneity was found to be low (I^2 = 29.6%) and results varied across countries, with five countries reporting a positive association, two reporting a negative association and one where the relationship was null. The Panel notes that this study was at low RoB (tier 1). The Panel also notes, however, that these results are inconsistent with data from two other cohorts included in the assessment (WHI, SCHS) which show a negative relationship between the intake of total sugars and CHD, and are not supported by PCs on the relationship between total sugars and CVD risk or risk factors for CVDs (namely obesity, T2DM, dyslipidaemia and hypertension).

The Panel therefore considers that the available evidence does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and incidence of CHD. **No comprehensive UA is performed**.

Conclusion sQ1.6. PCs. The Panel considers the available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of CVDs.

8.7.1.2. Overall conclusion on sQ1.6

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of CVDs. Total sugars were not investigated under other dietary conditions (e.g. not keeping TEI constant).

8.7.2. Added and free sugars

sQ2.6. Added and free sugars and risk of cardiovascular diseases

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity	sQ2.1	sQ2.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus	sQ2.3	sQ2.3
LoE4. Complementary	Risk of dyslipidaemia	sQ2.4	sQ2.4
LoE5. Complementary	Risk of hypertension	sQ2.5	sQ2.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ2.5	LoE3 for sQ2.5

8.7.2.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ2.6.

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: Risk of hypertension. RCTs. There is evidence for a positive and causal relationship between the intake of added and free sugars and risk of obesity (**moderate**, sQ2.1, Section 8.2.2.1), T2DM (**low**, sQ2.3, Section 8.4.2.1), dyslipidaemia (**moderate**, sQ2.4, Section 8.5.2.1) and hypertension (**very low**, sQ2.5, Section 8.6.2.1).

Complementary LoE6 (LoE3 for sQ2.5): Incidence of hyperuricaemia/uric acid. RCTs. There is evidence for a positive relationship between the intake of added sugars at doses between 16 to 30E% and uric acid levels, both when consumed ad libitum and in isocaloric exchange with starch. The effect appears to be independent of changes in body weight.

Conclusion sQ2.6. RCTs. Although there is some evidence for a positive and causal relationship between the intake of added and free sugars and adverse effects on established risk factors for cardiovascular diseases (i.e. body weight, glucose metabolism, blood lipids, blood pressure and uric acid), no RCTs on cardiovascular disease endpoints are available. In the absence of data from standalone LoEs, the available BoE from RCTs **cannot be used to conclude** on a positive relationship between the intake of added or free sugars and risk of cardiovascular diseases (see Section 8.1.3).

8.7.2.2. Observational studies

LoE1. Standalone (main): Incidence and mortality: CVD (composite endpoint), CHD or stroke. PCs. Three PCs investigated CVD (composite endpoint) in relation to the intake of added or free sugars (Mr and Ms Os, (Liu et al., 2018)), sucrose (MDCS, (Sonestedt et al., 2015)) and added sugars or sucrose (NIH-AARP, (Tasevska et al., 2014b) expressed as E% or in g/1,000 kcal across quintiles of intake. Of these, one (MDCS) reports on CVD incidence and two (Mr and Ms Os, NIH-AARP) on CVD mortality. The MDCS cohort also investigated sucrose in relation to the incidence of CHD and ischaemic stroke. The evidence table is in **Annex J**.

The three PCs analysed the exposure as categorical variable and used the energy density (energy adjusted) model or the residual model to account for TEI, and thus investigated sugars in isocaloric exchange with other macronutrients.

Preliminary UA

CVD (incidence and mortality). Negative and non-significant associations between the intake of added sugars, free sugars or sucrose and incidence of fatal CVD were reported in Mr and Ms Os and NIH-AARP cohorts. This was also the case for major sources of added sugars, including beverages, in the Mr and Ms Os cohort. Most adjusted models included TEI, dietary factors, BMI and other risk factors for CVD. In the MDCS cohort (Sonestedt et al., 2015), a positive but non-significant association was found between sucrose intake and incidence of CVD ($HR_{Q5\ vs.\ Q1}$: 1.08; 95% CI: 0.96, 1.21; P-trend = 0.18).

CHD, ischaemic stroke (incidence). When investigating the association with CHD or stroke separately (Warfa et al., 2016) in the MDCS cohort, sucrose intake was positively and significantly associated with the incidence of CHD ($HR_{Q5\ vs.\ Q1}$: 1.37; 95% CI: 1.13, 1.66; P-trend = 0.008). A non-linear dose-response relationship between sucrose intake and risk of coronary events was modelled using a restricted cubic spline with four knots and the median sucrose intake (8.2 E%) as reference. This analysis indicated that the coronary event risk associated with sucrose intake increased above the median intake, with statistically significant levels above 13 E% from sucrose. Conversely, the relationship between sucrose intake and incidence of ischaemic stroke was negative and non-significant (HR_{Q5} vs. Q1: 0.94; 95% CI: 0.77, 1.14; P-trend = 0.66).

The three PCs were a low RoB (tier 1) for all the exposures and endpoints assessed (**Annex K**).

The Panel notes that, whereas negative and non-significant associations are reported between the intake of added and free sugars (and sucrose as a proxy) and CVD mortality (Mr and Ms Os, NIH-AARP), a positive relationship was observed between the intake of sucrose and incidence of CVD mostly driven by a positive and significant relationship with the incidence of CHD (MDCS). However, the Panel also notes that only one PC is available for that exposure and endpoint. The Panel considers that the available BoE does not suggest a positive relationship between the intake of added or free sugars and risk of CVD. **No comprehensive UA is performed**.

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: Risk of hypertension. PCs. The available BoE does not support a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ2.1, Section 8.2.2.2), T2DM (sQ2.3, Section 8.4.2.2), dyslipidaemia (sQ2.4, Section 8.5.2.2) or hypertension (sQ2.5, Section 8.6.2.2).

Conclusions sQ2.6. PCs. The Panel considers that the available BoE does not support a positive relationship between the intake of added and free sugars in isocaloric exchange with other macronutrients and risk of CVD.

8.7.2.3. Overall conclusions on sQ2.6

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of CVD.

8.7.3. Fructose

sQ3.6. Fructose and risk of cardiovascular diseases

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**

sQ3.6. Fructose and risk of cardiovascular diseases			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE2. Complementary	Risk of obesity	sQ3.1	sQ3.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus	sQ3.3	sQ3.3
LoE4. Complementary	Risk of dyslipidaemia	sQ3.4	sQ3.4
LoE5. Complementary	Risk of hypertension	sQ3.5	sQ3.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ3.5	LoE3 for sQ3.5

8.7.3.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ3.6.

Complementary LoE4: risk of obesity, LoE5: risk of T2DM, LoE6: risk of dyslipidaemia and LoE7: Risk of hypertension. RCTs. The available BoE does not support a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity (sQ3.1, Section 8.2.3.1), T2DM (sQ3.3, Section 8.4.3.1), dyslipidaemia (sQ3.4, Section 8.5.3.1) or hypertension (sQ3.5, Section 8.6.3.1).

LoE8 (LoE3 for sQ3.5). **Complementary: Risk of incidence of hyperuricaemia/uric acid. RCTs**. There is some evidence from RCTs for a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (i.e. glucose, starch) at doses between 9 and 25E% and uric acid levels. The effect appears to be independent of changes in body weight.

Conclusion sQ3.6. RCTs. The Panel considers that the available BoE does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (glucose, starch) and risk of cardiovascular diseases.

8.7.3.2. Observational studies

LoE1. Standalone (main): Incidence and mortality: CVD (composite endpoint), CHD or stroke. PCs. Three PCs investigated CVD (composite endpoint) in relation to the intake of fructose expressed as E% or in g/1,000 kcal across categories of intake. Of these, one (TLGS; (Bahadoran et al., 2017)) reports on CVD incidence and two (NIH-AARP, (Tasevska et al., 2014b); Takayama; (Nagata et al., 2019)) on CVD mortality. The evidence table is in **Annex J**.

The three PCs analysed the exposure as categorical variable and used the energy density (energy adjusted) model to account to TEI, and thus investigated fructose in isocaloric exchange with other macronutrients. TLGS also analysed fructose as a continuous variable.

Preliminary UA

CVD (incidence and mortality). The three PCs report positive relationships between the intake of fructose and risk of CVD (incidence or mortality). The relationship was statistically significant in the TLGS cohort (incidence, males and females combined) and in the NIH-AARP and Takayama cohorts (mortality) for males only (**Appendix K, Figure K.16a**). In the NIH-AARP, fructose from solid foods was negatively associated with the incidence of fatal CVD, whereas the relationship was positive for fructose from beverages. These relationships were statistically significant for both males and females. The TLGS cohort also reported results for added and naturally occurring fructose separately. Similarly to the relationship with total fructose, a statistically significant positive association was observed for added fructose ($HR_{T3\ vs.\ T1}$ = 1.80, 95%CI: 1.04, 3.12), while the relationship with naturally occurring fructose was positive but non-significant ($HR_{T3\ vs.\ T1}$ = 1.19, 95%CI: 0.69, 2.05). The cohorts widely differed in the number of participants (2,369 in TLGS; 29,079 in Takayama; 353,751 in NIH-AARP), the length of follow-up (6.7 years in TLGS vs. 13 and 14 years in the NIH-AARP and Takayama, respectively) and the range of fructose intake (median intakes in the highest categories for the Takayama cohort corresponded to the lowest categories of intake for the NIH-AARP and TLGS cohorts). The strongest association was reported for the smaller study (TLGS) with the shortest follow-up, in which the number of cases was small (**Appendix K, Figure K.16a**).

These PCs were at low (RoB tier 1; NIH-AARP), moderate (RoB tier 2; Takayama) and high (RoB tier 3; TLGS) risk of bias. Critical domains were confounding, exposure and outcome assessment. The heat map is in **Appendix L, Table L.13**.

The Panel considers that the available evidence suggests a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of CVD.

Comprehensive UA

Selection of the endpoint. The only endpoint in this LoE for which data are available is CVD (composite endpoint). The pooled mean effect estimate of study-specific HRs for the highest vs. the lowest categories of intake is 1.11 (1.01, 1.21; I^2 = 31.7%) (**Appendix K, Figure K.16b**).

Dose-response relationship. Significant linear positive dose-response relationships were reported in two (TLGS, Takayama males only) out of the three PCs available. Dose-response relationships were not investigated across the BoE owing to the limited number of PCs available.

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: risk of hypertension. PCs. The available BoE does not support a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of obesity (sQ3.1, Section 8.2.3.2), T2DM (sQ3.3, Section 8.4.3.2), dyslipidaemia (sQ3.4, Section 8.5.3.2) or hypertension (sQ3.5, Section 8.6.3.2).

Consistency across LoE. An increased risk of CVD with increasing intakes of fructose in isocaloric exchange with other macronutrients is not supported by the results of PCs on the relationship between fructose intake and risk factors for CVDs (namely obesity, T2DM, dyslipidaemia and hypertension).

Table 26: sQ3.6. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of fructose and the risk of CVDs at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint: CVD (composite endpoint)** **3 PCs, 385,199 participants**. Pooled mean effect estimate (HR and 95%CI) on five estimates from three PCs = 1.11 (1.01, 1.21), I^2 = 31.7% **(Appendix K, Figure K16.b)**	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	1 PCs in tier 1; 1 PC in tier 2; 1 PC in tier 3 (**Appendix L, Table L.13**). Generally moderate Key questions: • Confounding: most probably low • Exposure assessment: most probably high • Outcome assessment: most probably high	Serious
Unexplained inconsistency	All 3 PCs report positive relationships between the intake of fructose and CVD (incidence or mortality). Heterogeneity for the pooled mean effect estimate of study-specific HRs for the highest vs. the lowest categories of intake was low (I^2 = 31.7%).	Not serious
Indirectness	Direct endpoint	Not serious
Imprecision	Low	Not serious
Publication bias	Limited number of studies, it cannot be assessed. Public funding (n = 3).	Undetected (cannot be assessed)
Upgrading factors	None	No
Final certainty	Started moderate, downgraded one level for RoB.	**Low (> 15–50% probability)**

Conclusion sQ3.6. PCs. The level of certainty in a positive and causal relationship between the intake of fructose and risk of cardiovascular diseases is **low** (rationale in **Table 26**).

8.7.3.3. Overall conclusion on sQ3.6

There is evidence from PCs for a positive and causal relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of cardiovascular diseases (**low** certainty). The available BoE from RCTs cannot be used to modify the level of certainty in this conclusion.

8.7.4. Sugar-sweetened beverages

sQ4.6. SSBs and risk of cardiovascular diseases

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**9**
LoE2. Complementary	Risk of obesity	sQ4.1	sQ4.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus	sQ4.3	sQ4.3
LoE4. Complementary	Risk of dyslipidaemia	sQ4.4	sQ4.4
LoE5. Complementary	Risk of hypertension	sQ4.5	sQ4.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ4.5	LoE3 for sQ4.5

8.7.4.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ4.6.

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: Risk of hypertension. RCTs. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate**, sQ4.1, Section 8.2.4.1), T2DM (**low**, sQ4.3, Section 8.4.4.1) and hypertension (**very low**, sQ4.5, Section 8.6.4.1), whereas the available BoE from RCTs does not support a positive relationship with the risk of dyslipidaemia (sQ4.4, Section 8.5.4.1).

Complementary LoE6 (LoE3 for sQ4.5): Incidence of hyperuricaemia/uric acid. RCTs. The available BoE does not suggest a positive relationship between the intake of SSBs and uric acid levels.

Conclusion sQ4.6. RCTs. Although there is some evidence for a positive and causal relationship between the intake of SSBs and adverse effects on risk factors for cardiovascular diseases (i.e. body weight, glucose metabolism and blood pressure), no RCTs cardiovascular disease endpoints are available. In the absence of data from standalone LoEs, the available BoE from RCTs **cannot be used to conclude** on a positive relationship between the intake of SSBs and risk of cardiovascular diseases (see Section 8.1.3).

8.7.4.2. Observational studies

LoE1. Standalone (main): Incidence and mortality: CVD (composite endpoint), CHD or stroke. PCs. Five PCs report on the relationship between SSBs consumption and CVD (composite endpoint) incidence (MDCS, (Sonestedt et al., 2015); CTS, (Pacheco et al., 2020)) or mortality (EPIC-Multicentre, (Mullee et al., 2019); NHS and HPFS, (Malik et al., 2019)), of which MDCS, CTS and EPIC-Multicentre also have CHD and stroke as separate endpoints and NHS, HPFS also report on incidence of stroke in separate publications (Bernstein et al., 2012). The EPIC-Multicentre includes data from seven European countries. The HPP (Keller et al., 2020), a pooled analysis of seven individual studies and REGARDS (Collin et al., 2019) report on CHD incidence and mortality, respectively, whereas the JPHC (Eshak et al., 2012) has incidence of CHD and stroke as endpoints. The Framingham-Offspring (Pase et al., 2017) reports on stroke incidence. The EPIC-Multicentre also provides results on the relationship between the intake of ASBs and all the endpoints assessed in relation to SSBs, whereas the NHS and HPFS only assess ASBs in relation to stroke incidence (Bernstein et al., 2012).

Most studies analyse the exposure as a categorical variable using the standard multivariate model for energy adjustment, and thus do not keep TEI constant. Exceptions are the MDCS, which used the nutrient residuals (energy-adjusted model) and the REGARDS, which used the energy density model with no further adjustment for energy. All studies include BMI as covariate in the adjustment strategy. The HPP, REGARDS, NHS and HPFS also provide a continuous analysis using the standard multivariate (energy-adjusted) model or nutrient density model (REGARDS), thus keeping TEI constant. Evidence tables are in **Annex J**.

Preliminary UA

CVD (incidence and mortality). Four (CTS, EPIC-Multicentre, NHS, HPFS) of the five PCs which investigate the relationship between SSBs and CVD (composite endpoint) report a positive association, which was statistically significant in the CTS and NHS cohorts. The exception is the MDCS cohort, in which TEI was kept constant in the analysis (**Appendix K**, **Figure K.17a1**). The pooled mean effect estimate (95%CI) of study-specific HR for the highest vs. the lowest categories of intake is 1.15 (1.03, 1.29), I^2 = 66.1% (**Appendix K**, **Figure K.17a2**).

In the EPIC-Multicentre, the relationship between the intake of ASBs and CVD mortality was stronger than for SSBs and statistically significant. The HR (95%CI) for the highest vs. the lowest categories of intake were 1.52 (1.30, 1.78) and 1.11 (0.95, 1.30), respectively. In the NHS and HPFS, the relationship between the intake of ASBs and CVD mortality was similar to that for SSBs, and statistically significant in the NHS. The HR (95%CI) for the highest vs. the lowest categories of ASBs intake was 1.43 (1.10, 1.87; P_{trend} = 0.02) and 1.21 (0.86, 1.70; P_{trend} = 0.23), in the NHS and HPFS, respectively.

CHD (incidence and mortality). Among the six studies reporting on this endpoint, three show a positive (non-significant) relationships between the intake of SSBs and CHD (HPP, REGARDS, CTS) and in three the relationship is close to the null (MDCS, JPHC, EPIC-Multicentre) (**Appendix K**, **Figure K.17b1**). The pooled mean effect estimate (95%CI) of study-specific HR for the highest vs. the lowest categories of intake is 1.08 (1.00, 1.18), I^2 = 0% (**Appendix K**, **Figure K.17b2**).

In the EPIC-Multicentre, the relationship between the intake of ASBs and CHD fmortality was positive and statistically significant. The HR (95%CI) for the highest vs. the lowest categories of intake for SSBs and ASBs were 1.04 (0.87, 1.23; p per trend = 0.84) and 1.41 (1.11, 1.79; p per trend = 0.003), respectively.

Stroke (incidence and mortality). A positive relationship between the intake of SSBs and stroke is reported in four PCs (CTS, JPHC in females, NHS, HPFS, EPIC-Multicentre; statistically significant in CTS), whereas in one PC the relationship was close to null (MDCS) and it was negative in another two (Framingham-Offspring and JPHC; statistically significant only in males in JPHC) (**Appendix K**, **Figure K.17c1**). The pooled mean effect estimate (95%CI) of study-specific HR for the highest vs. the lowest categories of intake is 1.07 (0.96, 1.19), I^2 = 45.9% (**Appendix K**, **Figure K.17c1**). The Framingham-Offspring also reports on ischaemic stroke and observes a similar association as for total stroke. The HPFS and NHS also report on ischaemic and haemorrhagic stroke separately. The association with haemorrhagic stroke is negative in both studies, whereas the association with ischaemic stroke is positive in the NHS and null in the HPFS. When SSBs intake was analysed as a continuous variable, the positive association with incidence of total stroke and ischaemic stroke was statistically significant in the NHS and positive (non-significant) for haemorrhagic stroke in the HPFS.

The relationship between ASBs and stroke was similar to that of SSBs in three PCs which reported on this exposure (positive and non-significant; EPIC-Multicentre, NHS and HPFS). In the Framingham-Offspring, which reports a negative relationship between the intake of SSBs and incidence of stroke, the association was positive for ASBs [HR (95%CI) $_{C3\ vs.\ C1}$**:** 1.97 (1.10, 3.55) for 'recent intake'; HR (95%CI) $_{C3\ vs.\ C1}$: 1.79 (0.91, 3.52) for 'cumulative intake']. The relationship between the intake of ASBs and incidence of ischaemic and haemorrhagic stroke was positive in both the HPFS and NHS, and statistically significant for ischaemic stroke in the NHS ($HR_{Qc3\ vs.\ non\text{-}c}$ 1.55 (95% CI: 1.20, 2.00); P per trend < 0.0001).

Five out of the nine PCs were at low RoB (tier 1; HPFS, JPHC, MDCS, NHS, Framingham-Offspring), two at moderate RoB (tier 2; CTS, HPP) and two at high RoB (tier 3; EPIC-Multicentre, REGARDS) for all the endpoints assessed in each study (**Appendix L**, **Table L.14**). Critical domains were exposure and outcome assessment and confounding for PCs in RoB tier 3.

In sensitivity analyses excluding studies at high RoB (tier 3, EPIC-Multicentre, REGARDS) the pooled mean effect estimates of study-specific HRs (95%CI) for the highest vs. the lowest categories of intake for CVD (composite endpoint), CHD and stroke were 1.17 (1.01, 1.35), 1.07 (0.98, 1.18) and 1.04 (0.92, 1.18), respectively.

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and risk of CVDs.

Comprehensive UA

Selection of the endpoint. The Panel decided to conduct the comprehensive UA on CVD (composite endpoint) owing to the consistency of the results across cohorts, the higher precision of the pooled mean effect estimates as compared to either CHD or stroke and the fact that these two endpoints are the major components of the CVD composite endpoint.

Dose-response relationship. A positive linear dose-response relationship was observed in three (CTS, HPFS, NHS) out of the five PCs in categorical analyses.

In the dose-response meta-analysis conducted by EFSA, parametric dose-response models were estimated based on summarised data. Both linear and non-linear (restricted cubic splines) dose-response relationships were investigated. The methodological approach applied was the same as for the dose-response meta-analyses of SSBs intake and incidence of T2DM (see Section 8.6.4.2 and **Annex M**).

Fifteen RRs from four study-specific analyses were included in the dose-response meta-analysis (I^2 = 0%; p = 552). The MDCS cohort was excluded (model diagnostics). The predicted pooled relative risk of CVD (composite endpoint) was 1.06 (95% CI: 1.04, 1.09) for an increase in SSBs intake of 250 mL/day in the linear model (p for linear trend < 0.0001), and 1.07 (95% CI: 1.03, 1.11) at 250 mL/day in the non-linear model (RCS with three knots at fixed percentiles, 10%, 50% and 90%, of the distribution; p for non-linearity = 0.800) (**Figure 17**). The subgroup analyses did not identify clear sources of heterogeneity, also given the limited number of studies across strata. The funnel plot and related Egger regression were not carried out as the number of studies was very limited.

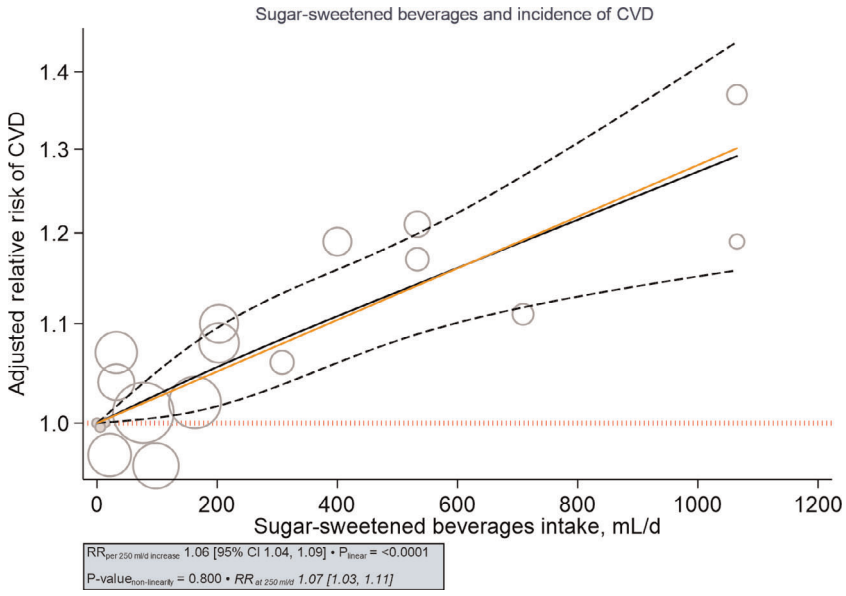


Figure 17: Dose-response meta-analysis on the relationship between the intake of sugar-sweetened beverages and risk of cardiovascular disease (CVD) – composite endpoint

Complementary LoE2: risk of obesity, LoE3: risk of T2DM, LoE4: risk of dyslipidaemia and LoE5: Risk of hypertension. PCs. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate**, sQ4.1, Section 8.2.4.2), T2DM (**high**, sQ4.3, Section 8.4.4.2), dyslipidaemia (**low**, sQ4.4, Section 8.5.4.2) and hypertension (**high**, sQ4.5, Section 8.6.4.2).

Consistency across LoE. The positive relationship between the intake of SSBs and risk of CVD (composite endpoint) is supported by the positive association between the intake of SSBs and risk of CHD and stroke, and by PCs on risk factors for CVDs, namely obesity, T2DM, dyslipidaemia and hypertension.

Table 27: sQ4.6. PCs. Comprehensive analysis of the uncertainties in the BoE and in the methods

What is the level of certainty in a positive and causal relationship between intake of SSBs and the risk of CVDs at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?		
BoE (standalone)	**LoE1. Standalone (main). Endpoint: CVD (composite endpoint)** **5 PCs, 575,966 participants.** Four study-specific analyses from four PCs were included in the dose-response analysis	**Initial certainty: Moderate (> 50–75% probability)**
Domain	**Rationale**	**Evaluation**
Risk of bias	3 PCs in tier 1; 1 PC in tier 2; 1 PC in tier 3 (**Appendix L**, **Table L.14**).	Serious

	Generally moderate Key questions: • Confounding: most probably low • Exposure assessment: most probably high • Outcome assessment: most probably high	
Unexplained inconsistency	Four out of the five PCs report positive relationships between the intake of SSBs and CVD (incidence or mortality). The exception is the MDCS, where TEI was kept constant in the analysis. Heterogeneity is low (I^2 = 0%) for the pooled mean effect estimate of study-specific RRs per unit increase of intake. RRs are similar across studies. No clear sources of heterogeneity identified.	Not serious
Indirectness	Direct endpoint	Not serious
Imprecision	Low	Not serious
Publication bias	Limited number of studies, it cannot be assessed. Public funding (n = 5).	Undetected (cannot be assessed)
Upgrading factors	**Dose-response relationship.** A significant linear dose-response relationship across categories of SSBs intake was reported in 3 of the 5 PCs which performed a categorical analysis. The dose-response meta-analysis conducted by EFSA showed a significant linear positive dose relationship (linear pooled mean effect estimate (95%CI) = 1.06 (1.04, 1.09) for 250 mL/d increase with no support for non-linearity (p = 0.800). In sensitivity analysis, exclusion of the PC at high RoB (tier 3) had a negligible impact on the dose-response relationship (**Annex M**). **Consistency across LoE.** The positive relationship between the intake of SSBs and risk of CVD (composite endpoint) is supported by the positive association between the intake of SSBs and risk of CHD and stroke, and by PCs on risk factors for CVDs, namely obesity, T2DM, dyslipidaemia and hypertension.	Yes (dose-response and consistency across LoE)
Final certainty	Started moderate, downgraded for RoB (one level); upgraded for consistency (one level) and dose-response (one level).	**High (> 75–100% probability)**

Conclusion sQ4.6. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of CVDs is **high** (rationale in **Table 27**). The relationship was observed for SSBs not keeping TEI constant.

8.7.4.3. Overall conclusion sQ4.6

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of CVDs (**high** level of certainty).

8.7.5. Fruit juices

sQ5.6. FJs and risk of cardiovascular diseases

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity	sQ5.1	sQ5.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus	sQ5.3	sQ5.3
LoE4. Complementary	Risk of dyslipidaemia	sQ5.4	sQ5.4
LoE5. Complementary	Risk of hypertension	sQ5.5	sQ5.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ5.5	LoE3 for sQ5.5

8.7.5.1. Observational studies

LoE1. Standalone (main): Incidence and mortality: CVD (composite endpoint), CHD or stroke. PCs. The MDCS (Sonestedt et al., 2015) reports on incidence of CVD, CHD and ischaemic stroke in relation to the intake of FJs. The NHS and HPFS report on the relationship between the

intake of FJs and incidence of ischaemic stroke (Joshipura et al., 1999). In the MDCS cohort, FJs was analysed as a categorical variable using the nutrient residuals model to adjust for energy intake, and thus was assessed keeping TEI constant across tertiles of intake vs. non-consumers (reference category). In the NHS and HPFS, FJs was analysed both as a categorical and continuous variable, using the multivariable model to adjust for TEI, thus keeping TEI constant. The evidence table is in **Annex J**.

Preliminary UA

The intake of FJs was unrelated to the incidence of CVD, CHD or ischaemic stroke in the MDCS cohort. In the NHS and HPFS, the intake of FJs was inversely related to the incidence of ischaemic stroke, significant in the NHS only.

The MDCS and HPFS were at low RoB (tier 1). The NHS was at moderate RoB (tier 2), with the critical domain being outcome and attrition (**Annex K**).

The Panel considers that the available BoE does not support a positive relationship between the intake of FJs and risk of CVDs. **No comprehensive UA is performed**.

Conclusion sQ5.6. PCs. The available BoE does not support a positive relationship between the intake of FJs and risk of CVDs.

8.7.5.2. Overall conclusion on sQ5.6

Since no studies were available for standalone LoEs in relation to this sQ, the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of FJs and risk of CVDs.

8.8. Risk of gout

8.8.1. Total sugars

sQ1.7. Total sugars and risk of gout

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ1.5	LoE3 for sQ1.5
LoE3. Complementary	Risk of obesity	sQ1.1	sQ1.1

8.8.1.1. Observational studies

No PCs were eligible for standalone LoEs in relation to sQ1.7.

LoE3 (sQ1.1). **Complementary: Risk of obesity. PCs**. The available evidence does not suggest a positive association between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity.

Conclusion sQ1.7. PCs The available evidence does not suggest a positive association between the intake of total sugars in isocaloric exchange with other macronutrients and risk of gout.

8.8.1.2. Overall conclusion on sQ1.7

Since no studies were available for standalone LoEs in relation to this sQ, the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars and risk of gout.

8.8.2. Added and free sugars

sQ2.7. Added and free sugars and risk of gout

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ2.5	LoE3 for sQ2.5
LoE3. Complementary	Risk of obesity	sQ2.1	sQ2.1

8.8.2.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ2.7.

LoE2 (LoE3 for sQ2.5). **Complementary: Incidence of hyperuricaemia/uric acid. RCTs**. There is evidence from RCTs for a positive relationship between the intake of added sugars and uric acid levels, both when consumed ad libitum and in isocaloric exchange with starch. The effect appears to be independent of changes in body weight.

LoE3 (sQ2.1). **Complementary: Risk of obesity. RCTs**. There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars ad libitum and risk of obesity (**moderate** level of certainty).

Conclusion sQ2.7. RCTs. Whereas there is evidence from RCTs for a positive relationship between the intake of added and free sugars and both uric acid levels and risk of obesity, which are established risk factors for gout, no RCTs on incidence of gout are available. In the absence of data from standalone LoEs, the available BoE from RCTs **cannot be used to conclude** on a positive relationship between the intake of added or free sugars and risk of gout (see Section 8.1.3).

8.8.2.2. Observational studies

No PCs were eligible for standalone LoEs in relation to sQ2.7.

LoE3 (sQ2.1). **Complementary: Risk of obesity. PCs**. The available evidence from PCs does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of obesity.

Conclusion sQ2.7. PCs. The available evidence from PCs does not suggest a positive relationship between the intake of added or free sugars in isocaloric exchange with other macronutrients and risk of gout.

8.8.2.3. Overall conclusions on sQ2.7

Since no studies were available for standalone LoEs in relation to this sQ, the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of added or free sugars and risk of gout.

8.8.3. Fructose

sQ3.7. Fructose and risk of gout

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ3.5	LoE3 for sQ3.5
LoE3. Complementary	Risk of obesity	sQ3.1	sQ3.1

8.8.3.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ3.7.

LoE2 (LoE3 for sQ3.5). **Complementary: Incidence of hyperuricaemia/uric acid. RCTs**. There is some evidence from RCTs for a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (i.e. glucose, starch) and uric acid levels. The effect appears to be independent of changes in body weight.

LoE3 (sQ1.3). **Complementary: Risk of obesity. RCTs**. The available evidence from RCTs does not suggest a positive relationship between the intake of fructose in isocaloric exchange with glucose and risk of obesity.

Conclusion sQ3.7. RCTs. Whereas there is evidence from RCTs for a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates (i.e. glucose, starch) and uric acid levels, an established risk factor for gout, no RCTs on incidence of gout are available. Therefore, the Panel considers that the available BoE from RCTs **cannot be used to conclude** on positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates and risk of gout.

8.8.3.2. Observational studies

LoE1. Standalone (main): Incidence of gout. PCs. Two PCs investigated the relationship between the consumption of total fructose and free fructose in isocaloric exchange with other macronutrients and the incidence of gout. Both studies, one in males (HPFS (Choi and Curhan, 2008)) and one in females (NHS (Choi et al., 2010)), were conducted in middle-aged health professionals living in the USA, used the same semiquantitative FFQ to assess the exposure and the same criteria to ascertain the endpoint, and considered similar confounders in multivariable models. Total and free fructose were analysed as categorical and continuous variables using the energy density (energy-adjusted) model. In addition, two energy partition models were built: one assessed total and free fructose in isocaloric exchange with fat and the second in isocaloric exchange with other carbohydrates. The evidence table is in **Annex J**.

Preliminary UA

A positive linear dose-response relationship between the consumption of total fructose and free-fructose and incidence of gout was observed in both sexes (**Annex J; Appendix K, Figures K.18a and K.18b**). Both in males and females, RRs were higher in models considering fructose in isocaloric exchange with other carbohydrates than in those considering fructose in isocaloric exchange with fat. The relationship was stronger for free fructose than for total fructose. In females, the multivariable RR for each 5 E% increment in energy intake from free fructose at baseline, compared with equivalent energy intake from other types of carbohydrates, was 1.86 (95% CI = 1.44, 2.40) and the corresponding RR for total fructose was 1.47 (95% CI = 1.20, 1.80). In males, the multivariable RR for each 5 E% increment in energy intake from free fructose, as compared with equivalent energy intake from other types of carbohydrates, was 2.10 (95% CI = 1.53–2.77), and the corresponding RR for total fructose was 1.52 (95% CI = 1.23–1.88).

In the systematic review on fructose intake and risk of gout by Jamnik et al. (2016), only these two PCs were eligible for this exposure. The pooled RR estimate (95%CI) for the highest quintile of fructose intake compared to the lowest (reference) quintile in most adjusted models considering fructose in isocaloric exchange with other carbohydrates was 1.62 (1.28, 2.03), I^2 = 0%.

HPFS was at low RoB (tier 1) and NHS at moderate RoB (tier 2), critical domains being attrition (NHS only) and outcome assessment (**Annex K**).

The Panel notes the consistency of results between sexes, the large sample size and number of cases (HPFS, n = 46,393, cases = 755; NHS, n = 78,906, cases = 778) over a long follow-up (12 and 22 years, respectively), and that the study was between low and moderate RoB.

The Panel considers that the available BoE suggests a positive relationship between the intake of fructose in isocaloric exchange with other carbohydrates and incidence of gout.

Comprehensive UA

The Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3).

The Panel notes the large sample size of the study, the long duration of follow-up, the magnitude of the effect, the low RoB and the biological plausibility of the relationship. There are indeed several mechanisms by which fructose could increase uric acid levels (see Section 3.6.1.4) and evidence from RCTs that it does in isocaloric exchange with glucose and starch (see Section 8.6.3.1). Considering the above, the Panel considers that the level of certainty in the relationship is **moderate** (> 50–75% probability).

LoE3 (sQ3.1). **Complementary: Risk of obesity. PCs**. The available evidence does not suggest a positive relationship between the intake of fructose in isocaloric exchange with other macronutrients and an increased risk of obesity.

Conclusions sQ3.7. PCs. The level of certainty in a positive and causal relationship between the intake of fructose in isocaloric exchange with other carbohydrates and risk of gout is **moderate** (>50–75% probability).

8.8.3.3. Overall conclusions for sQ3.7

There is evidence from PCs for a positive and causal relationship between the intake of fructose in isocaloric exchange with other carbohydrates and risk of gout (**moderate** certainty).

8.8.4. Sugar-sweetened beverages

sQ4.7. SSBs and risk of gout			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ4.5	LoE3 for sQ4.5
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1

8.8.4.1. Intervention studies

No RCTs were eligible for standalone LoEs in relation to sQ4.7.

LoE2 (LoE3 for sQ3.5). **Complementary: Incidence of hyperuricaemia/uric acid. RCTs**. The available BoE does not suggest a positive relationship between the intake of SSBs and uric acid levels.

LoE3 (sQ1.3). **Complementary: Risk of obesity. RCTs**. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate** certainty).

Conclusion sQ3.7. RCTs. Whereas there is evidence from RCTs for a positive relationship between the intake of SSBs and risk of obesity, an established risk factor for gout, no RCTs investigating the relationship between the intake of SSBs and incidence of gout are available. Therefore, the Panel considers that the available BoE from RCTs cannot be used to conclude on a positive relationship between the intake of SSBs and risk of gout.

8.8.4.2. Observational studies

LoE1. Standalone (main): Incidence of gout. PCs. The same two PCs which investigated the relationship between the intake of fructose and incidence of gout (see Section 8.8.3.2) also explored the relationship between the intake of SSBs (as source of fructose intake) and the intake of ASBs in relation to that endpoint (HPFS, (Choi and Curhan, 2008); NHS, (Choi et al., 2010)).

SSBs were analysed as categorical variable using standard multivariable model for energy adjustment, and thus, TEI was not kept constant in the analysis. The evidence table is in **Annex J**.

Preliminary UA

A positive linear dose-response relationship between the consumption of SSBs and incidence of gout was observed in both sexes across categories of intake (**Appendix K**, **Figure K.19**), whereas no association was found between the intake of ASBs and incidence of gout. In the systematic review on fructose intake and risk of gout by Ayoub-Charette et al. (2019), only these two PCs were eligible for this exposure. The pooled RR estimate (95%CI) for the highest (> 2 servings per day) category of SSBs intake compared to the lowest (reference, < 1 serving per month; serving size = 355mL) in most adjusted models was 2.08 (95%CI = 1.28, 2.03), I^2 = 0%.

As for fructose, HPFS was at low RoB (tier 1) and NHS at moderate RoB (tier 2), critical domains being attrition (NHS only) and outcome assessment (**Annex K**).

The Panel notes the consistency of results between sexes, the large sample size and number of cases over a long follow-up, and that the study was between low and moderate RoB. The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and incidence of gout.

Comprehensive UA

As for fructose, the Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3).

LoE2. **Complementary** (**LoE3 for sQ4.5): Incidence of hyperuricaemia/uric acid. PCs**. The available BoE does not suggest a positive relationship between intake of SSBs and incidence of hyperuricaemia.

LoE3 (sQ3.1). **Complementary: Risk of obesity. PCs**. There is evidence for a positive and causal relationship between the intake of SSBs and risk of obesity (**moderate** certainty, Section 8.2.4.2).

The Panel notes the large sample size of the study, the long duration of follow-up, the large magnitude of the effect, the low RoB and the biological plausibility of the relationship. SSBs were an important contributor to fructose and free fructose intake in the study, there are several mechanisms by which fructose could increase uric acid levels (see Section 3.6.1.4) and evidence from RCTs that it does in isocaloric exchange with glucose and starch (see Section 8.6.3.1), and evidence from PCs and RCTs on a positive and causal relationship between the intake of SSBs and increased risk of obesity, a risk factor for gout. Therefore, the Panel considers that the level of certainty in the relationship is **moderate** (> 50–75% probability). The relationship is observed for SSBs consumed not keeping TEI constant in the analysis.

Conclusions sQ4.7. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of gout is **moderate**.

8.8.4.3. Overall conclusions for sQ4.7

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of gout (**moderate** certainty). Evidence from RCTs on a positive and causal relationship between the intake of SSBs ad libitum and risk of obesity, a risk factor for gout, has already been considered by the Panel when assigning this level of certainty to the relationship.

8.8.5. Fruit juices

sQ5.7. FJs and risk of gout

LoE	Endpoints	RCTs (n)	PCs (n)
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ5.5)	LoE3 for sQ5.5	LoE3 for sQ5.5
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1

8.8.5.1. Observational studies

LoE1. Standalone (main): Incidence of gout. PCs. The same two PCs which investigated the relationship between the intake of fructose (see Section 8.8.3.2) and SSBs (see Section 8.8.4.2) and incidence of gout also explored the relationship between the intake of FJs (as source of fructose intake) and that endpoint (HPFS, (Choi and Curhan, 2008); NHS, (Choi et al., 2010)).

In the HPFS, the intake of total FJs was used for analysis. Data are also reported for orange or apple juice. In the NHS, the intake of orange juice and the intake of other FJs are reported and analysed separately. For this opinion, the Panel decided to extract orange juice as the exposure of interest because it was the major contributor among juices to free fructose intake (17% vs. 2.9% for apple juice and 2.65% for other juices).

In both PCs, FJs was analysed as categorical variable using standard multivariable model for energy adjustment, and thus, TEI was not kept constant in the analysis. The evidence table is in **Annex J**.

Preliminary UA

A positive linear dose-response relationship between the consumption of FJs and incidence of gout was observed in both sexes across categories of intake (**Appendix K**, **Figure K.20**). The RR estimate (95%CI) for the highest (> 2 servings per day) category of FJs intake compared to the lowest (reference, < 1 serving per month; serving size = 177mL) in most adjusted models was 1.81 (95%CI = 1.12, 2.93) for males and 2.42 (95%CI = 1.27, 4.63) for females.

As for fructose and SSBs, HPFS was at low RoB (tier 1) and NHS at moderate RoB (tier 2), critical domains being attrition (NHS only) and outcome assessment (**Annex K**).

The Panel notes the consistency of results between sexes, the large sample size and number of cases over a long follow-up, the large magnitude of the effect and that the study was between low and moderate RoB. The Panel considers that the available BoE suggests a positive relationship between the intake of FJs and incidence of gout.

Comprehensive UA

As for fructose and SSBs, the Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3). The relationship is observed for FJs not keeping TEI constant in the analysis.

LoE3 (sQ3.1). **Complementary: Risk of obesity. PCs**. There is evidence for a positive and causal relationship between the intake of FJs and risk of obesity (**very low** certainty).

The Panel notes the large sample size of the study, the long duration of follow-up, the larger magnitude of the effect as compared to SSBs (similar RR for half of the amount), the low RoB and the biological plausibility of the relationship. FJs were an important contributor to fructose and free fructose intake in the study, there are several mechanisms by which fructose could increase uric acid levels (see Section 3.6.1.4 and evidence from RCTs that it does in isocaloric exchange with glucose and starch (see Section 8.6.3.1), and limited evidence from PCs for a positive and causal relationship between the intake of FJs (not keeping TEI constant) and increased risk of obesity, a risk factor for gout. Therefore, the Panel considers that the level of certainty in the relationship is **moderate** (> 50–75% probability). The relationship is observed for FJs not keeping TEI constant.

Conclusions sQ3.7. PCs. The level of certainty in a positive and causal relationship between the intake of FJs and risk of gout is **moderate** (> 50–75% probability).

8.8.5.2. Overall conclusions for sQ5.7

There is evidence from PCs for a positive and causal relationship between the intake of 100%FJs and risk of gout (**moderate** certainty).

8.9. Overall conclusions on hazard identification: metabolic diseases

Conclusions on the level of certainty for a positive and causal relationship for each exposure and disease endpoint by study design, as well as the overall conclusions for both study designs combined, are summarised in **Table 28**.

Table 28: Summary conclusions on the level of certainty in the body of evidence for hazard identification[1]

Exposure, study design, dietary conditions	**Disease**						
Total sugars	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
RCTs.	No data	No data	No data	No data	No data	No data	No data
PCs. Mainly keeping TEI constant in the analysis	No support	No support	No support	No support	No support	No support	No data[2]
Overall conclusion	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]
Added and free sugars	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
RCTs. Ad libitum or in isocaloric exchange with other macronutrients (mainly starch)	Moderate *(Ad libitum)*	Low	Low	Moderate *(mostly in isocaloric exchange with starch)*	Very low	No data[2]	No data[2]
PCs. Mainly keeping TEI constant in the analysis	No support	No support	No support	No support	No support	No support	No data[2]
Overall conclusion	**Moderate** *(Ad libitum)*	**Low**	**Low**	**Moderate** *(mostly in isocaloric exchange with starch)*	**Very low**	**No conclusion**[3]	**No conclusion**[3]
Fructose	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
RCTs. Isocaloric exchange with glucose	No support	No support	No support	No support	No support	No data[2]	No data[2]
PCs. Keeping TEI constant in the analysis	No support	No data[2]	No support	No support	No support	Low	Moderate
Overall conclusion	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**Low**	**Moderate**
SSBs	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
RCTs. Ad libitum or at neutral energy balance	Moderate *(Ad libitum)*	Low	Low	No support *(Ad libitum)*	Very low	No data[2]	No data[2]
PCs. Mainly not keeping TEI constant in the analysis	Moderate	No data[2]	High	Low	High	High	Moderate
Overall conclusion	**High**	**Low**	**High**	**Low**	**High**	**High**	**Moderate**
FJs	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
RCTs.	No data	No data	No data	No data	No data	No data[2]	No data

Exposure, study design, dietary conditions	Disease						
Total sugars	**Obesity**	**NAFLD**	**T2DM**	**Dyslipidaemia**	**HTN**	**CVD**	**Gout**
PCs. Mainly not keeping TEI constant in the analysis	Very low	No data[2]	Moderate	No support	No support	No support	Moderate
Overall conclusion	**Very low**	**No conclusion**[3]	**Moderate**	**No conclusion**[3]	**No conclusion**[3]	**No conclusion**[3]	**Moderate**

CVD = cardiovascular disease; HTN = hypertension; NAFLD = non-alcoholic fatty liver disease; PCs = prospective cohorts; RCTs = randomised controlled trials; T2DM = type 2 diabetes mellitus; TEI = total energy intake.

1: Levels of certainty on a positive and causal relationship are associated with the following probability ranges: high (75–100% probability), moderate (50–75%), low (15–50% probability), very low (0–15% probability).

2: No data on standalone LoEs.

3: Since no standalone LoEs passed the screening step (preliminary uncertainty analysis), the available body of evidence cannot be used to conclude on a positive and causal relationship between the exposure and the disease risk.

8.9.1. Total sugars

Total sugars intake corresponds to all mono- and disaccharides supplied by the diet. In European populations, core food groups (i.e. fresh fruits and vegetables, milk and dairy and cereal products) represent a large proportion of total sugars intake while non-core food groups such as beverages (SSBs, fruit juices), fine bakery wares and sugars and confectionery are other major contributors (see Section 4.3). The contribution of such food groups to mean total sugars intake varies across population groups and among countries (e.g. between 30% and 60% for core food groups and between 10% and 30% for beverages in most population groups except infants and toddlers), so that very different dietary patterns may lead to similar total sugars intake.

Given the complex nature of this exposure, no RCT addressed the effect of total sugars intake on health outcomes. The BoE is limited to PCs on the intake of total sugars from all relevant dietary sources, which vary widely in their nutritional profile and role in the diet.

The eligible PCs investigated the associations between total sugars intake and the risk of obesity, NAFLD, T2DM, dyslipidaemia, hypertension and CVD. TEI was generally considered a potential confounder, thus models fully accounting for TEI were applied (see Section 5). Hence, the BoE addresses the potential role of total sugars in disease risk independent of their contribution to energy intake, i.e. the inherent properties of sugars as compared to other macronutrients.

The Panel notes that one large European cohort study (EPIC-Multicentre, (Sieri et al., 2020)) reports a positive and significant linear dose-response relationship between the intake of total sugars in isocaloric exchange with other macronutrients and incidence of CHD. The results of this study, however, were at odds with the results obtained in other cohorts outside Europe and not supported by PCs on total sugars and risk factors for CHD, namely obesity, T2DM, dyslipidaemia and hypertension. Overall, the Panel considers that the available BoE from PCs does not support a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and any of the chronic metabolic diseases assessed in this opinion.

The Panel notes that total sugars intake reflects very heterogeneous food sources and dietary patterns. The Panel considers that the relative contribution of different food groups to total sugars intake may be more relevant in relation to chronic disease risk than the intake of total sugars *per se*.

8.9.2. Added and free sugars

Added sugars intake corresponds to all mono- and disaccharides added to foods as ingredients during processing or preparation at home, and sugars eaten separately or added to foods at the table; free sugars include added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates. The Panel notes that the BoE considered in this opinion does not allow comparison of health effects based on the separate classification of dietary sugars as added or free (see Sections 8.1.1 and 8.1.2).

Food groups contributing the most to the intake of added and free sugars in European countries were 'sugars and confectionery', followed by beverages (SSBs, fruit and vegetable juices) and fine bakery wares in most population groups, with high variability across countries. The main difference between the intake of added and free sugars was accounted for by juices (mostly fruit juices). In infants, children and adolescents, sweetened milk and dairy products were also major contributors to mean intakes of added and free sugars. Different from total sugars, added and free sugars mainly originate from non-core food groups, except for sweetened milk and dairy products in young consumers.

In the present assessment, mean intakes obtained using the EFSA food composition and consumption databases may be accurate for free sugars, but possibly overestimated for added sugars because all sweetening ingredients were considered to be added sugars, and thus, the difference between added and free sugars is limited to sugars from fruit and vegetable juices, and to sugars from fruit and vegetable juice concentrates, honey and syrups only when used as such by the consumer. Mean intakes estimates for both added and free sugars calculated by EFSA using the EFSA food composition database were, however, generally lower than those estimated at national level using national food composition data for the same dietary surveys.

Evidence for a positive and causal relationship between the intake of added and free sugars and risk of chronic metabolic diseases arises from RCTs that were used to investigate the effect of 'high' vs. 'low' sugars intake on surrogate disease endpoints, i.e. body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure. Because the evidence from RCTs was limited to data on

surrogate endpoints, the conclusions of the Panel assume that a sustained adverse effect on the surrogate measures over time would eventually lead to an increased risk of disease.

Evidence from PCs on disease endpoints could not be used to address this uncertainty as there was no support from PCs for a positive and causal relationship between the intake of added or free sugars and risk of chronic metabolic diseases. The BoE from PCs mostly investigated whether the consumption of added (and/or free) sugars could affect the risk of these diseases independent from a contribution to excess energy intake (i.e. intake standardised to energy for the analyses). In addition, few PCs report on the intake of added and/or free sugars from all sources. A major uncertainty in the BoE in relation to observational studies lies on the different definitions and food composition databases used to assess the intake of added and free sugars. For example, when the exact food product consumed is not specified (as the case may be when FFQs are used for the dietary assessment), or the ingredient used for sweetening purposes (e.g. sucrose, fructose, syrups, honey, fruit juice concentrates, other) is not specified, then the amount of added and free sugars originating from the different foods cannot not be accurately assigned.

Overall, the Panel concludes that the level of certainty for a positive and causal relationship between the intake of added and free sugars and risk of chronic metabolic diseases is moderate for obesity and dyslipidaemia (> 50–75% probability), low for NAFLD/NASH and T2DM (> 15–50% probability) and very low for hypertension (0–15% probability).

Although RCTs conducted in isocaloric conditions provide some evidence that the mechanism by which added and free sugars could increase liver fat, fasting glucose, fasting triglycerides and SBP may not only be mediated by energy, the Panel notes the difficulty of fully controlling for energy intake in nutrition intervention studies. Across RCTs, mean changes in body weight were of a similar order of magnitude whether the interventions aimed at modifying sugars intake were conducted ad libitum or under neutral energy balance. Data were insufficient to adequately explore the modifying effect of body weight changes in these relationships. Regarding the risk of dyslipidaemia, the relationship was more apparent in studies conducted at neutral energy balance while controlling for the macronutrient and lipid profiles of the diet than in studies ad libitum. This suggests that the (uncontrolled) impact of modifying sugars intakes ad libitum on the macronutrient and lipid profile of the background diet may have attenuated the relationship in free living conditions.

The BoE includes RCTs on mixtures of fructose and glucose in solid foods, beverages and foods and beverages combined, as well as a few studies conducted with fructose in isocaloric exchange with starch. RCTs with SSBs (and on mixtures of glucose and fructose in beverages) were a substantial part of the BoE available for added and free sugars in relation to all endpoints investigated, except blood lipids. In subgroup analysis, the effect of added and free sugars in foods and/or mixtures of foods and beverages was as strong or stronger than the effect of added and free sugars in beverages for the majority of the endpoints assessed (e.g. body weight and other measures of body fatness; fasting glucose and other measures of glucose tolerance; measures of insulin sensitivity, blood lipids, uric acid). However, these RCTs also differ in other characteristics (e.g. sugars dose, study population, duration of the intervention), so that the available data were insufficient to explore whether the source of added and free sugars could be a modifying factor of the relationship between their intake and the endpoints investigated.

Regarding the external validity of the BoE, the Panel notes that:

1) Most RCTs were conducted in adult subjects from either the general population or specific risk groups (e.g. overweight/obese, hyperinsulinaemic) including males, females or individuals both sexes combined. RCTs in children were scarce and mainly investigated the relationship between added or free sugars and measures of body weight and body fat. Data from RCTs were insufficient to explore whether age, sex or risk factors for disease could be modifying factors of the relationship between the intake of added and free sugars and the endpoints investigated.
2) Most PCs were conducted in adult subjects from the general population or convenience samples thereof (e.g. health practitioners) living in Europe, the US or Asian countries. As for RCTs, PCs in children were scarce and mainly investigated the relationship between added and/or free sugars and measures of body weight and body fat. PCs conducted in Europe were available for most of the exposure–disease relationships assessed and the results were in line with those reported in other geographical areas.

Overall, the Panel notes that the BoE has adequate external validity because it covers the target population for the assessment (i.e. the general population and subgroups thereof, including children

and individuals at risk of disease but not on pharmacological treatment for a disease, as specified in Section 5.3 of the protocol). The Panel also notes that, although age, sex and other individual factors could impact the strength of the relationships, the mechanisms by which dietary sugars could increase the risk of metabolic diseases are expected to be the same across population groups (see Section 8.9.5). Therefore, the Panel considers that the conclusions on hazard identification apply to the general European population and subgroups thereof.

Major sources of uncertainty in the BoE and in the methods used for data analysis are as follows:

1) RCTs explored the relationship between the intake of added or free sugars and surrogate but not direct disease endpoints.
2) In RCTs, between-arm differences in added or free sugars intake only refer to the dietary fraction that was manipulated by the intervention, and not necessarily to the intake of added and free sugars from all sources. This requires the assumption that the effect observed for a given change in added or free sugars intake is independent of the background intake (i.e. that moving from 10 E% to 20 E% intake from added and free sugars from all sources would have the same impact on the endpoints as moving from 20% to 30 E% intake), and that the intervention equally affects the consumption of added and free sugars from the background diet in the two study arms that are being compared.
3) Dose-response relationships across the BoE from RCTs between the intake of added and free sugars and surrogate disease endpoints could not be explored for liver fat owing to the limited number of studies available and the narrow range of sugars doses investigated, whereas no apparent dose-response relationships were observed for SBP (visual inspection of data, not formally assessed) or body weight (formally assessed). In addition, the residual heterogeneity in the positive linear dose-response relationships identified between the intake of added and free sugars and fasting glucose and fasting triglycerides was high, so that they could only be used to conclude on the direction of the linear dose-response relationship, but not to make a quantitative prediction of the effect of added and free sugars on fasting glucose or triglyceride levels.
4) Data from RCTs were insufficient to explore whether the source of added and/or free sugars could be a modifying factor of the relationship between the intake of added and free sugars and the endpoints investigated.
5) In PCs, sources of uncertainty in the BoE include the use of self-reported methods to assess the intake of added and free sugars, limitations in the food composition databases used to classify sugars as added or free, the use of sucrose as a surrogate for added and free sugars and the unclear impact that different adjustment strategies to account for possible mediators and confounders (e.g. TEI, BMI, diet quality) could have on the results.

8.9.3. Fructose

Glucose and fructose as monosaccharides are found naturally in fruits, berries, juices and some vegetables and honey. Sucrose (glucose-fructose disaccharide) is naturally present in sugar cane and sugar beet, in honey and in many vegetables, berries and fruits. Sucrose and isoglucose (a source of glucose and fructose monosaccharides) are also used as sweetening agents. Pure fructose is seldom used as sweetening agent in Europe. Intakes of fructose and its sources in European populations could not be calculated in this assessment because data on the content of single mono- and disaccharides in foods in the EFSA Nutrient Composition Database are scarce and not adequate to provide estimates of intake for individual sugar types.

Eligible PCs investigated the relationship between fructose intake from all sources and disease risk, i.e. namely risk of obesity, T2DM, dyslipidaemia, HTN, CVD and gout. The available BoE supports a positive and causal relationship between the intake of fructose in isocaloric exchange with other macronutrients and risk of gout (fructose and free fructose) and risk of CVDs (fructose from all sources), respectively. No support was found for a positive relationship with other chronic metabolic diseases. The Panel notes that fructose and glucose intakes in mixed diets are highly correlated because they share the same dietary sources, and that it is difficult to disentangle the contribution of these specific sugar types to disease risk in PCs. The relationship between the intake of glucose (and free glucose) and risk of gout or CVDs was not investigated in these PCs. In addition, contributors to fructose intake widely vary in their nutritional profile and role in the diet, and disentangling the effect of fructose *per se* from that of the food sources from which it is obtained (or from associated dietary patterns thereof) in observational studies is difficult.

Eligible RCTs investigated the effect of added fructose as monosaccharide in isocaloric exchange with added glucose as monosaccharide on surrogate disease endpoints, i.e. namely body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure. The effects of fructose and glucose on these endpoints did not appear to be different from each other. The Panel notes that there is some evidence from RCTs for a specific effect of fructose on hepatic insulin resistance and uric acid levels. The Panel also notes that the latter is a risk factor for hypertension, CVDs and gout, and that mechanisms underlying such specific effect of fructose are well-established (see Section 3.6.1.4).

Overall, the Panel concludes that the level of certainty for a positive relationship between the intake of fructose and risk of chronic metabolic disease is moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability).

Regarding the external validity of the BoE, the Panel notes that:

1) The relationships between the intake of fructose and the risk of gout and CVDs have not been investigated in European populations, and the BoE for each relationship is limited to two and three cohorts, respectively.
2) The BoE does not include studies (RCTs or PCs) in children.

In this context, the Panel notes that it is unclear whether the conclusions on the relationship between the intake of fructose from all sources and the risk of CVDs (investigated in cohorts from US, Japan and Iran) and gout (investigated in US cohorts only) could be extrapolated to European populations because several factors could affect both the direction and the strength of the association (e.g. differences in the intake of fructose as E%, in the dietary sources of fructose and/or in the associated dietary patterns; differences in the incidence of CVDs and gout).

Major sources of uncertainty in the BoE and in the methods used for data analysis are as follows:

1) RCTs explored the relationship between the intake of fructose and surrogate (but not direct) disease endpoints.
2) In RCTs comparing the effects of fructose vs. glucose, the sugar dose (as free fructose or free glucose) only refers to the dietary fraction that was manipulated with the intervention, and not necessarily to the intake of fructose and glucose from all sources.
3) In RCTs comparing the effect of different doses of fructose as monosaccharide in isocaloric exchange with starch, between-arm differences in fructose intake only refer to the dietary fraction that was manipulated with the intervention, and not to the intake of fructose from all sources. As for added and free sugars, this leads to the assumption that the effect observed for a given change in fructose intake is independent of the background intake, and that the intervention equally affects the consumption of fructose from the background diet in the two study arms that are being compared.
4) Fructose and glucose intakes (as monosaccharides or bound as sucrose) in mixed diets are highly correlated because they share the same dietary sources, and it is difficult to disentangle the contribution of these specific sugar types to disease risk in PCs.

The Panel notes the uncertainties related to the external validity of the findings in relation to the risk of CVD and gout and the difficulties to disentangle the contribution of glucose and fructose to disease risk in PCs. The Panel also notes, however, that fructose is a component of added and free sugars in mixed diets and considers that the conclusions for added and free sugars also apply to fructose in that context.

8.9.4. Sources of added and free sugars

Intakes of added and free sugars from all sources in European countries were higher in consumers of SSBs (sugar-sweetened soft drinks and sugar-sweetened fruit drinks) than in consumers of any other food group in virtually all countries and population groups. The maximum contribution of SSBs to mean intakes of added and free sugars in consumers of these beverages ranged between 40% and 60% approx. depending on the population group, with high variation across countries. A notable exception is the intake of free sugars in toddlers, which was higher in consumers of fruit juices than in consumers of any other food group. Fruit juices contributed up to 48% to the intake of free sugars in this population group (see Section 4.3).

Conclusions from RCTs on SSBs are like those for added and free sugars. RCTs on SSBs (and on mixtures of glucose and fructose in beverages) were a substantial part of the BoE available for added and free sugars in relation to all endpoints except blood lipids. In that case, the effect of added and

free sugars was observed primarily in RCTs at neutral energy balance while controlling for the macronutrient and lipid profiles of the diet as mentioned above, whereas the few RCTs available on SSBs were conducted ad libitum.

Conversely, the overall evidence from PCs on SSBs supports a positive and causal relationship between the exposure and the risk of chronic metabolic diseases, whereas this was not the case for added and free sugars from all sources. Different from added and free sugars, SSBs were analysed not keeping TEI constant. Positive and causal relationships were identified in PCs between the intake of SSBs and incidence of obesity, T2DM, dyslipidaemia, hypertension, CVDs and gout. In addition, positive linear dose-response relationships were identified across the body of evidence between the intake of SSBs and incidence of T2DM, hypertension and CVD, with no evidence of non-linearity and no major sources of heterogeneity identified among those it was possible to explore (age, sex, study location, follow-up time, categorisation of exposure, tier of reliability).

A source of uncertainty is whether these relationships could be attributed, at least in part, to the sugars fraction of the beverages. The relationship between ASBs consumption and incidence of obesity, T2DM and risk of gout was null, negative or inconsistent in the studies included that also report on this exposure, suggesting that the positive relationship observed for SSBs in relation to these endpoints could be attributed, at least in part, to the sugars fraction of the beverage. Conversely, the relationship between the consumption of ASBs and incidence of hypertension and CVDs was similar to or stronger than for SSBs in these studies, suggesting that factors other than the sugar content of these beverages may play a role (e.g. associated dietary patterns and lifestyle factors), although reverse causality (i.e. individuals at higher risk of disease switching to ASBs) cannot be excluded. The Panel wishes to reiterate that such data do not allow drawing conclusions about the relationship between the intake of ASBs and risk of chronic disease because the systematic review was not set for that purpose, ASBs being out of the scope for this assessment.

Overall, the Panel concludes that the level of certainty for a positive and causal relationship between the intake of SSBs and risk of chronic metabolic disease is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability).

The number of PCs available for FJs, a major source of free sugars, was lower than for SSBs, as were the levels of intake. Only one RCT investigating different levels of intake of free sugars from FJs was identified, thus considered insufficient to draw conclusions. Overall, the Panel concludes that the level of certainty for a positive and causal relationship between the intake of FJs and risk of chronic metabolic disease is considered to be moderate for T2DM and gout (> 50–75% probability), and very low for obesity (0–15% probability), based on data from PCs. As for SSBs, FJs were analysed in most studies not keeping TEI constant.

As for added and free sugars, most RCTs on SSBs were conducted in adult subjects from either the general population, including males, females or individuals of both sexes combined, or specific risk groups. RCTs in children were scarce and mainly investigated the relationship between SSBs and measures of body weight and body fat. Most PCs on SSBs and FJs were conducted in adult subjects from the general population or convenience samples thereof (e.g. health practitioners) living in Europe, the US or Asian countries. PCs in children mainly investigated the relationship between the intake of these beverages and measures of body weight and body fat, and the results were consistent with those in adults. PCs conducted in Europe were available for most of the exposure–disease relationships assessed (as for fructose, a notable exception are PCs investigating the incidence of gout) and the results were in line with those reported in other geographical areas. Therefore, the Panel considers that, except for the risk of gout, the BoE has good external validity and that the conclusions on hazard identification apply to the general European population and subgroups thereof.

Major sources of uncertainty in the BoE and in the methods used for data analysis are as follows:

1) The available data from RCTs were insufficient to explore whether the source of added and free sugars could be a modifying factor of the relationship between their intake and the endpoints investigated.
2) No RCTs investigating different levels of intake of free sugars from FJs could be identified.
3) The BoE from PCs does not allow exploring whether the source of dietary sugars could be a modifying factor of the relationship between their intake and the endpoints investigated. This is because most PCs exploring the relationship between different sources of dietary sugars and disease risk did not quantify sugar intakes from those sources. In that context, it was possible to estimate sugar intakes from SSBs and FJs because the variability in the

sugar content per unit of volume was relatively low at the time intake estimates were assessed in the PCs available (i.e. a mean content of 10 g of sugars per 100 mL of the beverage is assumed). However, this was not possible for sources of sugars reported as combined categories including foods or food groups with very different sugar content, and for which the relative contribution of each food or food group to the combined category was unknown (e.g. 'sweets and cakes', 'sweet beverages including milkshakes, coffee and tea', 'cereal products', 'fruit and vegetable products', 'dairy products', etc.).

4) Differences in the classification of SSBs and fruit juices across PCs, in the methods used to assess their intake, and the fact that several PCs rely on one exposure assessment at the beginning of long follow-ups, through which subjects could have changed their habits in relation to the consumption of these beverages, are sources on uncertainty.
5) Adjusting for the rest of the diet when investigating the contribution of a single food source (SSBs, FJs) to disease risk is challenging, whereas the implications of different analytical strategies (e.g. adjustment for the energy contribution or the intake of other food sources, of specific nutrients, of specific foods; adjustment for total diet scores) on the results are unclear.
6) The relationship between the consumption of ASBs and incidence of hypertension and CVDs was similar to or stronger than for SSBs in the PCs included in the assessment, which questions the role of the sugar fraction in SSBs on the development of these metabolic diseases.

8.9.5. Mode of action

Exploring the relationship between the intake of dietary sugars, an energy-containing macronutrient and risk of chronic metabolic diseases is challenging. A notable limitation in the body of evidence (BoE) is that the energy and non-energy contribution (i.e. the molecule-specific effect) of dietary sugars from one or more sources to metabolic disease risk could not be systematically addressed across studies and endpoints. On the one hand, the characterisation of the specific (non-energy related) effects of sugars was hampered by the limitations of individual studies (e.g. incomplete control for energy in RCTs, inadequate control for energy in PCs), and by the disparity of available studies in terms of the choice and characterisation of the exposure of interest, the measurement of health endpoints and the analytical strategies used for data analysis and control for mediators/confounders. On the other hand, energy-related effects of dietary sugars from one or more sources could derive from excess energy intake likely owing to their hedonic properties, as suggested by the effect of sugars on body weight in RCTs conducted ad libitum and possibly to a lower satiating effect when consumed as liquids, as suggested by PCs not keeping TEI constant in the analysis (e.g. mostly on liquid sources of sugars). However, this was not addressed in the majority of eligible PCs on dietary (total/added/free) sugars from all sources, which mostly aimed at keeping TEI constant in the analysis.

Excess energy intake leading to positive energy balance and body weight gain is one mechanism by which the intake of dietary sugars can contribute to the risk of chronic metabolic diseases (Section 3.6.1.1). There is evidence for a positive and causal relationship between the intake of added and free sugars and their liquid sources, body weight gain and risk of obesity, both from RCTs conducted ad libitum and from PCs not keeping TEI constant in the analysis. Obesity is a well-established risk factor for several chronic metabolic diseases.

The available evidence also indicates a specific effect of dietary sugars on liver fat, glucose tolerance and blood triglycerides. High intakes of dietary sugars have been shown to induce *de novo* lipogenesis in the liver and the gut, increase the secretion of TG-rich lipoprotein particles (TRL) in the circulation and decrease their clearance. In addition, high *de novo* lipogenesis can lead to ectopic fat deposition (e.g. in the liver), increase hepatic insulin resistance and impair glucose tolerance in the long term (see Sections 3.6.1.2 and 3.6.1.3). Taking together studies conducted at neutral energy balance in isocaloric exchange with starch and studies conducted ad libitum, positive linear dose-response relationships were identified between the intake of added and free sugars (mostly as mixtures of glucose and fructose) and fasting glucose and triglyceride levels in RCTs, with no evidence for non-linearity. The dietary conditions in which the studies were conducted were not identified as a major source of heterogeneity. However, unexplained heterogeneity remained high and data were insufficient to adequately explore the modifying effect of body weight changes in these relationships.

Since starch is absorbed as glucose in the bloodstream, the fructose component could have been responsible for the specific metabolic effects of added and free sugars when consumed in isocaloric

exchange with starch. Fructose has been shown to increase hepatic insulin resistance more than equivalent amounts of glucose or sucrose. In addition, there are specific mechanisms by which fructose can increase uric acid levels, a risk factor for the development of hypertension and gout. High fructose intakes lead to an increase in hepatic fructose uptake and phosphorylation to fructose-1-P, while degradation of fructose-1-P to trioses phosphate is slightly delayed. This results in a transient depletion of intrahepatic ATP stores, leading to the formation of AMP and to the degradation of purines. Fructose may also impair renal uric acid clearance and fractional excretion (see Section 3.6.1.4).

Based on the available evidence, the Panel considers that excess energy intake leading to positive energy balance and body weight gain is the main mechanism by which the intake of dietary sugars may contribute to the development of chronic metabolic diseases in free living conditions. The Panel also considers that mechanisms which are specific to sugars as found in mixed diets (i.e. *de novo* lipogenesis leading to ectopic fat deposition, increased hepatic insulin resistance and impaired glucose tolerance in the long term; increase in uric acid levels) may also play a role, particularly in positive energy balance.

8.10. Metabolic diseases: data gaps and research needs

The Panel notes that the amount of evidence available across different exposures and endpoints is very variable. Main data gaps identified in the BoE relate to the characterisation of dietary sugars in the whole diet (as total, added and free sugars; as sugar types), the quantification of sugar intakes from different sources (not only beverages) and the relationship between all these variables and chronic disease endpoints.

To that end, the use of accurate food composition databases based on food analyses, repeated measures of the exposure through the studies to assess habitual intakes the development and validation of reliable methods and (bio)markers of intake are of paramount importance.

In the context of a safety assessment, PCs allow to assess the relationship between the intake of dietary sugars and their sources and chronic disease risk in free-living conditions across wide ranges of intake, provided that possible mediators and confounders are reliably measured and accounted for. Particular attention should be paid to the analytical strategies used to account for both energy intake and BMI (or measures thereof), which could be both mediators and confounders of the relationship. The contribution of RCTs investigating the effect of dietary sugars and their sources on surrogate disease endpoints are important to establish the causality to the relationships identified in epidemiological studies, as well as to investigate the mechanisms underlying such relationships.

9. Hazard identification: pregnancy endpoints

9.1. Body of evidence

9.1.1. Intervention studies

No intervention studies were identified in relation to pregnancy-related endpoints.

9.1.2. Observational studies

Among the seven PCs eligible for this review, three investigated the relationship between the intake of dietary sugars in women in child-bearing age and incidence of gestational diabetes mellitus (GDM) (ALSWH cohort, (Looman et al., 2018); SUN cohort, (Donazar-Ezcurra et al., 2018); NHS II, (Chen et al., 2009a)) among the women who became pregnant during the follow-up of the study. These studies did not assess the intake of dietary sugars or their sources during pregnancy. The remaining four PCs investigated the relationship between the intake of dietary sugars during pregnancy and birthweight-related endpoints (Camden cohort, (Lenders et al., 1997); HSS-USA cohort (Crume et al., 2016); MoBa cohort, (Grundt et al., 2017); GeliS cohort (Günther et al., 2019)) in women recruited in the first trimester of pregnancy. The exposures of interest investigated in these studies were total sugars, SSBs and fruit juice.

Evidence tables of the observational studies on pregnancy-related endpoints can be found in **Annex J**.

9.2. Principles applied to assess the body of evidence: evidence integration and uncertainty analysis

The principles applied to assess the body of evidence are as described for metabolic diseases (Section 8.1.3), including the elements considered for preliminary and comprehensive UAs.

Table 29 summarises the subquestions for hazard identification in relation to pregnancy endpoints, the LoEs and the number of studies included by study design and exposure. Total sugars, SSBs and FJs were investigated in relation to the risk of GDM (**sQA**), whereas total sugars and SSBs were assessed in relation to the risk of adverse birth-weight-related endpoints (**sQB**).

In relation to the risk of GDM, incidence of GDM was the only eligible endpoint, and thus, there is only one standalone (main) LoE. Obesity pre-pregnancy and weight gain during pregnancy could both increase the risk of GDM. The available studies in the BoE which investigated incidence of GDM did not assess the intake of dietary sugars during pregnancy, and studies on the relationship between the intake of dietary sugars and weight gain during pregnancy have not been systematically searched for in this assessment. However, the Panel considers that the conclusions regarding the risk of obesity as assessed in the section of metabolic diseases (Section 8.2) for the general population also apply to women in child-bearing age pre-pregnancy, and thus, risk of obesity will be considered as a complementary LoE. In addition, GDM increases the risk of T2DM, and factors increasing the risk of T2DM in women of child-bearing age could also increase the risk of GDM. For this reason, risk of T2DM as assessed in the section of metabolic diseases (Section 8.4) for the general population will also be considered as a complementary LoE. These complementary LoEs, on their own, cannot answer the sQ on risk of GDM (see Section 8.1.3).

In relation to the risk of adverse birth-weight related endpoints, a standalone (main) LoE includes incidence of low birthweight (LBW), small for gestational age (SGA), high birthweight (HBW) and large for gestational age (LGA) as eligible endpoints, whereas a standalone (surrogate) LoE includes birthweight.

Table 29: Subquestions for hazard identification, lines of evidence and number of studies included by exposure and study design

sQ1. Is the intake of **total sugars** positively and causally associated with adverse pregnancy endpoints at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
sQ1.A Risk of GDM			
LoE1. Standalone (main)	Incidence of GDM	0	1
LoE2. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
sQ1.B Risk of adverse birthweight-related endpoints			
LoE1. Standalone (main)	Incidence of LBW, SGA, HBW, LGA	0	1
LoE2. Standalone (surrogate)	Birthweight	0	1
sQ2. Is the intake of **SSBs** positively and causally associated with adverse pregnancy endpoints at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?			
LoE	**Endpoints**	**RCTs (n)**	**PCs (n)**
sQ2.A Risk of GDM			
LoE1. Standalone (main)	Incidence of GDM	0	2
LoE2. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
sQ2.B Risk of adverse birthweight-related endpoints			
LoE1. Standalone (main)	Incidence of LBW, SGA, HBW, LGA	0	2
LoE2. Standalone (surrogate)	Birthweight	0	2

sQ3. Is the intake of **FJs** positively and causally associated with adverse pregnancy endpoints at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?

LoE	Endpoints	RCTs (n)	PCs (n)
sQ4.A Risk of GDM			
LoE1. Standalone (main)	Incidence of GDM	0	2
LoE2. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3

9.3. Incidence of gestational diabetes mellitus

9.3.1. Total sugars

9.3.1.1. Intervention studies

No RCTs were available for sQ1.A

9.3.1.2. Observational studies

LoE1. Standalone (main): Incidence of GDM. PCs. One PC investigated the relationship between the intake of total sugars at baseline and incidence of GDM in the subset of women who became pregnant during follow-up. Total sugars intake during pregnancy was not assessed.

In the ALSWH cohort (Looman et al., 2018), 3,607 women between 25 and 30 years of age with complete data and no diagnosis of diabetes at baseline (type 1, type 2 or GDM) reported at least one pregnancy (total of 6,263 pregnancies) during a 12-year follow-up. Total sugars intake was analysed by categories of intake and adjusted for TEI using the nutrient residuals model, so TEI was kept constant in the analysis.

Preliminary UA. The incidence of GDM significantly decreased across increasing quartiles of total sugars intake when the model was adjusted for relevant covariates and TEI. With the additional adjustment for E% from fat and protein, the negative relationship became non-significant ($RR_{Q4\ vs.\ Q1}$: 0.83; 95% CI: 0.56, 1.23; p per trend = 0.32). Further adjustment for pre-pregnancy BMI had no impact on the relationship. This PC was at high RoB (tier 3). Critical domains were confounding, outcome assessment and attrition.

The Panel considers that the available BoE does not support a positive relationship between the intake of total sugars and incidence of GDM. **No comprehensive UA is performed**.

Complementary LoE2: Risk of obesity and LoE3: Risk of T2DM. **PCs**. The available BoE does not suggest a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of obesity (sQ1.1, Section 8.2.1.1) or risk of T2DM (sQ1.3, Section 8.4.1.1).

Conclusion sQ1.A. PCs. The available BoE does not support a positive relationship between the intake of total sugars in isocaloric exchange with other macronutrients and risk of GDM.

9.3.1.3. Overall conclusion on sQ1.A

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars and risk of GDM.

9.3.2. Sugar-sweetened beverages

9.3.2.1. Intervention studies

No RCTs were available for standalone LoEs in relation to sQ2.A.

Complementary LoE2: Risk of obesity and LoE3: Risk of T2DM. RCTs. There is evidence from RCTs for a positive and causal relationship between the intake of SSBs ad libitum and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.1) and T2DM (low certainty, sQ4.3, Section 8.4.4.1).

Conclusion sQ2.A. RCTs. Whereas there is evidence from RCTs for a positive relationship between the intake of SSBs and risk of obesity and T2DM, no RCTs investigating the relationship between the intake of SSBs and incidence of GDM are available. Therefore, the Panel considers that the available BoE from RCTs does not suggest a positive relationship between the intake of SSBs and risk of GDM.

9.3.2.2. Observational studies

LoE1. Standalone (main): Incidence of GDM. PCs. Two PCs (SUN, (Donazar-Ezcurra et al., 2018); NHSII, (Chen et al., 2009a)) report on the relationship between the intake of SSBs and incidence of GDM in the subset of women who became pregnant during follow-up. Data on SSBs were collected at baseline in both cohorts, and at 6 and 10 years of follow-up in the SUN cohort. None of the PCs assessed intake of SSBs during pregnancy.

Either the standard multivariable model was used for categorical analyses (SUN) or TEI was not included in the models (NHS II), so that TEI was not kept constant in the analyses. Both PCs include BMI in the most adjusted models. The evidence table can be found in **Annex J**.

Preliminary UA

In the SUN cohort, a significant positive dose-response relationship was observed between the intake of SSBs and incidence of GDM in a population of 3,396 women reporting a live birth during the 10.3 years of follow-up. In the model adjusted for relevant covariates, incidence of GDM significantly increased across categories of SSBs intake ($OR_{C4\ vs.\ C1}$ = 2.06, 95%CI = 1.28, 3.34) in a dose-response manner (p for trend=0.006). Additional adjustment for TEI did not substantially modify the results. The increased risk of GDM was already significant at intakes between 1 and 3 servings/month and < 1 serving/week (1 serving = 200 mL). When repeated measurements of SSBs intake were considered in the analysis (at baseline, 6 and 10 years of follow-up), the increase in incidence of GDM was only significant for the highest category of intake (> 2 servings/week) and the RR was reduced ($OR_{C4\ vs.\ C1}$ = 1.70, 95%CI = 1.02, 2.81; p for trend = 0.017). This PC was at low RoB (tier 1).

In the NHS II cohort (Chen et al., 2009a), a significant positive dose-response relationship was reported between the intake of SSBs and incidence of GDM in a population of 13,475 women reporting a live birth during the 10 years of follow-up. In the model adjusted for relevant covariates, including BMI, physical activity and family history of diabetes, each serving/day (334 mL/day) was associated with a RR of 1.23 (95%CI = 1.05, 1.43) of developing GDM. Additional adjustment for Western dietary pattern scores attenuated the association (RR = 1.16; 95%CI = 0.99, 1.36), suggesting that the relationship may be in part mediated and/or confounded by dietary habits associated with the consumption of SSBs. Models were not adjusted for TEI. This PC was at moderate RoB (tier 2), critical domains being outcome assessment and attrition.

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and risk of GDM.

Comprehensive UA

The BoE on the relationship between the intake of SSBs and risk of GDM is limited to two PCs. The Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3).

Complementary LoE2: Risk of obesity and LoE3: Risk of T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of SSBs ad libitum and risk of obesity (moderate certainty, sQ4.1, Section 8.2.4.2) and T2DM (moderate certainty, sQ4.3, Section 8.4.4.2).

The Panel notes that the BoE consists of two independent cohorts of women adequately powered with an appropriate follow-up and at low to moderate RoB. However, the Panel also notes that the relationship was strongest in the smallest study and apparent at levels of intake as low as 200 mL/week, corresponding to 20 g of sugars per week. Taking into account that the relationship between the intake of SSBs and risk of GDM is consistent with evidence from PCs and RCTs for an increased risk of obesity and T2DM in the general population, which includes women in childbearing age, the Panel considers that the level of certainty in the relationship is **low** (> 15–50% probability).

Conclusion sQ2.A. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of GDM is **low**. The relationship was observed not keeping TEI constant in the analysis.

9.3.2.3. Overall conclusion on sQ2.A

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of GDM (**low** level of certainty).

9.3.3. Fruit juices

9.3.3.1. Intervention studies

No RCTs were available for sQ3.A.

9.3.3.2. Observational studies

LoE1. Standalone (main): Incidence of GDM. PCs. Two PCs (ALSWH, NHSII) report on the relationship between the intake of FJs and incidence of GDM. The evidence table can be found in **Annex J**.

Preliminary UA

In the ALSWH cohort (Looman et al., 2018), the relationship between the intake of FJs (from fresh fruits and ready-to-eat) and incidence of GDM was negative and borderline significant in the most adjusted model (RR = 0.89; 95%CI = 0.80, 1.00 for each 100 g/day increase in intake). Fruit juice intake was adjusted for TEI using the nutrient residuals model (RoB tier 3), keeping TEI constant.

In the NHS II cohort, no association between the intake of FJs and incidence of GDM was reported. Analyses were performed by quintiles of absolute FJs intake and models were not adjusted for TEI (RoB tier 2).

The Panel considers that the available evidence does not suggest a positive relationship between the intake of fruit juice and risk of GDM. **No comprehensive UA is performed**.

Complementary LoE2: Risk of obesity and LoE 3: T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of obesity (very low certainty sQ5.1, Section 8.2.5.1) and T2DM (moderate certainty, sQ5.3, Section 8.4.5.1).

Conclusion sQ3.A. PCs. The available BoE does not suggest a positive relationship between the intake of fruit juices and risk of GDM.

9.3.3.3. Overall conclusion sQ3.A

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fruit juice and risk of GDM.

9.4. Birthweight-related endpoints

9.4.1. Total sugars

9.4.1.1. Intervention studies

No RCTs we available for sQ1.B.

9.4.1.2. Observational studies

LoE1. Standalone (main). **Incidence of LBW, SGA, HBW and LGA. PCs**. The relationship between the intake of total sugars and LBW and SGA was investigated in one PC (Cadmen, (Lenders et al., 1997)).

A total of 594 pregnant female adolescents between 12 and 19 years of age without history of diabetes or GDM in current pregnancy were recruited from two clinics at the time they attended for prenatal care (time not specified). Total sugar intake was assessed through a 24-h dietary recall at entry, 28 and 36 weeks of gestation. For data analysis, the sample was divided in two groups, being > or < the 90th percentile (cut-off = 206 g/day) for absolute intake of total sugars, and thus, TEI was not held constant before categorisation. The evidence table is in **Annex J**.

Preliminary UA

The risk of having infants SGA was double in the group consuming > 206 g/day of total sugars as compared to the reference group (OR = 2.01; 95% CI: 1.05,7.53) after adjusting for TEI and BMI, among other relevant covariates. Although it is stated that low birth weight (LBW) was also an endpoint for the study, logistic regression analyses were done on SGA only. It is reported that the percentage of infants with LBW was also higher in the group consuming more total sugars (13% vs. 7%) although not significantly so. This PC was at moderate RoB (tier 2), critical domains being

exposure, attrition and other sources of bias (e.g. statistical analysis on the extreme percentiles of intake, incomplete reporting).

The Panel notes that only one PC at moderate RoB was available for this LoE. The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars and risk of SGA or LBW. **No comprehensive UA is performed**.

LoE2. Standalone (surrogate). **Birthweight. PCs**. In the HSS-USA cohort (Crume et al., 2016), 1,040 pregnant women older than 16 years with no history or diabetes or GDM were recruited between 8 and 24 weeks of gestation (median 17 weeks). Birth weight was measured by trained nurses within 72h from birth (median 1 day). Total sugars intake was assessed monthly through pregnancy by repeated 24-h diet recalls. 82% of participants completed at least two 24-h recalls.

Preliminary UA

Non-significant (negative) relationships were reported between the intake of total sugars during pregnancy and birthweight in both energy substitution (for each 1E% increase in total sugars in isocaloric exchange with other macronutrients, TEI held constant) and energy partition models (for each 100 kcal/day increase in total sugars adjusting for the intake of other macronutrients, TEI not held constant) after adjusting for relevant covariates, including pre-pregnancy BMI. This PC was at low RoB (tier 1).

The Panel notes that the only PC available was at low RoB and reports non-significant associations between the intake of total sugars, either per se or in isocaloric exchange with other macronutrients and birthweight. The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars and adverse effects on birthweight. **No comprehensive UA is performed**.

Conclusion sQ1.B. **PCs**. The available BoE does not suggest a positive relationship between the intake of total sugars and risk of adverse effects on birthweight.

9.4.1.3. Overall conclusion on sQ1.B

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars and risk of adverse effects on birthweight.

9.4.2. Sugar-sweetened beverages

9.4.2.1. Intervention studies

No RCTs we available for sQ2.B.

9.4.2.2. Observational studies

LoE1. Standalone (main). **LBW, SGA, HBW, LGA**. Two PCs (MoBA, (Grundt et al., 2017); GeliS, (Günther et al., 2019)) report on the relationship between the consumption of SSBs during pregnancy and these endpoints. In the MoBA cohort, the relationship between carbonated SSBs consumption during pregnancy (mean intakes during weeks 15, 22 and 30) and adverse effects on birthweight-related endpoints was investigated in those that, not being diabetic at baseline, either developed or not GDM during pregnancy. In the GeliS cohort, the relationship between SSBs consumption in early (≤ 12th week of gestation) and late (> 29th week of gestation) pregnancy and adverse effects on birthweight-related endpoints was investigated. Both studies adjusted for pre-pregnancy maternal BMI and neither adjusted for TEI in the multivariable models.

The Panel notes that, whereas the cut-off for LBW was the same in both studies (birthweight < 2,500 g), the cut-off for HBW was higher in the MoBA than in the GeliS cohort (birthweight > 4,500 g and > 4,000 g, respectively). The evidence table can be found in **Annex J**.

Preliminary UA

In the MoBA cohort, in women who did not develop GDM during pregnancy, there was a non-significant higher risk of having infants with LBW (OR = 1.05; 95%CI: 0.99, 1.10, per 100 mL/day increase in intake) and a significantly lower risk of having infants with HBW (OR = 0.94; 95%CI: 0.90, 0.97, per 100 mL/day increase in intake) associated with the consumption of SSBs. Results are reported to be similar for SGA and LGA, respectively, but not provided in the publication. Similar results were obtained for SSBs (carbonated, cordials, fruit juices and nectars combined) in mL/day and for energy from added sugars (all sources), but not when volume or energy from carbonated SSBs,

respectively, was subtracted (data not shown in the publication). The relationship between consumption of carbonated SSBs and birthweight-related outcomes was in the opposite direction for women with GDM (higher risk of having infants with HBW) but not statistically significant. The Panel notes the high birthweight cut-off used to define HBW in this study (> 4,500 g) may have attenuated the strength of this association. This study was at low RoB (tier 1), with no critical domains.

In the GeliS cohort, SSBs consumption in early pregnancy was also non-significantly associated with increased risk of having a neonate with LBW (OR = 1.04; 95%CI: 0.99, 1.09 per 200 mL/day increase in intake) and with a decreased risk of having neonates with HBW (OR = 0.95; 95%CI: 0.88, 1.02 per 200 mL/day increase in intake). Similar results were reported for SSBs consumption in late pregnancy and risk of having neonates with HBW, whereas the association with having neonates with LBW was null. A similar pattern of results was reported for SSBs consumption in both early and late pregnancy and risk of having neonates SGA and LGA, respectively. The Panel notes that, in this cohort, 10.8% of the women developed GDM and 8% developed hypertension during pregnancy. Taking into account that both these variables could have been associated with both the exposure and the endpoints, and that the relationship between the intake of SSBs and birthweight in women with GDM was in the oppositive direction in the MoBA cohort, the Panel considers that not excluding women with GDM from data analysis may have attenuated the observed relationship. This study was at moderate RoB (tier 2). Critical domains were confounding and outcome assessment.

Consistent with the results obtained for dichotomous outcomes, both studies report a statistically significant inverse relationship between SSBs consumption and neonate birthweight analysed as a continuous endpoint **(LoE2. Standalone (surrogate))**. In the MoBA cohort, in women with no GDM, each additional 100 mL/day increase in carbonated SSBs consumption was associated with a mean neonate birthweight of −7.8 g (95%CI: −10.3, −5.3). Consumption of carbonated ASBs and of combined ASBs was also negatively and significantly associated with lower birthweight in this population of women with no GDM, although the magnitude of the association is reported to be 25 and 50% lower than that of carbonated SSBs, respectively (data not shown in the publication). In women who developed GDM (n = 432), mean birthweight per each 100 mL/day increase in carbonated SSBs consumption was in the opposite direction (+25.1 g, 95%CI: −2.0, 52.2). In the GeliS cohort, mean birthweight was −10.9 g (95%CI: −18.17, −3.64) and −8.19 g (95%CI: −16.26, −0.11) per each additional serving of SSBs (200 mL/day) consumed in early and late pregnancy, respectively.

The MoBa cohort was at RoB tier 1. The GeliS cohort was at RoB tier 2, critical domains being confounding and outcome assessment. The heat map for the RoB assessment is in **Annex K**.

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and adverse effects on birthweight (i.e. a decrease in birthweight, leading to a higher risk of low birthweight and being small for gestational age) in women not developing GDM during pregnancy.

Comprehensive UA

The Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3). The Panel did not identify any reason to increase this level of certainty.

Conclusion sQB2. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of adverse effects on birthweight is **very low**. The relationship is observed while not keeping TEI constant in the analysis.

9.4.2.3. Overall conclusion on sQ2.B

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of adverse effects on birthweight (**very low** level of certainty).

9.5. Overall conclusions on hazard identification: pregnancy endpoints

The Panel notes the scarcity of studies available on the relationship between the intake of dietary sugars and their sources and the pregnancy-related endpoints investigated in this assessment. Still, there is some evidence that habitual consumption of SSBs by women in child-bearing age could increase the risk of GDM during pregnancy (low certainty, > 15–50% probability), possibly through

excess energy intake leading to an increase in body weight, although a specific effect of the sugar fraction on glucose tolerance cannot be excluded.

There is also some evidence (very low certainty, 0–15% probability) that consumption of SSBs during pregnancy could increase the risk of having infants SGA in women not developing GDM during pregnancy. In women developing GDM, the risk appears to be having infants LGA. In women not developing GDM, the relationship could be mediated by lower intakes of other macronutrients (e.g. protein, fat), whereas an excess energy intake and the impaired glucose metabolism could play a role in women with GDM. However, TEI was not considered in the multivariable models used for data analysis in the two PCs that investigated these endpoints, and the limited data available preclude exploring these hypotheses.

9.6. Pregnancy endpoints: data gaps and research needs

The following major data gaps were identified in the BoE regarding the relationship between dietary sugars and their sources and risk of adverse effects on pregnancy-related endpoints:

[a]Lack of studies investigating the relationship between added and free sugars from all sources, and fructose, and incidence of GDM and adverse birthweight-related endpoints.
[b]Paucity of studies on total sugars, SSBs and FJs and incidence of GDM and adverse birthweight-related endpoints.

The data gaps identified in the BoE regarding the relationship between dietary sugars and risk of adverse pregnancy-related endpoints lead to the following research needs:

a) PCs that assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars; both habitual intakes and intakes during pregnancy) and their sources, and incidence of GDM.
b) PCs that assess the relationship between quantitative intakes of dietary sugars and their sources during pregnancy and birthweight in women developing and not developing GDM during pregnancy, accounting for factors that may confound the association (e.g. intake of other macronutrients, gestational age, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia).
c) Studies that measure the impact of interventions to reduce the amount of dietary sugars (habitual intakes, intake during pregnancy) on the development of GDM.
d) Studies that measure the impact of interventions to reduce the amount of dietary sugars during pregnancy on birthweight in women developing and not developing GDM.

10. Hazard identification: dental caries

10.1. Principles applied to assess the body of evidence

Ever since the pathogenesis of dental caries was elucidated, there is wide consensus among the scientific community that the intake of dietary sugars is causally related to the development of dental caries at all ages (Jepsen et al., 2017). For this reason, few human intervention studies investigating the effects of different doses of dietary sugars on the incidence of dental caries were undertaken over the years, owing to ethical considerations.

The BoE eligible for this assessment is presented below for the purpose of describing dose-response relationships between the exposure and the endpoint and possibly identifying a level of sugars intake that is/it is not associated with an increased risk of dental caries. The conclusions will be used for hazard characterisation.

To this end, EFSA requested all the authors of the observational studies potentially eligible for this assessment to share individual data. The purpose was to perform pooled analyses in order to identify dose-response relationships if possible.

10.2. Body of evidence

10.2.1. Intervention studies

Only one human intervention study met the inclusion criteria for this assessment (Scheinin et al., 1976).

The Turku sugar study is an open-label intervention in which free-living, healthy participants (mean age 27.7 years, age range 12–53 years) were allocated to three groups, half based on individual preference and half at random. Participants (n = 125) were asked to consume, for 2 years, all added sugars in the diet as either sucrose (n = 35), fructose (n = 38) or xylitol (n = 52).

Food products were given free of charge and were specifically manufactured for the trial (Mäkinen and Scheinin, 1976). Compliance with the dietary regimen was assessed through diaries and interviews when clarifications were needed through the 2-year period. Clinical and radiological evaluation of primary and secondary dental caries with and without defect, and of filled surfaces, was performed at baseline, and at months 3, 7, 13, 20 and 24 of the study. Details on the inter-observer variability in clinical and radiological diagnosis are thoroughly discussed in the publication. From these, several caries indices were derived for analysis.

A 25% dropout rate was foreseen, but only 10 participants (8%) discontinued participation or were removed from the trial, leaving 115 subjects for analysis (33, 35 and 47 in the sucrose, fructose or xylitol groups, respectively).

No significant differences were found between the groups for age, sex, number of primary and secondary carious surfaces with and without defect, number of filled surfaces and extracted teeth, or the decayed, missing and filled tooth surfaces (DMFS)-index. Mean intake of sucrose, fructose and xylitol was 2.2, 2.1 and 1.5 kg/month, respectively, corresponding to 73.5, 70 and 50 g/day, respectively.

After 2 years the mean (SD) increment in the DMFS-index was 7.2 (5.67), 3.8 (4.14) and 0.0 (5.35) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p < 0.01$ for sucrose vs. fructose). The mean (SD) increment in the modified DMFS-index (sum of increment in the DMFS-index and all secondary caries reversals) was 10.5 (7.97), 6.1 (5.44) and 0.9 (6.66) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p < 0.05$ for sucrose vs. fructose). The mean (SD) increment in the caries activity index (sum of increment in the DMFS-index, all secondary caries reversals and increase in size of total clinical and radiographic reversals) was 12.5 (9.35), 8.5 (6.26) and 1.9 (6.59) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p = 0.052$ for sucrose vs. fructose). No significant differences were observed in the number of filled surfaces among groups during the study. This study was at RoB tier 2, critical domains being randomisation, allocation concealment, blinding and exposure assessment (**Annex K**).

The Panel notes that full replacement of added sucrose and fructose in the diet led to a significant decrease in the incidence of dental caries over 2 years, and that fructose appeared to be less cariogenic than sucrose. The Panel also notes that, although this study confirms the cariogenic potential of sucrose and fructose, it does not allow investigating a potential dose-response relationship between the intake of these dietary sugars and the risk of developing dental caries.

10.2.2. Observational studies

A total of 11 publications reporting on seven cohorts met the inclusion criteria. One cohort included adults of both sexes (Finnish cohort, (Bernabé et al., 2016)), one was in adult and older adult men (VA-DLS, (Kaye et al., 2015)), two were in adolescents of both sexes (UK cohort (Rugg-Gunn et al., 1984; Rugg-Gunn et al., 1987); Michigan cohort (Burt et al., 1988) (Burt and Szpunar, 1994; Szpunar et al., 1995)) and three were in children, again of both sexes (IFS (Chankanka et al., 2011); STRIP-1 (Ruottinen et al., 2004); STRIP-2 (Karjalainen et al., 2001, 2015).

All children in the STRIP-1 and 2 cohorts participated in the STRIP trial, an RCT designed to restrict the intake of total fat and cholesterol for atherosclerosis prevention. The overlap between the two STRIP cohorts investigating the relationship between the intake of sucrose and dental caries is limited to one child, and thus, both cohorts are included in this assessment.

Five PCs report on total sugars (of which two also report on SSBs and one on FJs) and two cohorts (STRIP-1 and STRIP-2, Finland) report on sucrose. At the time these studies were conducted, sucrose was the major source of added sugars in Finland. Cohorts were very heterogeneous regarding the outcome of interest, consistently with the demographic characteristics of their participants. The Finnish cohort measured Decayed Missing and Filled Teeth (DMFT) including coronal and root lesions that were cavitated or extended into dentine. The VA-DLS study focused on root caries (adjusted root caries increment) only, a type of lesion that is more commonly encountered as age progresses and tooth root becomes exposed. The UK and Michigan cohorts visually assessed and reported not only the number of decayed teeth, but also tooth surfaces, and subclasses of tooth surfaces (i.e. fissure,

approximal, smooth) with cavitated carious lesions. The two studies based on data from the STRIP cohort measured the number of primary and permanent teeth with cavitated carious lesions, confirmed by radiographic assessment. The IFS measured pre-cavitated and cavitated carious surfaces in primary and permanent dentition by visual examination. The evidence table is in **Appendix M**.

Individual data were obtained for three cohorts (STRIP, IFS and VA-DLS). However, data from the VA-DLS cohort could not be used for the EFSA analysis because of difficulties in reproducing the outcome as in the original study due to lack of full information. The database was used to provide descriptive statistics on intakes for sugars in g/day (per quartiles of E%) and SSBs.

The STRIP-2 (Karjalainen et al., 2001, 2015) and IFS cohorts (Chankanka et al., 2011) were included at full-text screening because they were potentially eligible for the assessment, although the results as reported in the original publications were not (i.e. daily intakes of sugars and/or their sources were either not quantified or not used as independent variables in prospective analyses). However, authors provided individual data for EFSA to perform the analyses of interest for this opinion. A technical report with details on the statistical analysis conducted by EFSA using individual data from the STRIP and IFS cohorts can be found in **Annex N**.

The summary assessment of the RoB is in **Annex K**. Two cohorts were at low RoB (tier 1; Finnish cohort and Michigan cohort), and the remaining were at moderate RoB (tier 2) except for the VA-DLS cohort for total sugars (tier 3). Critical domains across the BoE were confounding, attrition and exposure assessment.

10.2.2.1. Total sugars

In the Finnish cohort (Bernabé et al., 2016), a positive linear dose-response relationship was observed between the intake of total sugars (in g/day) and the increment of cavitated caries in permanent dentition during the 11-year follow-up over a wide range of sugars intake (13.7 to 442.3 g/day). None of the 43 alternative curvilinear models tested improved the prediction of the linear model significantly. Mean intakes of total sugars (SD) at baseline were 110.9 g/day (47.8). After adjustment for relevant covariates, including frequency of sugars consumption, the relationship was stronger than in the crude model (**Appendix M**). Vice-versa, frequency of consumption was not associated with dental caries when the amount of total sugars was included in the model. Upon EFSA's request for additional information, the authors report that a level of total sugars associated with a zero increment in the DMFT index could not be identified in this study. The Panel also notes that the lowest intake of total sugars was low, corresponding to about 2.7 E% for a diet of 2,000 kcal/day. This PC was at low RoB (tier 1).

In the VA cohort (Kaye et al., 2015), no significant relationship was observed between quartiles of total sugars intake (E%; sum of sucrose, fructose and lactose) and adjusted root caries increment over the 11-year follow-up. Total sugars intake ranged from 3.8 to 36.7 E%. The study was at high RoB (tier 3) for total sugars. Critical domains were confounding, attrition and exposure.

In the UK cohort (Rugg-Gunn et al., 1984, 1987), there was a low but statistically significant correlation between the DMFS increment, measured over a 2-year period, and total sugars intake in g/day ($r = +0.105$ for the crude model, without adjusting for potential confounders; $p < 0.05$). When the analysis was controlled for tooth brushing frequency, the correlation between total sugars intake and caries increment was higher than in the bivariate analysis. The correlation was significant for the 2-year fissure caries increment (DFS; $r = +0.143$; $p < 0.02$) after adjusting for age, sex, gingival index, frequency of sugars intake and starch intake, but not for the caries increment for approximal or smooth tooth surfaces. Regression of DMFS increment on the amount of total sugars intake indicated that there was an average increase of 0.36 DMFS (95%CI −0.07, 0.80) over 2 years with each rise of 30 g of sugars per day in the most adjusted model. The 31 children with the highest intake of total sugars (> 163 g/day) developed 0.9 more DMFS per child per year than the 31 children with the lowest intake of total sugars (< 78 g/day, $p = 0.07$). The Panel notes that this study reports a linear dose-response relationship between the intake of total sugars and incidence of dental caries and does not allow identifying a level of intake at which the risk is not increased. The study was at moderate RoB (tier 2). Critical domains were confounding and other sources of bias (statistical analysis).

In the Michigan cohort (Burt et al., 1988; Burt and Szpunar, 1994; Szpunar et al., 1995), a higher proportion of energy intake from total sugars increased the probability of developing cavitated lesions in the permanent dentition over the 3-year follow-up period. Those in the highest quartile of total sugars intake (mean intake 29.5E%, 175 g/day) had a relative risk (95%CI) of 1.22 (1.04, 1.46) of developing caries compared with the lowest quartile (mean intake 23E%, 109 g/day). This risk rose to 1.80 (1.06, 3.10) for approximal caries. Models were adjusted for age and baseline DMFS. In most

adjusted models (including sex, age, history of previous residence in a fluoridated community, use of fluoride tablets, frequency of topical fluorides, toothbrushing frequency, antibiotic use, parental education and family income as covariates), E% from total sugars significantly correlated with total, approximal and fissures caries incidence, whereas the correlation was only significant for total caries when total sugars intake was expressed in g/day. Frequency of sugars intake did not correlate with caries risk. From these most adjusted models, it was estimated that the risk of cavitated caries increased by 1.6 times in those at +1SD of total sugars intake vs. those at −1SD, either expressed as E% or g/day. It was calculated that each additional 8 g/day of total sugars intake was associated with a 1% increase in the probability of developing cavitated lesions. In this study, the relationship between total sugars intake and caries risk appeared to be linear and it does not allow identifying a level of intake at which the risk is not increased. The Panel notes that the intake of total sugars in this population group was high. The study was at low RoB (tier 1).

In the IFS (Chankanka et al., 2011), the relationship between the intake of total sugars over the study period and risk of cavitated, non-cavitated and dental caries between the ages of 5 and 9 years in the mixed dentition was assessed. No relationship between the intake of either total sugars and risk of dental caries was observed after controlling for relevant confounders, including sex, SES, age at the dental exam at follow-up, prevalence of dental caries at baseline, mean daily toothbrushing frequency and composite water fluoride concentration (ppm). Similar results were obtained when the analyses were restricted to children free of caries at 5 years. Mean intakes of total sugars was 114 g/day (range 53 to 216 g/day). The study was at moderate RoB (tier 2). Critical domains were exposure assessment and attrition. The Panel notes that intakes of total sugars were high in this population group.

10.2.2.2. Added sugars

In the STRIP-1 cohort of Finnish children followed from infancy to age 10 (Ruottinen et al., 2004), the mean sucrose intake in a 'high' sucrose group was 48.4 g per day, and in the 'low' sucrose group, it was 22.5 g/day. The high sucrose group has a higher sucrose intake every year of the study. The sucrose consumption of the high sucrose group exceeded 10% of energy intake after 13 months of age. In the low sucrose group, the intake of sucrose did not exceed 7% of energy intake at any age. The mean dmft (primary dentition) was 2.7 (SD 3.3) in the 'high' sucrose intake group and 1.19 (SD 1.2) in the 'low' sucrose intake group ($p = 0.177$). The mean dmft+DMFT (mixed dentition) was 1.9 (SD 2.5) in the 'high' sucrose intake group and 0.5 (SD 1.1) in the 'low' sucrose intake group ($p = 0.032$). The mean DMFT (permanent dentition) in the 'high' sucrose intake group was 1.4 (SD 2.0) compared with 0.5 (SD 1.1) in the 'low' sucrose group ($p = 0.01$). Potential confounders were not included as covariates in the analysis. However, confounding by tooth brushing frequency was considered by comparing sucrose intake and dental health in different tooth brushing frequency groups. The association between sucrose intake and toothbrushing frequency was not significant, but this may have been due to the small size of the groups compared. The study was at moderate RoB (tier 2), critical domains being confounding and exposure assessment.

In the STRIP-2 (Karjalainen et al., 2001, 2015), the relationship between sucrose intakes (g/day) at years 3 and 12 and new cavitated caries in primary dentition at age 6 years and in permanent dentition at age 16 years, respectively, was investigated. Data on sex, STRIP study group, caries-free age (years), cavitated caries at baseline for each period and daily toothbrushing (yes/no) were available as covariates. The risk of developing cavitated caries in primary dentition at 6 years (yes/no) was about four times higher in the highest (mean intake = 44 g/day, range = 34.5–65.9 g/day) vs. the lowest quartile (mean intake = 15.9 g/day, range = 7.4–20.9 g/day) of sucrose intake at 3 years (OR = 4.32; 95%CI = 1.31, 14.25). Assuming an energy requirement of 1100 kcal/for a 3-year-old child, mean sucrose intakes in the highest and the lowest quartiles would correspond to 16E% (range 12.5 to 24E%) and 5.8E% (range 2.6 to 7.6E%), respectively. The risk increased by 1.64 (95%CI = 1.13, 2.37) for each 10 g/day increase in sucrose intake at 3 years. Mean intake (SD) of sucrose in the whole sample at 3 years was 28.5 g/day (11.3). The relationship between sucrose intake at 3 years and new cavitied caries in primary dentition at 6 years was not significant when new caries was expressed as counts (dmft increment). The relationship between sucrose intake at 12 years and new cavitied caries in permanent dentition at 16 years was not significant in any analyses. Mean intake (SD) of sucrose in the whole sample at 12 years was 34.7 g/day (11.3). The Panel notes that the number of children with data available from 12 to 16 years was lower (n = 81 vs. n = 128). The study was at moderate RoB (tier 2), critical domains being confounding and exposure assessment.

10.2.2.3. SSBs and FJs

In the VA cohort of adult and older adult men (Kaye et al., 2015), a significant positive linear trend ($p < 0.05$) was observed across quartiles of SSBs intake (servings per week) for adjusted root caries increment (the dental outcome variable) during the 11-year follow-up including years at risk of root caries, baseline age, smoking status, number of teeth at risk for root caries, existing root caries or restorations, subgingival calculus, dental prophylaxis in past year and removable denture status as covariates. Median intakes of SSBs ranged from 0 mL/week in the lowest quartile to 1,407 mL/week in the highest. In this PC the relationship between SSBs intake and adjusted root caries increment appears to be linear and a level of intake at which the risk is not increased cannot be identified [mean (95%CI) = 2.86 (2.28, 3.60) and 2.17 (1.68, 2.79) for the highest vs. the lowest quartile of intake]. The study was at moderate RoB for SSBs (tier 2). Critical domains were confounding and attrition.

In the IFS (Chankanka et al., 2011), the relationship between the intake of SSBs and FJs over the study period and risk of cavitated, non-cavitated and dental caries between the ages of 5 and 9 years in the mixed dentition was assessed. No relationship between the intake of SSBs or FJs and risk of dental caries was observed after controlling for relevant confounders. Similar results were obtained when the analyses were restricted to children free of caries at 5 years. Mean intakes of SSBs and FJs were 271 mL/day (range 0–1,079 mL/day) and 87 mL/day (0–525 mL/day), respectively. The study was at moderate RoB (tier 2). Critical domains were exposure assessment and attrition. The Panel notes that intakes of sugar-containing beverages were high in this population group.

10.2.2.4. Dose-response relationships

Most PCs (Finnish cohort, UK cohort, Michigan cohort) suggest a positive linear dose-response relationship between the intake of total sugars and risk of dental caries in permanent dentition across a wide range of sugars intakes. However, the Panel notes that the shape of the dose-response relationship was rather assumed in the UK and Michigan cohorts, where non-linear relationships were not explored. Two of these PCs were at low RoB (tier 1) and adequately controlled for confounding factors, including frequency of sugars intake (Finnish cohort, Michigan cohort). In these two PCs, frequency of sugars intake was either not significantly associated with risk of dental caries (Michigan cohort) or was no longer associated with the risk of caries when the amount of sugars was accounted for (Finnish cohort).

Limited data (STRIP-2 study, RoB tier 2) indicate a positive linear dose-response relationship between the intake of sucrose (a proxy for added sugars) and dental caries in primary dentition across a wide range of intakes, whereas no relationship was observed between sucrose intake and dental caries for permanent dentition in the same study.

Limited data were also available for the relationship between the intake of dietary sugars and sugar-containing beverages (SSBs and FJs) and risk of dental caries in mixed dentition (STRIP-1, IFS cohort) and in the older adults (root caries, VA cohort). No significant relationship was observed in these studies between the intake of dietary sugars and caries risk.

The low number of PCs for all age groups and the heterogeneity in available data with respect to both the measures of intake of dietary sugars and the indices used to assess the risk of dental caries (incidence (yes/no) vs. severity (counts)) did not allow pooled analyses or meta-analysis to characterise dose-response relationships between the intake of dietary sugars and caries risk across the body of evidence.

10.3. Overall conclusions on hazard identification: dental caries

The Panel notes that the relationship between the intake of dietary sugars and the development of dental caries in humans is well established. Positive linear dose-response relationships have been observed between the intake of total sugars and risk of dental caries in permanent dentition (endpoint most relevant for adults and children older than 12 years) and between the intake of sucrose (a proxy for added sugars) and risk of dental caries in primary dentition (endpoint most relevant for children younger than 6 years of age) in individual PCs across a wide range of total sugars and sucrose intakes.

However, the Panel also notes that dose-response relationships across the BoE could not be explored with the data available, that dose-response relationships between the intake of total sugars and risk of dental caries in permanent dentition were assumed to be linear in two cohorts (UK and Michigan cohorts) but tested for non-linearity only in one (Finnish cohort) and that the available data for other population groups (primary dentition in children, root caries in the older adults) and exposures (added and free sugars including sucrose and their sources) are scarce. In this context, the Panel considers that, although it is well established that dietary sugars are involved in the development

of dental caries at all ages, the available BoE does not allow conclusions on the shape of the relationship between the intake of dietary sugars and risk of dental caries for any age group, or to identify a level of sugars intake at which the risk of dental caries is not increased.

10.4. Dental caries: data gaps and research needs

The low number of PCs for all age groups and the heterogeneity in available data with respect to both the measures of intake of dietary sugars and the indices used to report dental caries counts (severity) did not allow pooled analyses or meta-analysis to characterise dose-response relationships between the intake of dietary sugars and caries risk across the body of evidence. This problem is compounded by deficits in method of nutritional assessment (e.g. lack of validation of reported intakes, use of retrospective and semi-quantitative approaches) and failure to measure and/or account for (also in the statistical analysis) factors that probably confound the relationship between the intake of dietary sugars and the development of dental caries (including indices of socio-economic status, exposure to fluoride and measures of oral hygiene).

Therefore, the data gaps identified in the BoE regarding the relationship between dietary sugars and risk of dental caries lead to the following research needs:

aProspective cohort studies that assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars) and the development of dental caries (both incidence and severity) in all age groups, including root caries in older adults, using validated methods of nutritional assessment and accounting for factors that may confound the association.

bStudies that measure the impact of interventions to reduce the amount of dietary sugars on the development of dental caries in all age groups.

11. Hazard characterisation: dose-response assessment and derivation of a Tolerable Upper Intake Level for sugars

The UL for (total/added/free) sugars is the maximum level of chronic daily intake of sugars from all sources judged to be unlikely to pose a risk of adverse health effects to humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. The UL is not a recommended level of intake (SCF SCoF, 2000). The underlying assumption is that a 'threshold' can be identified below which no risk from consumption of dietary sugars is expected for the general population, and above which the risk of adverse health effects, including risk of disease, increases.

If there are no, or insufficient, data on which to base a UL, an indication may be given on the highest level of chronic daily intake from all sources where there is reasonable confidence in data on the absence of adverse effects (i.e. a science-based cut-off value for a daily exposure which is not associated with adverse health effects, or a safe level of intake). This requires the identification of a level of sugars intake up to which no adverse health effects are observed.

11.1. Total sugars

The available BoE from PCs does not support a positive relationship between the intake of total sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases (Section 8.9.1) or pregnancy-related endpoints (Section 9.5) considered in this assessment.

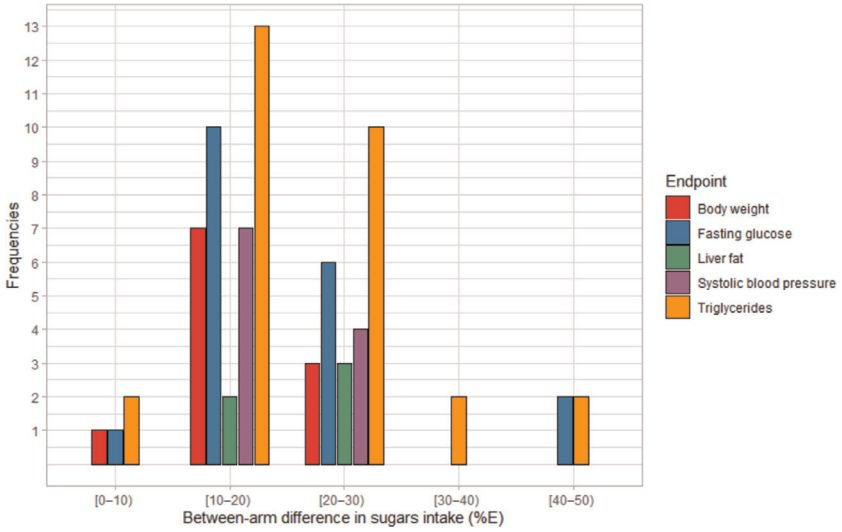
The relationship between the intake of dietary sugars and the development of dental caries in humans is well established. Positive and linear dose-response relationships between the intake of total sugars and risk of dental caries in permanent dentition have been reported in observational studies, with no evidence for non-linearity in the only cohort in which this hypothesis was tested (Finnish cohort, (Bernabé et al., 2016)). The data available, however, did not allow exploring dose-response relationships across the BoE, or to identify a level of total sugars intake at which the risk of dental caries is not increased (Section 10.3).

11.2. Added and free sugars

The available BoE from PCs does not support a positive relationship between the intake of added and free sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases (Section 8.9.2) or pregnancy-related endpoints (Section 9.5) considered in this assessment.

The level of certainty for a positive and causal relationship between the intake of added and free sugars and risk of chronic metabolic disease is considered to be moderate for obesity and dyslipidaemia (> 50–75% probability), low for NAFLD/NASH and T2DM (> 15–50% probability) and very low for hypertension (0–15% probability), based on data from RCTs which investigated the effect of 'high' vs. 'low' sugars intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and SBP (Section 8).

Figure 18 shows the distribution of RCTs addressing different endpoints by ranges of added or free sugars intake, corresponding to between-arm differences in intake. The Panel notes the limited number of measurements available for intakes of added and free sugars below 10 E% and above 30 E % for all endpoints investigated.



Legend to Figure 18. Since each randomised controlled trial (RCT) can investigate more than one endpoint, the total number of studies in the figure is higher than the number of RCTs included in the assessment.

Figure 18: Distribution of randomised controlled trials addressing different endpoints by ranges of added or free sugars intake, corresponding to between-arm differences in intake

Dose–response relationships between the intake of added and free sugars and the above-mentioned endpoints were characterised as part of the hazard identification step, where possible:

Body weight: Based on meta-regressive dose-response analysis, no dose–response relationship could be established between the intake of added and free sugars (dose range 6–24 E%) and body weight (Section 8.2.2). Dose-response was not investigated in individual studies (Section 8.2.2).

Liver fat: A dose–response relationship between the intake of added sugars and liver fat could not be established in the single study which tested it using three sugar doses (8, 18 and 30 E% in the respective study arms) (Lowndes et al., 2014b). The dose-response relationship between the intake of added and free sugars and liver fat could not be explored by meta-regression analysis owing to the limited number of RCTs available and the narrow range of sugars intakes investigated (between-arm difference range 18–22 E%) (Section 8.3.2).

Fasting glucose: A linear dose-response relationship was observed between the intake of sucrose (2, 15 and 30 E% in the respective study arms) in isocaloric exchange with starch and fasting glucose and insulin levels in the RCT by Israel et al. (1983) conducted in men and women with hyperinsulinaemia. Meta-regression analysis of the relationship between the intake of added and free sugars (between-arm difference range 8–28 E%) and fasting glucose concentrations across the BoE from RCTs identified a positive and linear dose-response (see Section 8.4.2.1 and **Annex L**).

Fasting triglycerides: A dose-response relationship between the intake of sucrose (2, 15 and 30 E% in the respective study arms) in isocaloric exchange with starch and fasting triglycerides was observed in the RCT by Israel et al. (1983) conducted in men with hyperinsulinaemia. A dose-response relationship between the intake of fructose (0, 7.5 and 15 E% in the respective study arms) in isocaloric exchange with starch and fasting triglycerides was also reported in the RCT by Hallfrisch et al. (1983a) conducted in men with hyperinsulinaemia. A meta-regressive dose-response relationship

across the BoE from RCTs was identified between the intake of added and free sugars (between-arm difference range 6–30 E%) and fasting triglycerides. The relationship was positive and linear, with no evidence for non-linearity. Most of the heterogeneity in the data set could not be explained. In this context, the Panel considers that no quantitative prediction of the effect of added (or free) sugars on fasting triglycerides can be made based on this model. The Panel notes that, for the same difference in added and free sugars intake, a higher absolute difference in fasting triglycerides was found in individuals with obesity, hypertriglyceridaemia or hyperinsulinaemia compared to other population subgroups (see Section 8.5.2.1 and **Annex L**).

Blood pressure: Dose-response was not investigated in individual RCTs. No meta-regression analysis could be performed owing to the small number of RCTs available. Visual inspection of the forest plots did not suggest a dose-response relationship (between-arm difference range 10–28E%) (Section 8.6.2).

Regarding the risk of dental caries, positive relationships with the intake of sucrose (a proxy for added sugars) have been reported in the STRIP cohort (STRIP-1; (Ruottinen et al., 2004); STRIP-2; (Karjalainen et al., 2001, 2015). A positive and linear dose-response relationship between the intake of added sugars and risk of dental caries in primary dentition was identified in the STRIP-2 cohort. The data available, however, did not allow exploring dose-response relationships across the BoE, or to identify a level of added sugars intake at which the risk of dental caries is not increased.

11.3. Conclusions on hazard characterisation

Overall, the Panel concludes that available data do not allow the setting of a UL or a safe level of intake for either total, added or free sugars. The Panel notes that the BoE considered in this opinion does not allow comparison of health effects based on the classification of dietary sugars as added or free (sections 8.1.1 and 8.1.2).

- The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. The data available, however, did not allow identifying a level of (total/added/free) sugars intake at which the risk of dental caries is not increased over the range of observed intakes.
- There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases, with levels of certainty ranging from moderate (50–75% probability) to very low (0–15% probability) depending on the disease. The data available, however, did not allow identifying a level of added/free sugars intake at which the risk of chronic metabolic disease is not increased over the range of observed intakes. The Panel notes that the relationship between the intake of added and free sugars and risk of chronic metabolic diseases could not be adequately explored at levels of intake $<$ 10 E% owing to the low number of RCTs available, and that the uncertainty about the shape and direction of the relationship at these levels of intake is higher than at intakes $\geq$ 10 E%.
- The available BoE from PCs does not support a positive relationship between the intake of dietary (total/added/free) sugars and any of the chronic metabolic diseases or pregnancy-related endpoints considered in this assessment. Dietary sugars were mostly assessed keeping TEI constant (i.e. in isocaloric exchange with other macronutrients).

Based on the available BoE and related uncertainties, the Panel considers that the intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. The Panel notes that decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent.

The information provided in this opinion can assist EU Member States in setting goals for populations and/or recommendations for individuals in their country, taking into account the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed (see Section 6). The Panel notes that the lowest amount of added/free sugars that is compatible with a nutritionally adequate diet in Europe may vary across population groups and countries.

12. Assistance to Member States when developing food-based dietary guidelines

Owing that the available data did not allow the setting of a UL or a safe level of intake for dietary sugars (total/added/free) from all sources, scientific advice is provided in relation to intakes of individual sugar types (e.g. fructose) and food sources of dietary sugars in order to assist Member States when developing FBDGs, as foreseen in the protocol.

12.1. Sugar types: fructose

The level of certainty for a positive and causal relationship between the intake of fructose and risk of chronic metabolic diseases is considered to be moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability), based on PCs. However, the external validity of the findings for European populations is unclear (see Section 8.9.3). In the eligible RCTs, the effects of fructose and glucose on body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure did not appear to be different, whereas fructose appeared to increase hepatic insulin resistance and uric acid levels more than equivalent amounts of glucose.

The Panel notes that fructose is a component of added and free sugars in mixed diets i.e. containing comparable amounts of fructose and glucose. The Panel considers that the conclusions for added and free sugars also apply to fructose in that context. In addition, the Panel notes that limiting the intake of added and free sugars in mixed diets would also limit the intake of fructose. This may not be the case if pure fructose or isoglucose with high fructose content (> 55%) are used to replace sucrose in foods and beverages (Section 4.2).

12.2. Sources of dietary sugars

12.2.1. Sugar-sweetened beverages

The level of certainty for a positive and causal relationship between the intake of SSBs and risk of chronic metabolic disease is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability), based on data from RCTs and PCs. When dose-response relationships between the intake of SSBs and incidence of disease (i.e. T2DM, hypertension and CVD) could be investigated using data from PCs, these were positive and linear, with no evidence for non-linearity. Whereas the relationship between the intake of SSBs and risk of obesity, NAFLD, T2DM, dyslipidaemia and gout could be attributed, at least in part, to the sugars fraction of the beverage, this is more questionable in relation to the risk of hypertension and CVD (see Section 8.9.4). In addition, the external validity of the findings in relation to the risk of gout for European populations is unclear. Based on data from PCs, there is low certainty (> 15–50% probability) that habitual consumption of SSBs by women of child-bearing age could increase the risk of GDM, and very low certainty (0–15% probability) that consumption of SSBs during pregnancy by women not developing GDM increases the risk of having infants SGA (Sections 9.3.2.2 and 9.4.2.2).

The proportion of consumers of SSBs (SSSD+SSFD) in Europe varied widely across population groups and countries, ranging from 0% to 97% of the dietary survey's sample. Intakes of added and free sugars from all sources were higher in consumers of SSBs than in consumers of any other non-core food group significantly contributing to sugars intake (fine bakery wares, confectionery, sugar and similar, fruit and vegetable juices) in virtually all countries and population groups (Section 4.3, **Annex E**).

In consumers, the mean contribution of added and free sugars in SSBs (SSSD+SSFD) to total energy intake ranged from 1 to 8 E%, depending on the survey. With few exceptions, the contribution of SSBs to the mean intake of added and free sugars ranged from 15% to about 50% (**Annex E**).

12.2.2. Fruit juices

The level of certainty for a positive and causal relationship between the intake of FJs and risk of chronic metabolic diseases is considered to be moderate for T2DM and gout (> 50–75% probability) and very low for obesity (0–15% probability), based on data from PCs. The dose-response relationship between the intake of FJs and incidence of T2DM was positive and linear, with no evidence for non-linearity. The external validity of the findings in relation to the risk of gout for European populations is

unclear. The Panel notes that the levels of intake of FJs are lower than for SSBs in prospective cohort studies and that the BoE on FJs is restricted to a lower number of studies compared to SSBs.

The proportion of consumers of fruit juices varied widely across population groups and countries, ranging from 15% to 96% of the sample. In toddlers, intakes of free sugars from all sources were higher in consumers of fruit juices than in consumers of any other non-core food group in most countries (Section 4.3, **Annex E**). In consumers, the mean contribution of free sugars in fruit juices to total energy intake ranged from 1 to 11 E% depending on the survey (**Annex E**). With few exceptions, the contribution of fruit juices to the mean intake of free sugars ranged from 15% to about 50%.

12.2.3. Other sources of dietary sugars

Data from PCs on other sources of dietary sugars were not extracted (Section 7.3.2). However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDGs.

In addition to SSBs and FJs, food groups contributing the most to the intake of added and free sugars in European countries were 'sugars and confectionery' (i.e. table sugar, honey, syrups, confectionery and water-based sweet desserts) and fine bakery wares, as well as sweetened 'milk and dairy' products in young consumers, with high variability among population groups and countries (Section 4.3, **Annex E**).

Conclusions

Based on the available scientific evidence and related uncertainties, the Panel concludes that:

Dietary sugars

- A UL or a safe level of intake for either total, added or free sugars could not be established.
- The health effects of added vs. free sugars could not be compared.
- The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. However, a level of (total/added/free) sugars intake at which the risk of dental caries is not increased over the range of observed intakes could not be identified.
- There is evidence for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be moderate for obesity and dyslipidaemia (> 50–75% probability), low for NAFLD/NASH and T2DM (> 15–50% probability) and very low for hypertension (0–15% probability), based on data from RCTs which investigated the effect of 'high' vs. 'low' sugars intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and SBP. However, a level of added/free sugars intake at which the risk of chronic metabolic disease is not increased over the range of observed intakes could not be identified.
- The relationship between the intake of added and free sugars and risk of chronic metabolic diseases could not be adequately explored at levels of intake < 10 E% owing to the low number of RCTs available. The uncertainty about the shape and direction of the relationship at these levels of intake is higher than at intakes ≥ 10 E%.
- PCs do not support a positive relationship between the intake of dietary (total/added/free) sugars and chronic metabolic diseases or pregnancy-related endpoints. Dietary sugars were mostly assessed keeping TEI constant (i.e. in isocaloric exchange with other macronutrients).
- Excess energy intake leading to positive energy balance and body weight gain appears to be the main mechanism by which the intake of dietary sugars may contribute to the development of chronic metabolic diseases in free living conditions. Mechanisms which are specific to sugars as found in mixed diets (i.e. *de novo* lipogenesis leading to ectopic fat deposition, increased hepatic insulin resistance and impaired glucose tolerance in the long term; increase in uric acid levels) may also play a role, particularly in positive energy balance.
- The intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. Decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent.
- Food groups contributing most to the intake of added and free sugars in European countries were 'sugars and confectionery' (i.e. table sugar, honey, syrups, confectionery and water-based sweet desserts), followed by beverages (SSBs, fruit juices) and fine bakery wares, with high variability across countries. The main difference between the intake of added and free sugars

was accounted for by fruit juices. In infants, children and adolescents, sweetened 'milk and dairy' products were also major contributors to mean intakes of added and free sugars.
- The information provided in this opinion can assist EU Member States in setting goals for populations and/or recommendations for individuals in their country, taking into account the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed. The lowest amount of added/free sugars that is compatible with a nutritionally adequate diet in Europe may vary across population groups and countries.

Sugar types

- There is evidence for a positive and causal relationship between the intake of fructose and risk of some chronic metabolic diseases, based on data from PCs. The level of certainty in the relationship is considered to be moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability), although the external validity of the findings for European populations is unclear. In the eligible RCTs, fructose appeared to increase hepatic insulin resistance and uric acid levels more than equivalent amounts of glucose. The effects of fructose and glucose on body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure did not appear to be different.
- Fructose is a component of added and free sugars in mixed diets i.e. containing comparable amounts of fructose and glucose. Therefore, the conclusions for added and free sugars also apply to fructose in that context. Limiting the intake of added and free sugars in mixed diets would also limit the intake of fructose. This may not be the case if pure fructose or isoglucose with high fructose content (> 55%) are used to replace sucrose in foods and beverages.

Sugars from specific sources

- There is evidence for a positive and causal relationship between the intake of SSBs and risk of some chronic metabolic diseases, based on data from RCTs and PCs. The level of certainty in the relationship is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability).
- There is also evidence for a positive and causal relationship between the intake of fruit juices and risk of some chronic metabolic diseases, based on data from PCs. The level of certainty in the relationship is considered to be moderate for T2DM and gout (> 50–75% probability) and very low for obesity (0–15% probability).
- The external validity of the findings in relation to the risk of gout for European populations is unclear.
- Based on data from PCs, there is low certainty (> 15–50% probability) that habitual consumption of SSBs by women of child-bearing age could increase the risk of GDM, and very low certainty (0–15% probability) that consumption of SSBs during pregnancy by women not developing GDM increases the risk of having infants SGA.
- In PCs, SSBs and FJs were mostly assessed not keeping TEI constant in the analysis, thus allowing for the possible contribution of energy to the associations.
- No conclusions could be drawn on specific sources of dietary sugars other than SSBs and FJs. However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDG.

Recommendations for research

Main data gaps and recommendations for research are addressed in Sections 8.10, 9.6 and 10.4 of this scientific opinion.

The Panel considers that the priorities for research in order to inform the setting of an UL for dietary sugars are as follows:

1) To develop and validate reliable methods and (bio)markers for the assessment of intake for dietary sugars.
2) To make individual data collected in human studies available for reanalyses and pooled analyses.

3) To improve the reporting of the methods and results of research studies by following international quality and transparency guidelines.[17]
4) To use standardised definitions for the characterisation of dietary sugars, their fractions (added and free sugars) and their sources (food groups in which they are contained).
5) To measure the impact of interventions to reduce the amount of added and free sugars from all sources (especially to below 10 E%) in controlled settings on the development of chronic metabolic diseases and surrogate endpoints thereof in all age groups. The impact of potential effect modifiers and the mechanisms involved should be further investigated.
6) To assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars), and the risk of developing GDM, and birthweight-related endpoints in women developing and not developing GDM.
7) To use reliable methods to measure possible mediators and confounders of the relationship between the intake of dietary sugars and the incidence of chronic metabolic diseases, in particular energy intake, body fatness, diet quality and physical activity.
8) To define appropriate data analysis strategies (i.e. choice of energy adjustment models, selection of covariates, testing of potential mediators) and formally evaluate and report the robustness of results (e.g. through sensitivity analysis).
9) To measure the impact of interventions in clinical and community settings to reduce the amount of dietary sugars (as E% and in g/day) on the development of dental caries in all age groups.
10) To assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars) and the development of dental caries (both incidence and severity) in all age groups, including root caries in older adults, accounting for factors that may confound the association, in order to allow the characterisation of the hazard.

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Glossary, abbreviations and acronyms

100% FJs	100% fruit juices, with no added sugars
24-h DR	24-h dietary recall
24uSF	Urinary sucrose and fructose in 24-h urine samples
Added sugars	Mono- and disaccharides added to foods as ingredients during processing or preparation at home, and sugars eaten separately or added to foods at the table
AGAHLS	Amsterdam Growth and Health Longitudinal Study
AI	Adequate intake
AIC	Akaike Information Criteria
ALSPAC	Avon Longitudinal Study of Parents and Children
ALSWH	Australian Longitudinal Study on Women's Health
AMP	Adenosine monophosphate
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AOAC	Association of Official Analytical Chemists
ARIC	Atherosclerosis Risk in Communities Study
ASBs	Artificially sweetened beverages
ASSDs	Artificially sweetened drinks
ATP	Adenosine triphosphate
AUC	Area under the curve
BF	Body fat
BIA	Bioelectrical impedance analysis
BMES	Blue Mountain Eyes Study
BMI	Body mass index
BoE	Body of evidence
BP	Blood pressure
BW	Body weight
BWHS	Black Women's Health Study
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
CI	Confidence interval
CoSCIS	Copenhagen School Child Intervention Study
CTS	California Teachers Study
CVD	Cardiovascular disease
Daily-D	Daily-D Health Study
DBP	Diastolic blood pressure
DCH	Diet, Cancer and Health Study
DDHP	Detroit Dental Health Project
DFS	Decayed, filled surfaces
DMFS	Decayed, missing and filled tooth surfaces
DMFT	Decayed, missing and filled teeth
DNL	De novo lipogenesis
DONALD	Dortmund Nutritional and Anthropometric Longitudinally Designed Study
DRI	Dietary Reference Intake
DRV	Daily reference values
E%	Percent energy intake
EC	European Commission
EFSA	European Food Safety Authority
EKE	Expert Knowledge Elicitation
ELEMENT	Early Life Exposure in Mexico to Environmental Toxicants
EPIC-Diogenes	European Prospective Investigation into Cancer and Nutrition-Diet, Obesity and Genes project
EPIC-E3N	European Prospective Investigation into Cancer and Nutrition-French cohort

EPIC-InterAct	European Prospective Investigation into Cancer and Nutrition-InterAct project
EPIC-Morgen	European Prospective Investigation into Cancer and Nutrition-Morgen cohort
EPIC-Multicentre	European Prospective Investigation into Cancer and Nutrition-Multicentre
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition-Norfolk cohort
EPICOR	European Prospective Investigation into Cancer and Nutrition-Italian cohort
EPIC-Utrecht	European Prospective Investigation into Cancer and Nutrition-Utrecht cohort
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EU	European Union
FBDG	Food-based dietary guidelines
FCD	Food composition database
FFQ	Food frequency questionnaire
FJ	Fruit juice
FMCHES	Finnish Mobile Clinic Health Examination Survey
Framingham-3Gen	Framingham third Generation cohort
Framingham-Offspring	Framingham offspring's cohort
Free sugars	Added sugars plus sugars naturally present in honey, syrups, fruit juices and juice concentrates
GDM	Gestational diabetes mellitus
GeliS	Healthy living in pregnancy study
Generation R	Generation R Study
GI	Glycaemic index
GL	Glycaemic load
GLP1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
GUTS	Growing Up Today Study
GUTS II	Growing Up Today Study II
HBW	High birth weight
HDL	High-density lipoprotein
HFCS	High fructose corn syrup
HHS	U.S. Department of Health and Human Services
HOMA	Homeostatic model assessment
HPFS	Health Professionals Follow-up study
HPAEC-PAD	High Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection
HPLC	High Performance Liquid Chromatography
HPP	Harvard Pooling Project of Diet and Coronary Disease
HR	Hazard ratio
HSS-DK	Healthy Start Study-Denmark
HSS-USA	Healthy Start Study-USA
HTN	Hypertension
IFS	Iowa Fluoride Study
IGT	Impaired glucose tolerance
IL6	Interleukin 6
Inter99	Inter99 study
IoM	Institute of Medicine
IR	Insulin resistance
ISI	Insulin sensitivity index
IUGR	Intrauterine growth retardation
iv	Intravenous
IVGTT	Intravenous glucose tolerance test
IVITT	Intravenous insulin tolerance test
JPHC	Japan Public Health centre-based study Cohort
KoCAS	Korean Child–Adolescent cohort Study
KoGES	Korean Genome and Epidemiology Study
LBW	Low birth weight
LDL	Low-density lipoprotein
LF	Liver fat

LGA	Large-for-gestational age
Linking category	Categories established based on the distribution of total sugar values within each FoodEx2 level in order to match the total sugar content from the EFSA Nutrient Composition Database with the foods reported in the EFSA Comprehensive European Food Consumption Database
LoE	Line of Evidence
MDCS	Malmo Diet Cancer Study
MIT-GDS	Massachusetts Institute of Technology Growth and Development Study
MoBa	Norwegian Mother and Child Cohort Study
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MOVE	MOVE project
Mr and Ms OS	Mr and Ms OS of Hong Kong
MTC	Mexican Teachers' Cohort
Na^+/K^+ ATPase	Sodium–potassium adenosine triphosphatase
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PCC	Prospective case-cohort
NDA Panel	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NGHS	National Lung, Heart and Blood Institute's Growth and Health Study
NGT	Normal glucose tolerance
NHS	Nurses' Health Study
NHS-II	Nurses' Health Study-II
NIH-AARP	National Institutes of Health-American Association for Retired Persons Diet and Health Study
NK cells	Natural killer cells
NPAAS	Nutrition and Physical Activity Assessment Study
NSHDS	Northern Sweden Health and Disease Study
NTP	National Toxicology Program
OGTT	Oral glucose tolerance test
OHAT	Office of Health Assessment and Translation
OPEN	Observing Protein and Energy Nutrition
P/S	Polyunsaturated/Saturated fat
PCs	Prospective cohort studies
PHHP	Pawtucket Heart Health Program
PHI	Planet Health Intervention
ppm	parts per million
Project Viva	Project Viva
PROMETHEUS	PROmoting METHods for Evidence Use in Scientific assessments
PYY	Peptide YY
QUALITY	Quebec Adipose and Lifestyle InvesTigation in Youth
RCS	Restricted cubic splines
RCTs	Randomised controlled trials
REGARDS	Reasons for Geographic and Racial Differences in Stroke study
RI	Reference intake
RoB	Risk of bias
RR	Relative risk
SACN	Scientific Advisory Committee on Nutrition
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SCES	Sydney Childhood Eye Study
SCF	Scientific Committee on Food
SCHS	Singapore Chinese Health Study
SD	Standard deviation
SE	Standard error
SES	Social economic score
SFFQ	Semi-quantitative food frequency questionnaire
SGA	Small-for-gestational age

SGLT1	Sodium-Glucose-coTransporter 1
SLIVGTT	Stable labelled intravenous glucose tolerance test
sQ	Subquestion
SSBs	Sugar sweetened beverages
SSFDs	Sugar sweetened fruit drinks
SSFJs	Sugar sweetened fruit juices
SSSDs	Sugar sweetened soft drinks
STRIP	Special Turku Coronary Risk Factor Intervention Project
SUN	Seguimiento Universidad de Navarra
T2DM	Type 2 diabetes mellitus
Table sugar	Sucrose
TEI	Total energy intake
TFJ	Total fruit juice
TG	Triglyceride
TLGS	Teheran Lipid and Glucose Study
TNF-α	Tumour necrosis factor alpha
Total sugars	All mono- and disaccharides found in mixed diets i.e. glucose, fructose, sucrose, galactose, lactose, trehalose and maltose
TRL	Triglyceride rich lipoprotein
UA	Uncertainty analysis
UK	United Kingdom
UL	Tolerable Upper Level of Intake
US	United States
USDA	U.S. Department of Agriculture
VA-DLS	Department of Veterans Affairs-Dental Longitudinal Study
VAT	Visceral adipose tissue
VLDL	Very low-density lipoprotein
WAPCS	Western Australia Pregnancy Cohort (Raine) Study
WC	Waist circumference
WGHS	Women's Genome Health Study
WHI	Women's Health Initiative
WHO	World Health Organisation
WHS	Women's Health Study

Appendix A – Summary results_intake and percent contribution_whole population

Table A.1: Intake of total, free and added sugars across EU dietary surveys from selected food groups and percent contribution of the selected food groups to the intake of total, free and added sugars[18]

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)																		
Sugars and confectionery	0	10	0	31	0%	20%	0	10	0	31	1%	80%	0	10	0	31	1%	82%
SSSD+SSFD	0	2	0	12	0%	3%	0	2	0	12	0%	18%	0	2	0	12	0%	25%
Fine bakery wares	0	2	0	9	0%	4%	0	2	0	9	0%	34%	0	2	0	9	0%	36%
Fruit/veg. juices	0	5	0	30	0%	9%	0	5	0	30	2%	33%	0	2	0	7	0%	23%
Fruit/veg., processed	0	16	0	75	0%	20%	0	2	0	10	0%	16%	0	2	0	10	0%	19%
Fruit/veg., fresh	2	17	24	52	3%	28%	N/A						N/A					
Cereals	0	2	0	8	0%	3%	0	1	0	11	0%	14%	0	1	0	11	0%	16%
Milk and dairy	5	37	23	114	13%	60%	0	2	0	11	0%	47%	0	2	0	11	0%	50%
Baby foods	10	45	41	104	12%	65%	0	4	0	11	0%	52%	0	4	0	11	0%	52%
Others	0	2	0	11	0%	4%	0	1	0	8	0%	17%	0	1	0	2	0%	11%
TODDLERS (≥ 12 to < 36 months)																		
Sugars and confectionery	1	13	6	51	2%	19%	1	12	6	49	6%	54%	1	12	2	36	8%	61%
SSSD+SSFD	0	18	0	83	0%	19%	0	18	0	83	0%	37%	0	16	0	77	0%	42%
Fine bakery wares	0	7	1	37	0%	10%	0	7	1	34	1%	28%	0	7	1	34	1%	34%
Fruit/veg. juices	2	19	5	72	3%	19%	2	19	5	72	10%	36%	0	4	0	17	0%	20%
Fruit/veg., processed	1	9	2	52	1%	14%	0	4	0	19	0%	13%	0	4	0	19	1%	15%
Fruit/veg., fresh	6	21	33	94	9%	30%	N/A						N/A					

[18] Data extracted from Annex D-Results of the intake assessment. Whole population.

[19] *Sugars and confectionery* includes sugar and similar, confectionery and water-based sweet desserts; *SSSD+SSFD* are sugar sweetened soft drinks and sugar sweetened fruit drinks; *Fruit/veg. juices* include nectars; *Fruit/veg. processed* excludes beverages; *Cereals* include cereal-based products and exclude fine bakery wares; *Milk and dairy* also includes dairy alternate products; Baby foods are foods for infants and young children.

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Cereals	1	4	5	17	1%	6%	0	3	0	11	0%	14%	0	3	0	11	0%	20%
Milk and dairy	10	31	56	110	17%	37%	2	15	13	45	5%	32%	2	15	13	45	7%	48%
Baby foods	1	20	2	89	1%	32%	0	4	0	12	0%	13%	0	3	0	12	0%	15%
Others	0	3	2	11	1%	4%	0	2	0	9	0%	7%	0	0	0	3	0%	2%
OTHER CHILDREN (≥ 36 months to < 10 years)																		
Sugars and confectionery	4	28	20	105	6%	24%	4	26	18	101	12%	41%	3	26	14	86	14%	62%
SSSD+SSFD	1	29	1	115	2%	24%	1	29	1	115	3%	36%	1	27	1	108	5%	39%
Fine bakery wares	0	16	0	72	0%	16%	0	15	0	65	0%	26%	0	15	0	65	0%	33%
Fruit/veg. juices	4	23	15	99	6%	20%	4	23	15	99	9%	35%	0	4	0	17	0%	11%
Fruit/veg., processed	1	13	3	57	1%	13%	0	7	1	37	1%	13%	0	7	1	37	1%	16%
Fruit/veg., fresh	9	27	39	119	12%	26%	N/A						N/A					
Cereals	2	8	5	34	2%	12%	0	6	0	25	0%	19%	0	6	0	25	0%	25%
Milk and dairy	14	37	51	139	17%	40%	3	14	21	70	8%	30%	3	14	21	70	9%	33%
Others	1	5	3	20	1%	5%	0	1	0	5	0%	2%	0	1	0	5	0%	2%
ADOLESCENTS (≥ 10 to < 14 years)																		
Sugars and confectionery	6	30	24	110	7%	24%	6	29	22	106	12%	39%	4	28	13	100	13%	56%
SSSD+SSFD	3	37	22	176	3%	27%	3	37	22	176	6%	38%	3	35	21	166	7%	41%
Fine bakery wares	0	16	0	80	0%	16%	0	15	0	75	0%	25%	0	15	0	75	0%	32%
Fruit/veg. juices	6	23	26	104	5%	19%	6	23	26	104	8%	33%	0	5	0	20	0%	12%
Fruit/veg., processed	1	11	6	56	2%	11%	1	5	1	35	1%	9%	1	5	1	35	1%	11%
Fruit/veg., fresh	9	29	40	134	8%	26%	N/A						N/A					
Cereals	2	9	7	43	2%	12%	0	6	2	32	0%	16%	0	6	2	32	1%	23%
Milk and dairy	8	36	31	143	11%	32%	1	14	3	79	3%	18%	1	14	3	79	4%	26%
Alcoholic beverages	0	1	0	8	0%	2%	0	1	0	8	0%	3%	0	1	0	0	0%	1%
Others	1	4	2	17	1%	4%	0	1	1	5	0%	2%	0	1	1	5	1%	2%
ADOLESCENTS (≥ 14 to < 18 years)																		
Sugars and confectionery	6	28	25	105	6%	24%	6	26	23	102	11%	42%	5	26	23	97	12%	59%
SSSD+SSFD	4	36	28	188	4%	28%	4	36	28	188	6%	39%	3	35	27	181	7%	44%

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Fine bakery wares	0	14	0	70	0%	14%	0	13	0	64	0%	22%	0	13	0	64	0%	30%
Fruit/veg. juices	6	34	27	167	5%	27%	6	34	27	167	8%	38%	0	3	0	19	0%	10%
Fruit/veg., processed	2	9	7	45	2%	10%	0	5	1	26	1%	8%	0	5	1	26	1%	10%
Fruit/veg., fresh	9	27	39	136	9%	25%	N/A						N/A					
Cereals	2	9	7	46	2%	11%	0	6	2	32	1%	13%	0	6	2	32	1%	16%
Milk and dairy	9	34	34	131	11%	30%	1	12	1	69	4%	16%	1	12	1	69	4%	22%
Alcoholic beverages	0	2	0	11	0%	2%	0	1	0	8	0%	2%	0	1	0	4	0%	2%
Others	1	4	3	17	1%	4%	0	1	1	5	0%	2%	0	1	1	5	1%	3%
ADULTS (≥ 18 to < 65 years)																		
Sugars and confectionery	7	28	34	95	11%	29%	7	28	32	91	18%	52%	5	26	23	90	20%	57%
SSSD+SSFD	3	19	10	119	3%	18%	3	19	10	119	7%	30%	3	19	10	115	8%	34%
Fine bakery wares	1	14	7	64	1%	14%	1	13	5	63	2%	23%	1	13	5	63	2%	30%
Fruit/veg. juices	1	24	0	124	1%	20%	1	24	0	124	2%	31%	0	2	0	21	0%	5%
Fruit/veg., processed	1	9	4	49	2%	9%	0	6	0	28	1%	12%	0	6	0	28	1%	14%
Fruit/veg., fresh	14	30	63	132	14%	39%	N/A						N/A					
Cereals	2	7	10	31	3%	8%	0	3	0	16	1%	7%	0	3	0	16	1%	9%
Milk and dairy	7	28	29	125	10%	26%	1	10	4	57	3%	14%	1	10	4	57	4%	20%
Alcoholic beverages	1	7	5	31	1%	8%	0	3	1	15	1%	5%	0	1	0	8	0%	3%
Others	1	7	3	25	2%	7%	0	2	1	6	1%	3%	0	2	1	6	1%	4%
OLDER ADULTS (≥ 65 years)																		
Sugars and confectionery	6	26	27	92	8%	27%	6	26	27	90	15%	60%	3	25	13	73	10%	66%
SSSD+SSFD	1	7	0	38	1%	7%	1	7	0	20	2%	21%	1	6	0	20	2%	22%
Fine bakery wares	2	17	4	98	1%	21%	1	16	4	84	2%	36%	1	16	4	84	2%	45%
Fruit/veg. juices	0	14	0	73	0%	13%	0	14	0	73	1%	25%	0	1	5	25	0%	3%
Fruit/veg., processed	1	13	2	62	2%	14%	0	9	0	44	2%	21%	0	9	0	44	2%	26%
Fruit/veg., fresh	17	30	74	136	19%	44%	N/A						N/A					
Cereals	2	6	8	24	3%	8%	0	2	0	9	0%	6%	0	2	0	9	0%	7%
Milk and dairy	7	24	28	123	11%	24%	0	10	0	53	2%	17%	0	10	0	53	3%	22%

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Alcoholic beverages	1	6	3	23	1%	5%	0	3	0	15	0%	9%	0	1	0	7	0%	4%
Others	1	6	4	23	2%	8%	0	2	1	10	1%	4%	0	2	1	10	1%	5%
PREGNANT WOMEN																		
Sugars and confectionery	8	16	39	67	9%	16%	7	15	36	62	17%	29%	5	14	21	54	17%	31%
SSSD+SSFD	2	10	9	55	2%	11%	2	10	9	55	4%	24%	2	10	9	55	5%	32%
Fine bakery wares	7	11	32	61	9%	11%	7	10	31	57	17%	22%	6	10	31	57	22%	29%
Fruit/veg. juices	5	10	24	54	5%	11%	5	10	24	54	10%	23%	0	2	19	23	0%	5%
Fruit/veg., processed	2	8	7	23	2%	9%	1	5	6	18	2%	9%	1	5	6	18	2%	11%
Fruit/veg., fresh	17	25	89	108	22%	30%	N/A						N/A					
Cereals	3	9	10	39	3%	9%	0	5	3	25	1%	12%	0	5	3	25	2%	16%
Milk and dairy	14	29	53	133	16%	31%	3	10	19	63	9%	22%	3	10	19	63	12%	25%
Alcoholic beverages	0	0	0	0	0%	0%	0	0	0	0	0%	0%	0	0	0	3	0%	0%
Others	2	3	10	14	3%	4%	0	1	1	4	1%	2%	0	1	1	4	1%	2%
LACTATING WOMEN																		
Sugars and confectionery	15	26	54	97	15%	23%	14	25	53	92	28%	48%	7	22	29	77	27%	52%
SSSD+SSFD	2	2	10	11	2%	2%	2	2	10	11	4%	4%	2	2	10	11	5%	8%
Fine bakery wares	6	11	26	57	5%	12%	5	11	26	53	11%	21%	5	11	26	53	13%	39%
Fruit/veg. juices	7	17	26	66	6%	17%	7	17	26	66	13%	33%	0	1	17	18	1%	1%
Fruit/veg., processed	2	9	8	44	2%	8%	1	5	7	29	2%	10%	1	5	7	29	3%	12%
Fruit/veg., fresh	18	35	92	148	19%	31%	N/A						N/A					
Cereals	4	5	16	21	4%	5%	1	2	5	6	2%	4%	1	2	5	6	2%	7%
Milk and dairy	21	21	54	82	18%	22%	4	6	12	30	7%	12%	4	6	12	30	14%	14%
Alcoholic beverages	0	0	0	2	0%	0%	0	0	0	0	0%	0%	0	0	0	0	0%	0%
Others	3	4	8	12	2%	4%	0	1	0	2	0%	1%	0	1	0	2	1%	1%

Numbers in red indicate identical estimated intake values for added and free sugars.
(a): Minimum (min) and maximum (max) means and 95th percentiles across EU surveys, for each age class.

Appendix B – Summary results_intake and percent contribution_consumers

Table B.1: Intake of free sugars across EU dietary surveys from selected food groups in consumers and percent contribution of the selected food groups to the intake of free sugars

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)										
Fine bakery wares	0	52	0	5	2	13	3	23	1%	51%
Confectionery	0	27	0	10	3	8	5	30	3%	54%
Sugar and similar	1	93	1	13	6	33	6	26	6%	82%
SSSD+SSFD	0	26	1	35	7	7	11	38	3%	100%
Fruit/veg. juices	5	52	1	14	2	23	2	32	7%	53%
TODDLERS (≥ 12 to < 36 months)										
Fine bakery wares	26	97	1	8	3	18	15	63	4%	33%
Confectionery	14	92	1	12	3	24	19	64	5%	32%
Sugar and similar	6	99	2	13	7	31	18	60	5%	53%
SSSD+SSFD	2	80	2	22	10	63	18	71	7%	41%
Fruit/veg. juices	32	89	4	24	15	47	14	66	19%	48%
OTHER CHILDREN (≥ 36 months to < 10 years)										
Fine bakery wares	1	98	1	15	5	37	32	82	1%	28%
Confectionery	36	100	7	16	17	46	35	82	14%	22%
Sugar and similar	21	100	3	15	9	39	29	82	5%	29%

[20] Data extracted from Annex E. Results of the intake assessment. Consumers.

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
SSSD+SSFD	14	97	5	31	21	72	42	86	11%	38%
Fruit/veg. juices	39	96	8	26	23	67	31	87	13%	42%
ADOLESCENTS (≥ 10 to < 14 years)										
Fine bakery wares	3	96	0	16	5	61	32	106	0%	30%
Confectionery	35	97	7	20	18	60	39	99	14%	31%
Sugar and similar	27	98	5	17	14	47	31	98	6%	28%
SSSD+SSFD	23	93	10	39	27	101	44	99	19%	47%
Fruit/veg. juices	30	93	13	26	36	71	37	105	15%	47%
ADOLESCENTS (≥ 14 to < 18 years)										
Fine bakery wares	0	88	2	19	24	54	34	101	2%	30%
Confectionery	27	94	8	21	20	59	49	111	12%	34%
Sugar and similar	32	97	6	19	21	53	34	100	9%	33%
SSSD+SSFD	20	90	12	41	40	118	46	109	16%	48%
Fruit/veg. juices	25	93	11	55	35	146	44	111	15%	49%
ADULTS (≥ 18 to < 65 years)										
Fine bakery wares	28	84	2	20	5	53	34	84	3%	31%
Confectionery	13	91	5	17	15	57	39	92	10%	30%
Sugar and similar	25	97	8	27	25	60	30	85	13%	51%
SSSD+SSFD	16	88	9	40	30	123	30	109	24%	47%
Fruit/veg. juices	15	81	1	45	5	134	30	97	3%	46%
OLDER ADULTS (≥ 65 years)										
Fine bakery wares	34	90	2	21	5	66	23	62	3%	43%
Confectionery	9	86	4	12	13	33	31	67	8%	32%
Sugar and similar	36	99	8	24	22	55	20	62	16%	59%

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
SSSD+SSFD	6	89	5	25	18	71	24	79	18%	48%
Fruit/veg. juices	24	78	0	30	13	94	20	71	2%	42%
PREGNANT WOMEN										
Fine bakery wares	59	76	9	15	23	43	39	55	20%	32%
Confectionery	24	39	8	18	27	46	46	62	16%	30%
Sugar and similar	33	76	7	11	23	31	38	53	15%	23%
SSSD+SSFD	15	40	13	30	33	85	42	64	22%	46%
Fruit/veg. juices	37	70	8	17	28	53	36	58	22%	35%
LACTATING WOMEN										
Fine bakery wares	55	86	10	12	27	27	52	59	17%	24%
Confectionery	46	54	7	13	35	35	55	60	12%	22%
Sugar and similar	74	93	15	19	49	49	54	56	27%	36%
SSSD+SSFD	16	37	6	13	42	42	50	69	12%	19%
Fruit/veg. juices	46	86	15	19	46	46	51	63	23%	37%

Confectionery includes water-based desserts; SSSD+SSFD are sugar sweetened soft drinks and sugar sweetened fruit drinks.
(a): Minimum (min) and maximum (max) means (and 95th percentiles when calculated) across EU surveys, for each age class.

Table B.2: Intake of added sugars across EU dietary surveys from selected food groups in consumers and percent contribution of the selected food groups to the intake of free sugars

Food groups[21]	Added sugars									
	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)										
Fine bakery wares	0	52	0	5	2	13	3	19	1%	53%
Confectionery	0	27	0	10	3	8	5	27	3%	54%
Sugar and similar	1	93	1	13	5	33	2	22	6%	82%
SSSD+SSFD	0	26	1	31	6	6	10	31	4%	100%
Fruit/veg. juices	5	52	0	8	0	7	2	25	0%	32%
TODDLERS (≥ 12 to < 36 months)										
Fine bakery wares	26	97	1	8	3	18	11	43	5%	41%
Confectionery	14	92	1	12	3	24	17	47	6%	36%
Sugar and similar	6	99	0	12	3	29	11	40	3%	61%
SSSD+SSFD	2	80	2	21	9	59	16	62	8%	46%
Fruit/veg. juices	32	89	0	8	0	18	9	41	0%	32%
OTHER CHILDREN (≥ 36 months to < 10 years)										
Fine bakery wares	1	98	1	15	5	37	25	71	3%	37%
Confectionery	36	100	7	16	17	46	27	72	17%	29%
Sugar and similar	21	100	1	13	5	37	20	70	3%	38%
SSSD+SSFD	14	97	5	29	20	67	32	73	14%	41%
Fruit/veg. juices	39	96	0	10	0	21	23	68	0%	16%

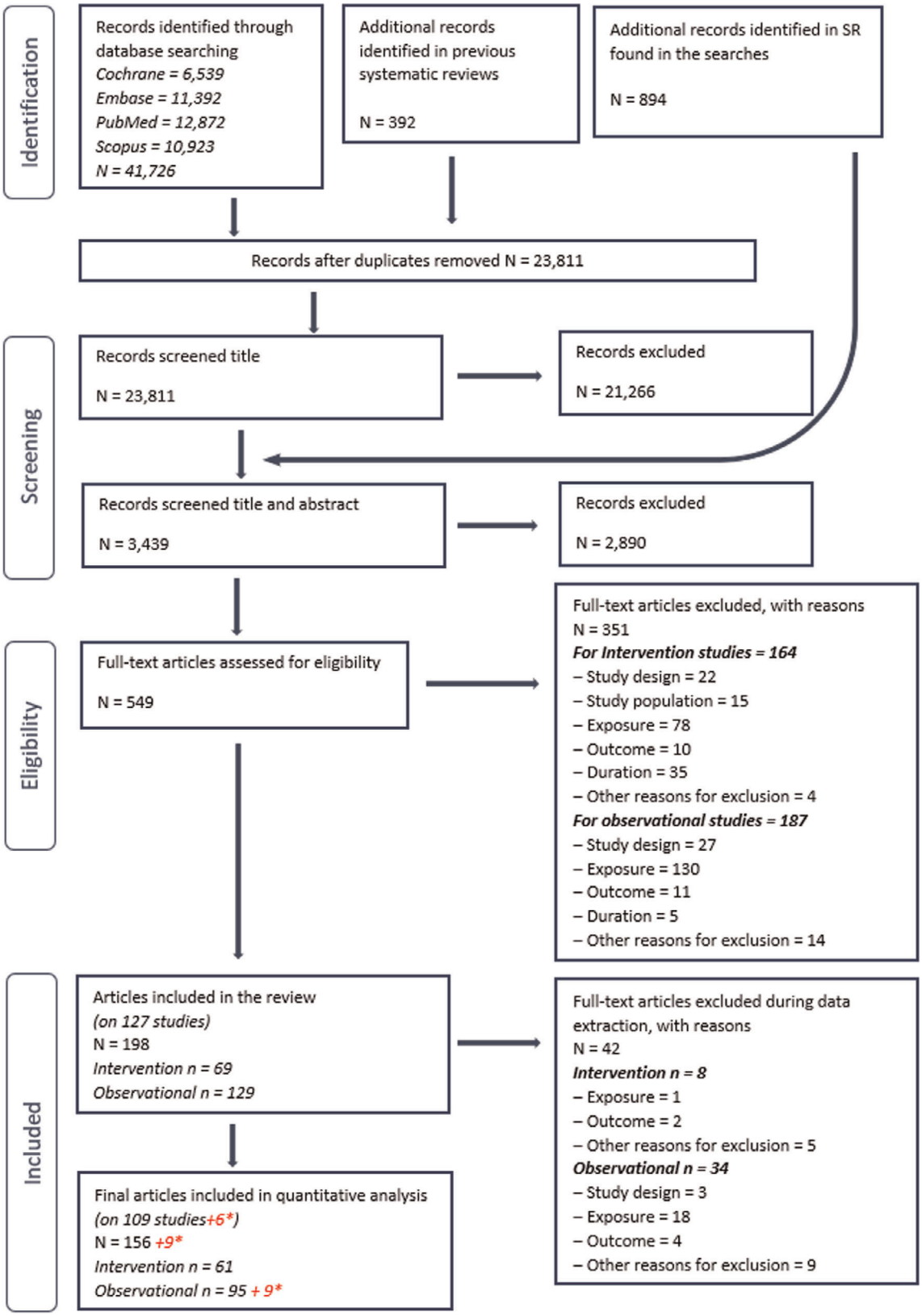
[21] Data extracted from Annex E. Results of the intake assessment. Consumers.

Added sugars										
Food groups[21]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
ADOLESCENTS (≥ 10 to < 14 years)										
Fine bakery wares	3	96	0	16	5	61	26	87	1%	36%
Confectionery	35	97	7	20	18	60	34	89	16%	38%
Sugar and similar	27	98	1	16	13	47	22	85	3%	31%
SSSD+SSFD	23	93	10	37	26	97	37	88	21%	56%
Fruit/veg. juices	30	93	0	10	0	25	25	83	0%	26%
ADOLESCENTS (≥ 14 to < 18 years)										
Fine bakery wares	0	88	2	19	24	54	29	83	3%	38%
Confectionery	27	94	8	21	20	59	39	89	14%	39%
Sugar and similar	32	97	3	18	12	53	28	88	7%	37%
SSSD+SSFD	20	90	12	40	40	118	41	88	24%	59%
Fruit/veg. juices	25	93	0	12	0	26	33	81	0%	21%
ADULTS (≥ 18 to < 65 years)										
Fine bakery wares	28	84	2	20	5	53	27	61	3%	39%
Confectionery	13	91	5	17	15	57	33	71	11%	36%
Sugar and similar	25	97	4	25	19	59	23	62	9%	55%
SSSD+SSFD	16	88	9	40	29	123	28	83	26%	51%
Fruit/veg. juices	15	81	0	10	0	23	21	58	0%	17%
OLDER ADULTS (≥ 65 years)										
Fine bakery wares	34	90	2	21	5	66	19	48	4%	52%
Confectionery	9	86	4	12	13	33	25	54	9%	39%
Sugar and similar	36	99	2	22	15	53	15	47	7%	65%
SSSD+SSFD	6	89	5	25	18	71	22	64	20%	53%
Fruit/veg. juices	24	78	0	2	0	12	15	49	0%	9%

Added sugars										
Food groups[21]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
PREGNANT WOMEN										
Fine bakery wares	59	76	9	15	23	43	31	49	26%	40%
Confectionery	24	39	8	18	27	46	36	56	17%	34%
Sugar and similar	33	76	2	9	7	30	27	47	5%	25%
SSSD+SSFD	15	40	13	30	33	85	33	57	24%	55%
Fruit/veg. juices	37	70	0	4	0	13	26	42	0%	11%
LACTATING WOMEN										
Fine bakery wares	55	86	10	12	27	27	29	49	20%	42%
Confectionery	46	54	7	13	35	35	33	51	20%	26%
Sugar and similar	74	93	6	16	48	48	30	44	20%	37%
SSSD+SSFD	16	37	6	13	42	42	32	61	18%	22%
Fruit/veg. juices	46	86	0	1	8	8	26	47	1%	2%

Confectionery includes water-based desserts; *SSSD+SSFD* are sugar sweetened soft drinks and sugar sweetened fruit drinks.
(a): Minimum (min) and maximum (max) means (and 95th percentiles when calculated) across EU surveys, for each age class.

Appendix C – Flow chart for the selection of human studies



*: Articles identified through the update of the literature search that were incorporated into the assessment (see Annex A).

Figure C.1: Flow chart for the selection of studies on metabolic diseases

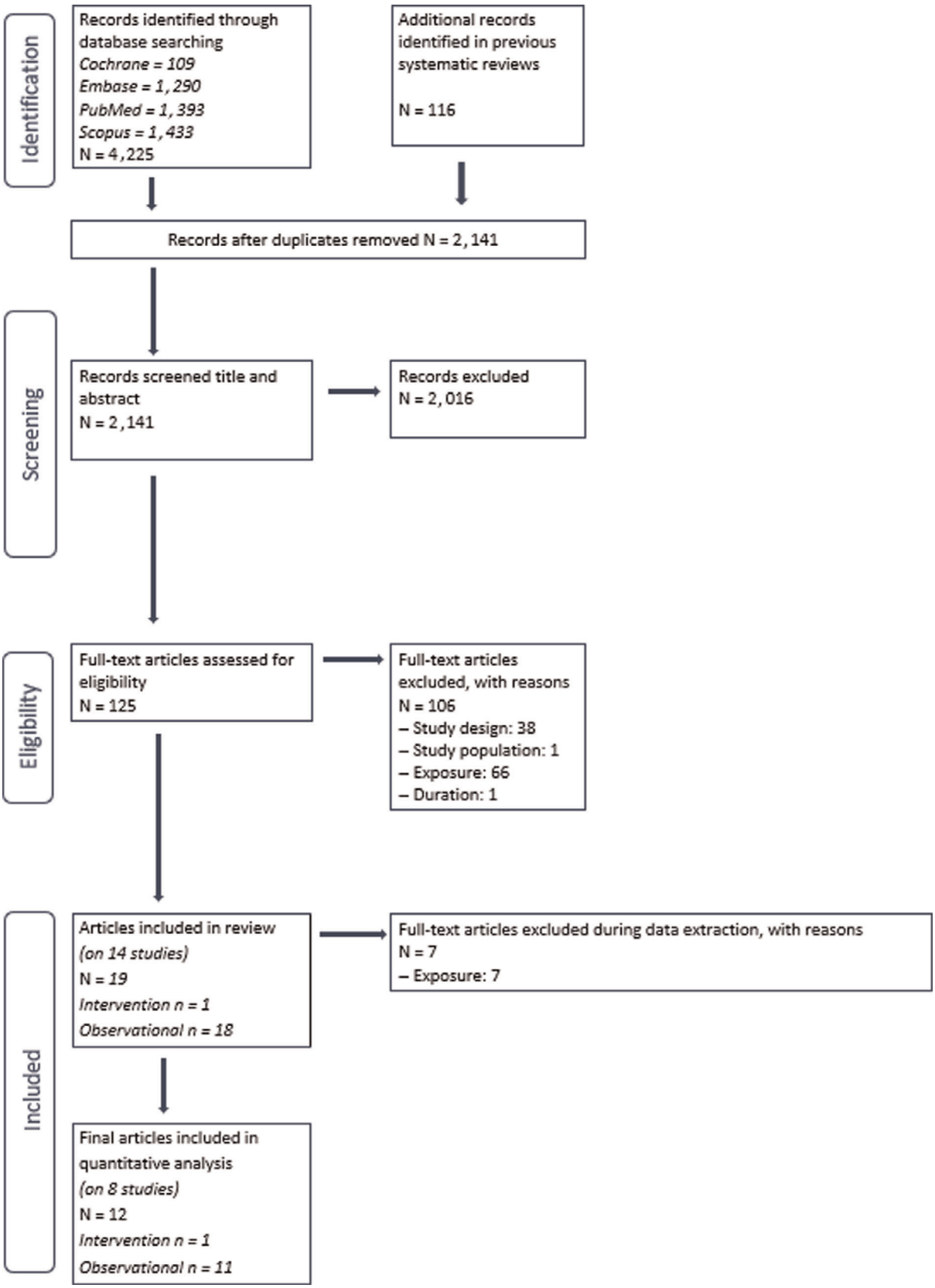


Figure C.2: Flow chart for the selection of studies on caries

Appendix D – Intervention studies on metabolic diseases reported in multiple references

Several randomised controlled trials that were eligible for this assessment were reported in multiple references. To facilitate the identification of the individual studies when reporting the results in forest plots, a main reference was identified for each of them. In some cases, data on different endpoints were extracted from linked references, and not from the main reference indicated in the forest plots or the text. In other cases, linked references did not provide additional data for this assessment with respect to the main reference and were excluded at data extraction (e.g. report on reanalysis of data already presented in the main reference or other linked references). Main references for studies with data extracted from linked references appear in forest plots with an asterisk (e.g. Angelopoulos et al., 2015*).

Main reference and endpoints extracted	Linked references and endpoints extracted	Linked references excluded at data extraction
Angelopoulos et al. (2015)* Uric acid, SBP, DBP	Angelopoulos et al. (2016) Triglycerides, total cholesterol, HDL-c, LDL-c, fasting glucose, body weight, BMI, WC	
Hallfrisch et al. (1983a)* Glucose at 120′ during an OGTT, insulin at 120′ during an OGTT, fasting insulin, fasting glucose	Hallfrisch et al. (1983b) Triglycerides, total cholesterol, HDL-c, LDL-c, SBP, DBP	
Israel et al. (1983)* Uric acid, SBP, DBP	Reiser et al. (1981a) Triglycerides, total cholesterol, HDL-c, LDL-c	
	Reiser et al. (1981b) fasting glucose, fasting insulin, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT	
Ebbeling et al. (2012) Body weight, BMI		Ebbeling et al. (2006)
Ruyter et al. (2014) Body weight, WC		Katan et al. (2016)
Lowndes et al. (2014b)* WC, BF, fasting glucose, SBP, DBP, total cholesterol, triglycerides, HDL-c, LDL-c, uric acid	Bravo et al. (2013) Liver fat	Yu et al. (2013)
Maersk et al. (2012)* VAT, Liver fat	Engel et al. (2018) Body weight, BF, triglycerides, total-c, HDL-c, LDL-c, fasting insulin, fasting glucose, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT, Matsuda index, SBP, DBP	
	Bruun et al. (2015) Uric acid	
Raben et al. (2002)* Body weight, BMI, BF, SBP, DBP,	Raben et al. (2011) Triglycerides, total cholesterol, HDL-c, fasting glucose, fasting insulin, HOMA-IR, HOMA-β	

Main reference and endpoints extracted	Linked references and endpoints extracted	Linked references excluded at data extraction
Reiser et al. (1979a)* Total cholesterol, triglycerides	Reiser et al. (1979b) Glucose at 120′ during an OGTT, insulin at 120′ during an OGTT	
	Solyst et al. (1980) Uric acid	
Reiser et al. (1989a) Triglycerides, total cholesterol, HDL-c, LDL-c, uric acid		Reiser et al. (1989b)
Saris et al. (2000) Body weight, fasting glucose, fasting insulin, triglycerides, total cholesterol, HDL-c, LDL-c		Poppitt et al. (2002)
Stanhope et al. (2009)* WC, VAT, SBP, DBP, triglycerides, total cholesterol, HDL-c, LDL-c, fasting glucose, fasting insulin, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT		Stanhope et al. (2011)
	Cox et al. (2012) Uric acid	
	Rezvani et al. (2013) Body weight, BF	

BF, body fat; BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model of assessment; IR, insulin resistance; LDL-c, low density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; VAT, visceral adipose tissue; WC, waist circumference.

Appendix E – Main characteristics of intervention studies on metabolic diseases

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Isocaloric with neutral energy balance[5]														
Bantle et al. (2000)	US	Public	CX, 6	Fructose Glucose	14 14	24/12 F BMI ≤ 32 kg/m^2	Range: 18–80 12/6F[3] 40 12/6F < 40	CHO: 55 Protein: 15 Fat: 30 Fibre: 23 P/S: 0.947	Mixed diet	BL	–	I:14 Fr R:14 G	–	–
Black et al. (2006)	UK	Private	CX, 6	Sucrose Sucrose	10 25	13 M BMI < 35 kg/m^2	33.3 ± 3	CHO: 55 Protein: 12 Fat: 33 Fibre: 18	Mixed diet	GH, BP, BL	I: 25 R: 10	–	–	–
Despland et al. (2017)	CH	Public	CX, 8d	Starch Honey Glucose/ Fructose	0 25 25	8 M GP	NR	CHO: 55 Protein: 15 Fat: 30	Mixed diet	GH	I: 25 Gl/Fr R:0	–	–	–
Gostner et al. (2005)	DE	NR	CX, 4	Isomalt Sucrose (30 g/ day)	0 6	19 /12F GP	Median: 30.5	CHO: 46 Protein: 14 Fat: 40 Fibre: 14	Foods	GH, BL	I:6 R:0	–	–	–
Groen et al. (1966)	US	Mixed	CX, 5	Starch Sucrose (140 g/ day)	0 30	8/6F 7/4F GP	40.2 ± 3.16	*Starch/sucrose* CHO: 62.1/66.4 Protein: 18.4/14.6 Fat: 19.3/18.9		BL	I:30 R:0	–	–	–
Hallfrisch et al. (1983a)*	US	NR	CX, 5	Starch Fructose Fructose	0 7.5 15	12 M N-I 12 M H-I	39.8 ± 2.4 39.5 ± 2.1	CHO: 45 Protein: 15 Fat: 40 Fibre: 5 P/S: 0.4	Foods	GH, BP, BL	I:15 R:0	–	–	–
Israel et al. (1983)*	US	NR	CX, 6	Sucrose Sucrose Sucrose	2 15 30	24/12F H-I	Mean: 36.8 Range: 21–51	CHO: 44 Protein: 14 Fat: 42 Fibre: 4 P/S: 0.29	Foods	GH, BP, BL, UA	I:30 R:2	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Johnston et al. (2013)	US	Mixed	P, 2	Fructose Glucose	25 25	32 M, AO	35 ± 11 33 ± 9	CHO: 55 Protein: 15 Fat: 30	Beverages	EFD, GH, BL, UA	–	I:25 Fr R:25 Gl	–	–
Kelsay et al. (1974)	US	NR	CX, 4	Glucose Sucrose	42.5 42.5	7F GP	Range: 18–23	CHO: 50 Protein: 12 Fat: 38 P/S: 0.23	Foods	GH	–	–	–	–
Koh et al. (1988)	US	NR	CX, 4	Fructose Glucose	15 15	9/6F NGT 9/6F IGT	50 ± 5 54.6 ± 6	CHO: 51 Protein: 17 Fat: 32 Fibre: 22.5 P/S: 0.9	Mixed diet	GH, BP, BL	–	I:15 Fr R:15 Gl	–	–
Lewis et al. (2013)	IE	Private	CX, 6	Sucrose Sucrose	5 15	13/4F, OW/OB	46.1 ± 1.9	*5E% / 15 E%:* CHO: 54.8/55 Protein: 12.3 /12.1 Fat: 32.9/32.8 Fibre: 18.3/17.9 P/S: 0.35/0.31	Mixed diet	GH, BP, BL	I:15 R:5	–	–	–
Lowndes et al. (2014a)	US	Private	P, 10	Sucrose HFCS Sucrose HFCS	10 10 20 20	18/6F 17/8F 13/ 8F 17/9F OW/OB	39.82 ± 11.6 39.33 ± 10.94 41.15 ± 12.24 36.48 ± 12.5	NR	Beverages	BF, BP, BL	I:20 Suc R:10 Suc	–		–
Lowndes et al. (2014b)*	US	Private	P, 10	Sucrose HFCS Sucrose HFCS Sucrose HFCS	8 8 18 18 30 30	58/26F 69/42F 64/38F 60/30F 53/26F 51/28F BMI < 35	38.62 ± 12.33 38.93 ± 11.65 41.3 ± 11.1 40.43 ± 11.33 38.85 ± 11.56 43.41 ± 11.33	NR	Beverages	BF, EFD, GH, BP, BL, UA	I: 30 Suc R: 8 Suc	–		–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Lowndes et al. (2015)	US	Private	P, 10	Control milk Fructose Glucose Sucrose HFCS	0 9 9 18 18	31/21F 30/14F 34/17F 33/18F 31/21F BMI < 35	35.3 ± 12.5 35.6 ± 10.4 37 ± 11.7 34.1 ± 11 36.5 ± 11.3	NR	Beverages	GH	I: 18 Suc R: 0	I:9 Fr R:9 Gl		
Moser et al. (1986)	US	NR	CX, 4	Starch Sucrose	0 43	6F non-OC users 6F OC users	Range: 19–25	CHO: 51 Protein: 13 Fat: 36	Foods	GH, BL	I:43 R:0	–	–	–
Reiser et al. (1979a)*	US	NR	CX, 6	Starch Sucrose	0 30	19/9F GP	Mean: 42 Range: 35–55	CHO: 43 Protein: 15 Fat: 42 Fibre: 4.2 P/S: 0.26	Foods	GH, BL, UA	I:30 R:0	–	–	–
Reiser et al. (1989a)*	US	NR	CX, 5	Starch Fructose	0 20	11 M N-I 10 M H-I	Mean: 38 Range: 23–64 Mean: 47 Range: 23–64	*Starch / fructose:* CHO: 51 / 51 Protein: 13 / 13 Fat: 36 / 36 Fibre: 12.1 / 11 P/S: 0.33 / 0.33	Foods	BL, UA	I:20 R:0	–	–	–
Schwarz et al. (2015)	US	Public	CX, 9d	Starch Fructose	0 20	8 M Non-OB	42 ± 3	*Starch / fructose:* CHO: 50 / 50 Protein: 15 / 15 Fat: 35 / 35 Fibre: 28 / 17	Beverages	GH	I:20 R:0	–	–	–
Sunehag et al. (2008)	US	Mixed	CX, 1	Fructose Fructose	6 24	6/3F OB	15.2 ± 0.5	CHO: 60 E% Protein: 15 E% Fat: 25 E%	Mixed diet	GH	I:24 Fru R:6 Fru	–	–	–
Swanson et al. (1992)	US	Mixed	CX, 4	Starch Fructose	0 16.6	14/7F GP	Mean: 34 Range: 19–60	*Starch / fructose:* CHO: 55 / 55 Protein: 15 / 15 Fat: 30 /30 Fibre: 27 /26 P/S: 1 / 1	Mixed diet	GH, BL	I:16.6 R:0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Szanto and Yudkin (1969)	UK	Public	CX,2	Starch Sucrose (438 g/day)	0 54	19 M GP	Mean: 28 Range: 22–44	NR	Mixed diet	GH	I:54 R:0	–	–	–
Thompson et al. (1978)	US	Mixed	CX, 10d	Corn syrup Sucrose Corn syrup Sucrose	45 45 65 65	8 M GP	Range: 19–24	*45E% / 65E%:* CHO: 45 / 65 Protein: 15 /15 Fat: 40 / 20 P/S: 0.7 /0.7	Beverages	GH	I:65 Suc R:45 Suc	–	–	–
Umpleby et al. (2017)	UK	Public	CX, 12	NMES NMES	6 26	14 M OW/no NAFLD 11 M OW/NAFLD	Mean: 54 Range: 41–65 Mean: 59 Range: 49–64	NR	Mixed diet	EFD, GH, BL	I:6 R:26	–	–	–
Isocaloric with positive energy balance[6]														
Beck-Nielsen et al. (1978)	DK	Mixed	P, 2	Fat (250 g/day) Sucrose (250 g/day)	0 32	6 NR 6 NR GP	Range: 23–33	NR	Mixed diet	GH	I:32 R:0	–	–	–
Beck-Nielsen et al. (1980)	DK	NR	P, 1	Fructose (250 g/day) Glucose (250 g/day)	33 33	8NR 7NR GP	Range: 21–35	CHO: 44 Protein: 18 Fat: 35	Beverages	GH	–	I:36 Fr R:36 Gl	–	–
Johnston et al. (2013)	UK	Private	P, 2	Fructose Glucose	25 25	32 M, AO	35 ± 11 33 ± 9	NR	Beverages	EFD, GH	–	I:25 Fr R:25 Gl	–	–
Silbernagel et al. (2011)	DE	Mixed	P, 4	Fructose (150 g/day) Glucose (150 g/day)	22 22	10/3F 10/5F BMI < 35	30.5 ± 2	CHO: 50 Protein: 15 Fat: 35	Beverages	EFD, GH, BP, BL, UA	–	I:22 Fr R:22 Gl	–	–
Hypercaloric [7]														
Le et al. (2009)	US	NR	CX, 1	No sugars Fructose	0 35	8 M non-OffT2DM 16 M OffT2DM	24.0 ± 1.0 24.7 ± 1.3	CHO: 55 Protein: 15 Fat: 30	Beverages	GH	I:35 R:0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Ad libitum														
Aeberli et al. (2013)	CH	Mixed	CX, 3	Fructose (40 g/day) Fructose (80 g/day) Glucose (80 g/day) Sucrose (80 g/day)	8 16 16 16	9 M NW	22.8 ± 1.7	No target	Beverages	GH	I:16 Fr R:8 Fr	I:16 Fr R:16 Gl	–	–
Angelopoulos et al. (2015)*	US	NR	P, 10	Fructose Glucose Sucrose HFCS	9 9 18 18	65NR 77NR 64NR 61NR BMI < 35 kg/m^2	38.65 ± 12.19 36.1 ± 12.06 39.83 ± 12.19 36.32 ± 10.72	No target	Beverages	BF, GH, BP, BL, UA	–	I:9 Fr R:9 Gl	–	–
Campos et al. (2015)	CH	Mixed	P, 12	ASSD SSSD	0 18	14/6F 13/7F OW/OB	NR	No target	Beverages	BF, EFD, GH, BP, BL, UA	I: 18 R: 0	–	–	–
Ruyter et al. (2014)	NL	Public	P, 72	ASSD SSSD (26 g/day)	0 5	319/147F 322/151F GP	8.2 ± 1.8 8.2 ± 1.8	No target	Beverages	BF	I: 5 R: 0	–	–	–
Ebbeling et al. (2012)	US	Public	P, 52	ASSD+water SSSD+SSFD+TFJ	0 17	110/48F 114/52F OW/OB	15.3 ± 0.7 15.2 ± 0.7	No target	Beverages	BF	I: 17 R: 0	–	–	–
Hayashi et al. (2014)	JP	Public	P, 12	HFCS (28 g/day; 26 g sugar) RSS (30 g/day; 23 g sugar)	– –	17/8F 17/9F OB	42.4 ± 2.6 41.7 ± 2.8	No target	Beverages	BF, GH, BP, BL, UA	–	–	–	–
Hernandez-Cordero et al. (2014)	MX	Private	P, 36	Water SSBs	0 20	120F 120F OW/OB	33.5 ± 6.7 33.3 ± 6.7	No target	Beverages	BF, GH, BP, BL	I: 20 R: 0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Hollis et al. (2009)	US	Private	P, 12	No beverage Grape juice (82 g/day) Grape drink (82 g/day)	0 18 18	25NR 25NR 26NR OW	28 ± 10 22 ± 4 26 ± 9	No target	Beverages	BF, GH, BL	I: 18 GD R: 0	–	–	–
Houchins et al. (2012)	US	NR	CX, 8	Fruits/ vegetables (20E %) Fruit Juice (20E %)	– –	34NR GP	23 ± 1	No target	Beverages	BF	–	–	–	–
Huttunen et al. (1976)	FI	NR	P, 72	Xylitol Fructose (70 g/ day) Sucrose (73.5 g/ day)	0 14 16	48NR 35NR 33NR GP	Range: 13–55	No target	Mixed diet	GH, BL, UA	I: 16 Suc R: 0	I: 15 Fr R:15 Gl	–	–
Jin et al. (2014)	US	Mixed	P, 4	Fructose (99 g/ day) Glucose (99 g/ day)	20 20	9/6F 12/4F NAFLD	14.2 ± 0.88* 13.0 ± 0.71*	No target	Beverages	BF, EFD, GH, BL	–	I: 20 Fr R:20 Gl	–	–
Maersk et al. (2012)*	DK	Mixed	P, 24	Semi-skim milk Water ASSD SSSD (106 g/ day)	– 0 0 18	15/11F 16/11F 15/12F 14/6F OW/OB	37.7 ± 9.1 39 ± 7.3 39 ± 7.6 37.8 ± 8	No target	Beverages	BF, EFD, GH, BP, BL, UA	I:18 R:0 ASSD	–	–	–
Majid et al. (2013)	PK	Public	P, 4	No beverage Honey (46 g/ day)	0 8	31 M 32 M GP	20 ± 0.15 20.13 ± 0.14	No target	Beverages	GH, BL	I:8 R:0	–	–	–
Mark et al. (2014)	DK	Public	P, 4	Fructose (60 g/ day) Glucose (66 g/ day)	14 16	35F 38F OW/OB	Range: 20–50	No target	Beverages	BF, GH	–	I: 15 Fr R:15 Gl	–	–
Markey et al. (2016)	UK	Private	CX, 8	NMES (29 g/ day) NMES (75 g/ day)	6 16	50/34F Non-OB	31.6 ± 9.5	No target	Mixed diet	BF, GH, BP, BL	I:6 R:16	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms(1)	Sugars dose (E%)(2)	Participants	Age, years (mean ± SEM)	Background diet(3)	Food form	Outcome clusters(4)	Q1	Q2	Q3	Q4
Raben et al. (2002)*	DK	NR	P, 10	Artificial sweeteners Sucrose	0 23	21NR 21NR OW	37.1 ± 2.2 33.3 ± 2.0	No target	Mixed diet	BF, GH, BP, BL	I:23 R:0	–	–	–
Rasad et al. (2018)	IR	Public	P, 6	Honey (70 g/day) Sucrose (70 g/day)	– –	30 M 30 M GP	21.53 ± 1.63 24.23 ± 1.88	No target	Beverages	BP, BL	–	–	–	–
Saris et al. (2000)*	EU	Mixed	P, 24	High complex CHO Control High simple CHO	19 22 38	83/40F 77/40F 76/40F OW/OB	38 ± 9 38 ± 9 41 ± 9	No target	Mixed diet	BF, GH, BL	I:38 R:19	–	–	–
Smith et al. (1996)	NZ	Public	P, 24	Sugar-free diet Sucrose (66 g/day)	0 12	22NR 10NR HTG	53 ± 9 50 ± 11	No target	Mixed diet	BF, BL	I: 12 Sucr R: 0	–	–	–
Stanhope et al. (2009)*	US	Public	P, 8	Fructose Glucose	25 25	17/8F 15/8F OW/OB	Range: 40–72	No target	Beverages	BF, EFD, GH, BP, BL, UA	–	I:25 Fr R:25 Gl	–	–
Werner et al. (1984)	UK	Mixed	CX, 6	Artificial sweeteners Sucrose (100 g/day)	0 24	12/8F gallstones	Mean: 48 Range: 26–69	No target	Mixed diet	BF, GH, BL	I:24 R:0	–	–	–
Yaghoobi et al. (2008)	IR	Private	P, 4	Honey (70 g/day) Sucrose (70 g/day)	– –	38NR 17NR OW/OB	39.6 ± 10.6 42.4 ± 8.7	No target	Beverages	GH, BL	–	–	–	

AO = abdominal obesity; ASSD = artificially sweetened soft drinks; BF = body fatness; BL = blood lipids; BP = blood pressure; UA = uric acid; CHO = carbohydrates; CX = cross-over; EFD = ectopic fat deposition; F = females; Fr = fructose; GD = grape drink; GH = glucose homeostasis; GP = general population; HFCS = high fructose corn syrup; HGP = healthy general population; H-I = hyperinsulinaemia; HTG = hypertriglyceridaemia; I: intervention group; IGT = impaired glucose tolerance; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose tolerance; N-I = normo-insulinaemia; NMES = non-milk extrinsic sugars; NR = not reported; NW = normal weight; OB = obese; OC = oral contraceptives; OffT2DM = Offspring's from parents with type 2 diabetes mellitus; OW = overweight; P = parallel; R = reference group; RSS = rare sugars syrup; S = sucrose; SSFD = sugar-sweetened fruit drinks; SSSD = sugar-sweetened soft drinks; TFJ = total fruit juices. Columns Q1 and Q2 identify the arms that were selected from each study to answer questions 1 and 2, respectively. Columns Q3 and Q4 identify the studies that address questions 3 and 4, respectively.

*: Identifies whether the study has been reported in other publications from which one or more outcome variables could have been extracted (see **Appendix D**).

(1): In parenthesis, amount of sugars in g/day, either provided in the publication or calculated from the amount consumed from a given source (e.g. honey, sugar-sweetened beverages).

(2): Refers to the sugars contribution of the dietary fraction manipulated in the study to total energy intake.

(3): Carbohydrates (CHO), protein and fat are expressed as % of total energy (E%); fibre is given in g/day; P/S is the ratio of polyunsaturated to saturated fatty acids.

(4): Identifies the outcome variables that have been assessed in a study (by cluster) which are eligible for this assessment considering the duration of the intervention, as described in the protocol. Measures of body fatness (BF) include one or more of the following: body weight, BMI, body fat, waist circumference, lean body mass. For studies conducted in isocaloric conditions, changes in body weight and BMI have only been considered as explanatory variables, and not as outcome variables. Measures of ectopic fat deposition (EFD) include one or more of the following: visceral adipose tissue, liver fat, skeletal muscle fat. Measures of glucose homeostasis (GH) include either static measurements (fasting glucose, insulin and derived indices, such as HOMA-IR), dynamic measurements (measures of glucose and insulin and derived indices during an OGTT or an euglycaemic–hyperinsulinaemic clamp) or both.
(5): All arms in neutral energy balance.
(6): All arms in positive energy balance.
(7): Only sugars arm in positive energy balance (vs. a control on neutral energy balance).

Appendix F – Results of intervention studies on metabolic diseases

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Isocaloric with neutral energy balance(2)												
Bantle et al. (2000)	24/12F BMI ≤ 32 kg/m^2	CX, 6	i: Fructose c: Glucose	14 14	Mixed Diet	**NSD:** *Bw*		**Note:** glucose and insulin reported only 90 min after breakfast and AUC 24-h not eligible x this outcome		↑TG (men only) **NSD**: T-c, LDL-c, HDL-c		High fructose intake increased fasting triglycerides only in men as compared to glucose
Black et al. (2006)	13 M BMI < 35 kg/m^2	CX, 6	c: Sucrose i: Sucrose	10 25	Mixed Diet	**NSD:** *Bw*		**NSD:** WB-IS and Hep IS (clamp); FG and FI	**NSD**	↑ T-c, LDL-c **NSD:** HDL-c, TG		High sucrose intake had no effect on insulin sensitivity or BP but increased total and LDL-cholesterol
Despland et al. (2017)	8 M GP	CX, 8d	c: Starch i1: Honey i2: Glu/Fr	0 25 25	Mixed Diet	***NSD:*** *Bw*		**NDS:** glucose and insulin responses on OGTT				Fructose (pure or from honey) did not affect insulin sensitivity when consumed with glucose
Gostner et al. (2005)	19/12F GP	CX, 4	i: Isomalt c: Sucrose	0 6	Foods	***NSD:*** *Bw*		**NSD:** fructosamine		↓ Apo A-1 **NSD:** T-c, LDL-c, HDL-c, LDL-c:HDL-c ratio, TG, Apo B_{100}		No effect of isomalt on blood lipids or fructosamine
Groen et al. (1966)	8/6F 7/4F GP	CX, 5	i: Starch c: Sucrose	0 30		***NSD:*** *Bw*				↑ T-c		High sucrose intake increased total cholesterol
Hallfrisch et al. (1983a)*	12 M H-I 12 M N-I	CX, 5	c: Starch i1: Fructose i2: Fructose	0 7.5 15	Foods			↑ FG (data given for H-I and N-I combined) ↑ glucose and insulin responses (AUC) on OGTT (i2)	↓ SBP **NSD:** DBP	↑ T-c ↑ TG (i2 > i1, H-I only) ↑ LDL-c **NSD:** HDL-c, VLDL-c		Fructose increased glucose and insulin responses but reduced SBP; it also **increased TG (dose-response)** in men with hyperinsulinaemia

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Israel et al. (1983)*	24/12F H-I	CX, 6	c: Sucrose i1: Sucrose i2: Sucrose	2 15 30	Foods	***NSD:*** *Bw*		↑ FG ↑ FI (i2 > i1) ↑ glucose response (AUC) on OGTT[3] ↑ insulin response (AUC) on OGTT (i2 > i1)	↑ DBP (i2) **NSD:** SBP	↑ TG (i2 > i1, men only) ↑ T-c, LDL-c, HDL-c, VLDL-c ↓ HDL-c:T-c ratio[22] (i2, men only)	↑ FUA ↑ UA response (i1 in men only, i2)	High sucrose intakes **increased** fasting glucose and **insulin (dose-response)**, **TG (men only, dose-response),** DBP, blood lipids and uric acid in subjects with hyperinsulinaemia
Johnston et al. (2013)	15 M 17 M AO	P, 2	i: Fructose c: Glucose	25 25	Beverages	***NSD:*** *Bw*	**NSD:** liver fat, Skm fat	**NSD:** W-B IS and Hep IS (clamp; 12 subjects only, not powered for these outcomes as reported by the authors)				High fructose intake had no effect on glucose homeostasis or ectopic fat deposition as compared to glucose
Koh et al. (1988)	9/6F IGT 9/6F NGT	CX, 4	i: Fructose c: Glucose	15 15	Mixed diet	***NSD:*** *Bw*		↓ FG (IGT only) ↓ FI ↓ glucose and insulin responses (iAUC) on OGTT[4]	↓ SBP (IGT only) ↓ DBP (IGT only)	↓ TG (IGT only) ↓ T-c **NSD:** VLDL-c, LDL-c, HDL-c		Moderate intake of fructose lead to lower fasting glucose and insulin, lower BP and lower cholesterol and triglycerides compared to glucose in subjects with impaired glucose tolerance
Lewis et al. (2013)	9/4F, OW/OB	CX, 6	c: Sucrose i: Sucrose	5 15	Mixed diet	***NSD:*** *Bw*		↑ FG, FI, insulin response (iAUC) on OGTT **NSD:** glucose response (iAUC) on OGTT; W-B IS and Hep IS (clamp)	**NSD**	**NSD:** T-c, LDL-c, HDL-c, TG		A low sucrose diet reduced fasting glucose and the incremental insulin area under the curve during an OGTT with no effect on insulin sensitivity, blood pressure or blood lipids

[22] Calculated as HLD-cholesterol/(total cholesterol-HDL-cholesterol).

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Lowndes et al. (2014a)	18/6F 17/8F 13/ 8F 17/9F OW/OB	P,10	i1: Sucrose i2: HFCS i3: Sucrose i4: HFCS	10 10 20 20	Beverages	↑ Bw, BF (pooled cohort) **NSD:** Bw, WC, BF, LBM (for sugars dose or sugars type)			**NSD** (all arms combined) BP per study arm at the end of the intervention: NR	↓ HDL-c (pooled cohort) ↓ T-c, LDL-c, ApoB (i3 vs. i4) ↑ T-c/HDL-c ratio (pooled cohort) **NSD:** TG; HDL-c for sugars dose or type		Sugar consumption increased body fatness and decreased HDL-c but no effect of sugars dose or source
Lowndes et al. (2014b)*	58/26F 69/42F 64/38F 60/30F 53/26F 51/28F BMI < 35	P, 10	i1: Sucrose i2: HFCS i3: Sucrose i4: HFCS i5: Sucrose i6: HFCS	8 8 18 18 30 30	Beverages	↑ Bw, *BMI* and BF *(significant time x sugar dose interaction)* ↑ BW, BMI, WC, BF, LBM (pooled cohort) **NSD** for time x sugar dose x sugar type interaction	**NSD:** liver fat, Skm fat (data available for 64 subjects)	**NSD:** FG, FI (data available for 138 subjects)	↓ SBP (i1) **NDS:** DBP	↑ TG (pooled cohort) ↓ HDL-c (pooled cohort) **NSD:** TG, HDL-c for sugars dose or type **NSD**: T-c, LDL-c	**NSD**	**Dose-response** increase in measures of body fatness. No effect of sugar source. Changes in the lipid profile compatible with changes in body weight, unaffected by sugars dose or source
Lowndes et al. (2015)	31/21F 30/14F 34/17F 33/18F 28/17F BMI < 35 kg/m^2	P, 10	c1: Milk i1: Fructose c2: Glucose i2: Sucrose i3: HFCS	0 9 9 18 18	Beverages	↑ Bw (pooled cohort) **NSD** for sugars dose or sugars type interaction		↑ insulin response (AUC) and hepatic insulin response on OGTT (i1) (data available for 93 subjects) **NSD:** glucose response (AUC) and ISI on OGTT; FG, FI and HOMA-IR				Fructose increased the insulin response and hepatic insulin resistance during an OGTT. Effect not observed when consumed together with glucose.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Moser et al. (1986)	6F non-OC 6F OC	CX, 4	c: Starch i: Sucrose	0 43	Foods	***NSD:*** *Bw*		↓ insulin response (AUC) on OGTT[5] **NSD:** glucose response (AUC) on OGTT		↑ TG (OC vs. non-OC) **NSD:** T-c		Sucrose decreased insulin responses compared to starch with no effect on blood lipids
Reiser et al. (1979a)*	19/9F GP	CX, 6	Starch Sucrose	0 30	Foods	***NSD:*** *Bw*		**NSD:** insulin and glucose response on OGTT[3] (insulin ↑ only at 1 h)		↑ T-c, TG	↑ FUA ↑ UA response	Sucrose consumption increased total cholesterol, fasting triglycerides and uric acid. Glucose and insulin response to the sucrose load was not influenced by the nature of the carbohydrate fed (insulin response was significantly greater in those consuming sucrose only at 1 h during the OGTT).
Reiser et al. (1989a)*	10 M H-I 11 M N-I	CX, 5	c: Starch i: Fructose	0 20	Foods					↑ TG, T-c (H-I and N-I) ↑ VLDL-c, B-100 (H-I only) ↑ LDL-c (N-I only) **NSD:** HDL-c	↑ FUA (pooled H-I and N-I)	Fructose worsened the blood lipid profile and increased uric acid (background diet high in saturated fat)
Schwarz et al. (2015)	8 M Non-OB	CX, 9d	c: Starch i: Fructose	0 20	Beverages	***NSD:*** *Bw*	↑ *Liver fat*	↓ Hep-IS (clamp) **NSD:** WB-IS (clamp)				Fructose blunted suppression of endogenous glucose production
Sunehag et al. (2008)	6/3F OB Tanner 5	CX, 1	c: Fructose i: Fructose	6 24	Mixed diet			**NSD:** WB-IS (SLIVGTT), indices of insulin secretion				Fructose had no effect on insulin sensitivity in obese adolescents

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Swanson et al. (1992)	14/7F GP	CX, 4	c: Starch i: Fructose	0 16.6	Mixed diet	***NSD:*** *Bw*		**NSD:** FG, glycosylated albumin		↑ T-c, LDL-c **NSD:** TG, HDL-c, HDL-c/LDL-c ratio		Fructose increased total and LDL-c compared to starch
Szanto and Yudkin (1969)	19 M GP	CX, 2	c: Starch i: Sucrose	0 52	Mixed diet	↑ *Bw*		↑ insulin response on OGTT **NSD:** glucose response on OGTT				Sucrose increased body weight and insulin response on OGTT compared to starch. Changes driven by a subgroup of six responders
Thompson et al. (1978)	8 M GP	CX, 10d	i1:Corn syr i2:Sucrose i3:Corn syr i4:Sucrose	45 45 65 65	Beverages			↓ glucose response (AUC) on OGTT (i4 vs. i1) **NSD:** insulin response on OGTT				No clear effect of high intakes of sucrose or corn syrup on glucose homeostasis
Umpleby et al. (2017)	11 M NAFLD 14 M no NAFLD OW	CX, 12	c: NMES i: NMES	6 26	Mixed diet	↑ Bw Statistical analyses for other variables adjusted for changes in Bw	↑ Liver fat (NAFLD and no-NAFLD) **NSD:** VAT (all in 17 subjects with available data)	**NSD:** FI, FG, HOMA-IR		↑ TG, VLDL-c (NAFLD only) **NSD:** LDL-c, HDL-c, T-c		High sugars intakes increased liver fat. High liver fat lead to a differential increase in blood lipids in response to high or low intake of free sugars
Isocaloric with positive energy balance[6]												
Beck-Nielsen et al. (1978)	6 NR 6 NR GP	P, 2	c: Fat i: Sucrose	0 32	Mixed diet	***NSD:*** *Bw*		↓ WB-IS (IVITT)				High sucrose intake (and not fat) reduced insulin sensitivity
Beck-Nielsen et al. (1980)	8NR 7NR GP	P, 1	i: Fructose c: Glucose	33 33	Beverages	***NSD:*** *Bw*		↓ WB-IS (IVITT)				High fructose (and not glucose) intake reduced insulin sensitivity

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Johnston et al. (2013)	15 M 17 M AO	P, 2	i: Fructose c: Glucose	25 25	Beverages	↑ Bw *(vs neutral energy balance)*	↑ liver fat, Skm fat (vs neutral energy balance)	**NSD:** W-B IS and Hep IS (clamp; 12 subjects only, not powered for these outcomes as reported by the authors)				Increases in liver and muscle fat correlated with the increase in body weight in both groups
Silbernagel et al. (2011)	10/3F 10/5F BMI < 35kg/m^2	P, 4	i: Fructose c: Glucose	22 22	Beverages	***NSD:*** *Bw*	**NSD:** liver fat, SKm fat, VAT	**NSD:** FG, FI, HOMA-IR; ISI (Matsuda) index on OGTT (ISI ↓ in both groups)	**NSD**	↑ TG **NSD:** T-c, LDL-c, HDL-c	**NSD**	Fructose increased triglycerides vs. glucose with no effect on other metabolic variables
Hypercaloric(7)												
Le et al. (2009)	8 M no-offT2DM 16 M offT2DM	CX, 1	No sugars Fructose	0 35	Beverages	↑ *Bw (vs neutral energy balance)*		↑ Hep-IS (clamp) **NSD:** WB-IS (clamp)				A hypercaloric diet with high intake of fructose had no effect on WB-IS but decreased hepatic insulin sensitivity
Ad libitum												
Aeberli et al. (2013)	9 M, NW	CX, 3	i1: Fructose i2: Fructose c: Glucose i3: Sucrose	8 16 16 16	Beverages	↓ *Bw (i1, i2)*		↓ Hep-IS (clamp, i2) **NSD:** WB-IS (clamp)				High fructose intake reduced hepatic insulin sensitivity
Angelo-poulos et al. (2015)*	65NR 77NR 64NR 61NR BMI < 35 kg/m^2	P, 10	i1: Fructose c: Glucose i2: Sucrose i3: HFCS	9 9 18 18	Beverages	↑ Bw, BMI, WC (pooled cohort) **NSD:** Bw, BMI, WC for sugars dose or sugars type interaction		**NSD:** FG	↓ SBP, DBP (pooled cohort) **NSD** for sugars type interaction	↑ TG (pooled cohort, men only) ↑ TG (i3, men only) **NSD:** T-c, LDL-c, HDL-c	**NSD**	Moderate fructose intakes had no effect on fasting glucose or uric acid. Increased energy intake leads to an increase in body weight in the whole cohort, while blood pressure decreased. Triglycerides increased only in men.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Campos et al. (2015)	14/6F 13/7F OW/OB	P, 12	i: ASB c: SSB	0 18	Beverages	**NSD:** Bw, BMI, BF, LBM	↓ Liver fat **NSD:** VAT	**NSD:** FG, FI, HOMA-IR	**NSD**	**NSD:** T-c, HDL-c, TG	**NSD**	Replacing SSBs in high consumers with ASBs decreases liver fat
Ruyter et al. (2014)	319/147F 322/151F GP	P, 72	i: ASSD c: SSSD	0 5	Beverages	↓ BMI z score, Bw, WC						Consumption of ASSDs reduced weight gain in children as compared to SSSDs
Ebbeling et al. (2012)	110/48F 114/52F OW/OB	P, 52	i: ASSD +water c: SSSD+SSFD +TFJ	0 17	Beverages	↓ Bw, BMI (greatest in Hispanics)						Increase in BMI and body weight were smaller in the experimental group
Hernandez-Cordero et al. (2014)	120F 120F OW/OB	P, 36	i: Water c: SSBs	0 20	Beverages	**NSD:** Bw, BMI, BF, WC		**NSD:** HbA1c, FG	**NSD**	↓ TG (obese only) **NSD:** T-c, LDL-c, HDL-c, TG		Replacing SSBs in high consumers with water did not affect body fatness or metabolic variables, except for a decrease in triglycerides in the obese (secondary analysis)
Hollis et al. (2009)	25NR 25NR 26NR OW	P, 12	c2: No drink i: GJ c1: GD	0 18 18	Beverages	**NSD:** Bw, BMI, WC		↑ glucose and insulin responses (AUC) on OGTT (vs c1 and c2)		**NSD:** T-c, LDL-c, HDL-c, TG		Grape juice increased glucose and insulin responses vs. grape sugar drink or no intervention
Huttunen et al. (1976)	48NR 35NR 33NR GP	P, 72	i1:Xylitol i2:Fructose i3:Sucrose	0 14 16	Mixed diet			**NSD:** FG, FI, glucose and insulin response on OGTT[8]		↓ T-c (i2 only) **NSD:** TG	**NSD**	Total cholesterol was lower in the fructose group. The change was driven by hypercholesterolaemic participants.
Jin et al. (2014)	9/6F 12/4F OW NAFLD	P, 4	c: Fructose i: Glucose	20 20	Beverages	***NSD:*** *Bw*	**NSD:** Liver fat	↓ Adipose tissue IR index[9] **NSD:** FG, FI, HOMA-IR		↓ VLDL **NSD:** TG		Sugar type had no effect on body weight, liver fat or triglycerides. Adipose tissue IR and VLDL decreased with glucose vs. fructose

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Maersk et al. (2012)*	15/11F 16/11F 15/12F 14/6F OW/Obese	P, 24	c1: SK milk c2: Water c3: ASSD i: SSSD	0 0 0 18	Beverages	**NSD:** Bw, BMI, BF, LBM	↑ Liver fat ↑ VAT ↑ SKm fat (data available for 47 subjects)	**NSD:** FG, FI, HOMA-IR; glucose and insulin responses (AUC) and derived indices of IR on OGTT	↑ SBP (c1, c3) **NSD:** DBP	↑ T-c (vs c3) ↑ TG (vs c2 and c3) **NSD:** LDL-c, HDL-c, T-c/HDL-c ratio	↑ FUA (data available for 47 subjects)	Consumption of SSSD increased triglycerides, uric acid and ectopic fat deposition with no effect on body weight, total body fat or glucose homeostasis
Majid et al. (2013)	31 M 32 M GP	P, 4	c: No drink i: Honey	0 8	Beverages			↓ FG		↓ T-c, LDL-c, TG ↑ HDL-c		Honey consumption limited the rise in blood glucose and improved the blood lipid profile. Background diet and changes in body weight were not assessed.
Mark et al. (2014)	35F 38F OW/OB	P, 4	i: Fructose[10] c: Glucose[10]	15 15	Beverages	**NSD:** BW, BMI, WC		**NSD:** FG, FI, HOMA-IR; glucose and insulin responses and ISI on OGTT		**NSD:** T-c, LDL-c, HDL-c, TG		The type of sugar had no effect on glucose homeostasis, blood lipids or body weight.
Markey et al. (2016)	50/34F Non-OB	CX, 8	i: NMES c: NMES	6 16	Mixed diet	**NSD:** Bw		**NSD:** FG, FI	**NSD**	**NSD:** T-c, LDL-c, HDL-c, TG, T-c/HDL-c ratio		Reduction of free sugars intake did not affect body weight, fasting glucose or insulin, or blood lipids.
Raben et al. (2002)*	20NR 21NR OW	P, 10	i1: AS i2: Sucrose	0 23	Mixed diet	↑ Bw, BMI, BF (all i2) **NSD:** Sagittal height, LBM		↑ FI (i2) **NSD:** FG, HOMA-IR, HOMA-β (data available for 23 subjects)	↑ SBP, DBP (i2)	↑ TG (i2) **NSD:** T-c, HDL-c (data available for 23 subjects)		High intakes of sucrose increased body weight, fat mass and blood pressure. Sucrose increased fasting insulin and triglycerides.
Saris et al. (2000)*	83/40F 77/40F 76/40F OW/OB	P, 24	i1: LF/LS c: Control i2: LF/HS	19 22 38	Mixed diet	↓ Bw (i1, i2) **NSD:** Bw (i1 vs. i2)		**NSD:** FG, FI		**NSD:** T-c, zLDL-c, HDL-c, TG, HDL-c/LDL-c ratio		The type of carbohydrates in low fat diets did not affect body weight, the blood lipid profile, or fasting glucose or insulin.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Smith et al. (1996)	22 NR 10 NR HTG	P, 24	i: Sugar-free c: Sucrose	0 12	Mixed diet	↓ Bw				↓ TG **NSD:** T-c, HDL-c		Lower sucrose intake reduced triglycerides accounting for changes in body weight in subjects with hypertriglyceridaemia.
Stanhope et al. (2009)*	17/8F 15/8F OW/OB	P, 8	i: Fructose c: Glucose	25 25	Beverages	↑ Bw, WC, BF (both groups)	↑ VAT (men)	↑ FG; insulin response on OGTT ↑ ISI on OGTT ↑ Glucose response on OGTT (both groups) **NSD:** FI, fructosamine	**NSD**	↑ T-c, LDL-c, ApoB, ApoB/ApoA1 ratio **NSD:** TG, HDL-c	↑ FUA	Fructose decreased insulin sensitivity, increased insulin excursions, visceral adiposity and uric acid and promoted dyslipidaemia vs. glucose.
Werner et al. (1984)	12/8F Gallstones	CX, 6	c: AS i: Sucrose	0 24	Mixed diet	↑ Bw		**NSD:** FG (data not shown in the paper)		↓ HDL-c ↑ TG **NSD:** T-c, LDL-c		High sucrose intake increased body weight and triglycerides while decreasing HDL-c concentrations.

Results presented in *italics* were not eligible as the studies did not meet the duration criteria outlined in the opinion protocol.
AO = abdominal obesity; AS = artificial sweeteners; ASB = artificially sweetened beverages; ASSD = artificially sweetened soft drinks; AUC = area under the curve; BF = body fat; BMI = Body mass index; Bw = Body weight; C = control; CX = Crossover; DBP = diastolic blood pressure; D/D = study design and duration (in weeks); F = females; FG = fasting glucose; FI = fasting insulin; FUA = fasting uric acid; GD = grape drink; GJ = grape juice; GR = glucose response; GP = General Population; HbA1c = Glycated haemoglobin; HDL-c = High density lipoprotein cholesterol; Hep-IS = hepatic insulin sensitivity; HFCS = high fructose corn syrup; H-I = hyperinsulinaemia; HOMA-IR = homeostatic model assessment IR; HTG = hypertriglyceridaemia; I = intervention; IGT= impaired glucose tolerance; IR = insulin resistance; IS = insulin sensitivity; ISI = insulin sensitivity (Matsuda) index; IVITT= intravenous insulin tolerance test; LBM = Lean body mass; LDL-c= Low density lipoprotein cholesterol; LF/HS = low fat diet high in sugars; LF/LS = low fat diet low in sugars; OB = Obese; OC = oral contraceptives; offT2DM = offspring from parents with type 2 diabetes mellitus; OGTT = Oral glucose tolerance test; OW = Overweight; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose tolerance; N-I = normoinsulinaemia; NMES = non-milk extrinsic sugars; NR = not reported; NSD = no significant difference; NW = normal weight; M = males; P = Parallel; Skm = skeletal muscle; SBP = systolic blood pressure; SLIVGTT = stable labelled intravenous glucose tolerance test; SSFD = sugar sweetened fruit drink; SSSD = sugar sweetened soft drinks; T-c = total cholesterol; TG = Triglycerides; TFJ = total fruit juice; UA = uric acid; VAT = Visceral adipose tissue; VLDL = Very low density lipoprotein; WB-IS = whole body insulin sensitivity; WC = waist circumference.
*: Only within-group comparisons tested in the study.
(1): Refers to the sugars contribution of the dietary fraction manipulated in the study to total energy intake.
(2): All arms in neutral energy balance.
(3): OGTT with sucrose load of 2 g/kg body weight over 3 h.
(4): OGTT with 100 g dextrose solution over 3 h.
(5): OGTT with glucose load of 1 g/kg body weight over 3 h.
(6): All arms in positive energy balance.
(7): Only sugar arm in positive energy balance (vs a control on neutral energy balance).

(8): OGTT with glucose load of 1 g/kg body weight.
(9): Adipose tissue IR index was calculated as fasting FFA (mEq/L) × insulin (mU/L).
(10): These intervention arms were in combination with either high or low advanced glycation end product diets.

Appendix G – Forest plots. Intervention studies on metabolic diseases

Figure G.1: Randomised controlled trials: effect of high vs. low sugar intake on measures of body fatness.

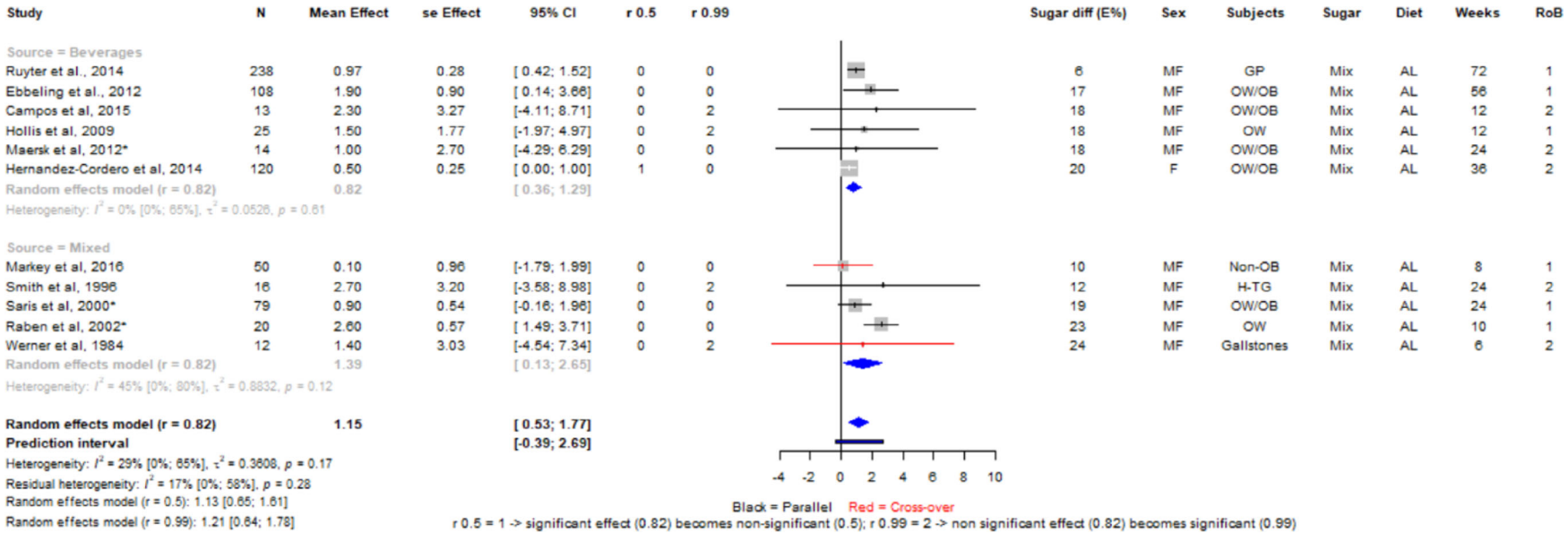


Figure G.1a: Effect of high vs low sugar intake on body weight (kg)

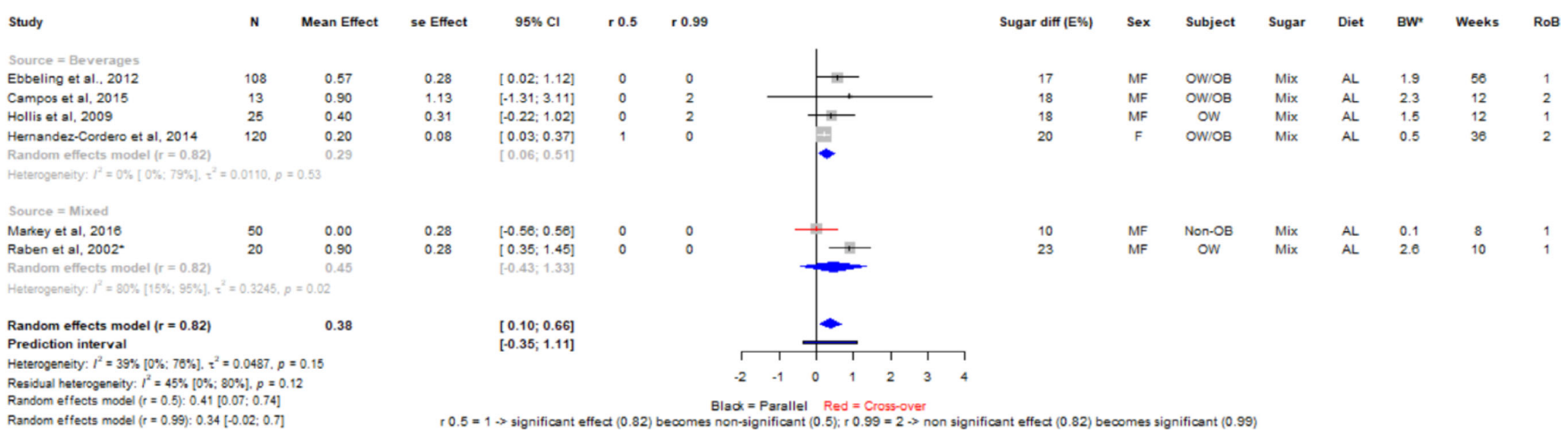


Figure G.1b: Effect of high vs low sugar intake on BMI (kg/m2)

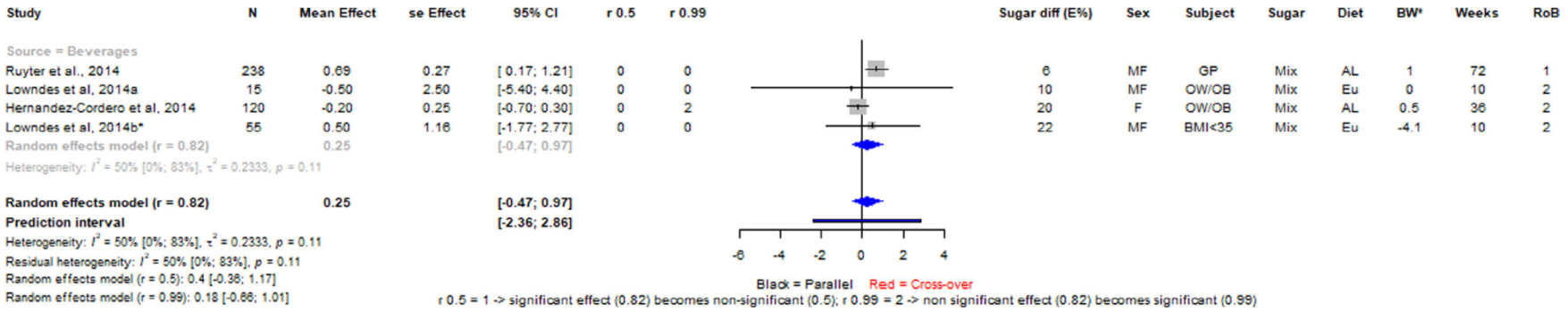
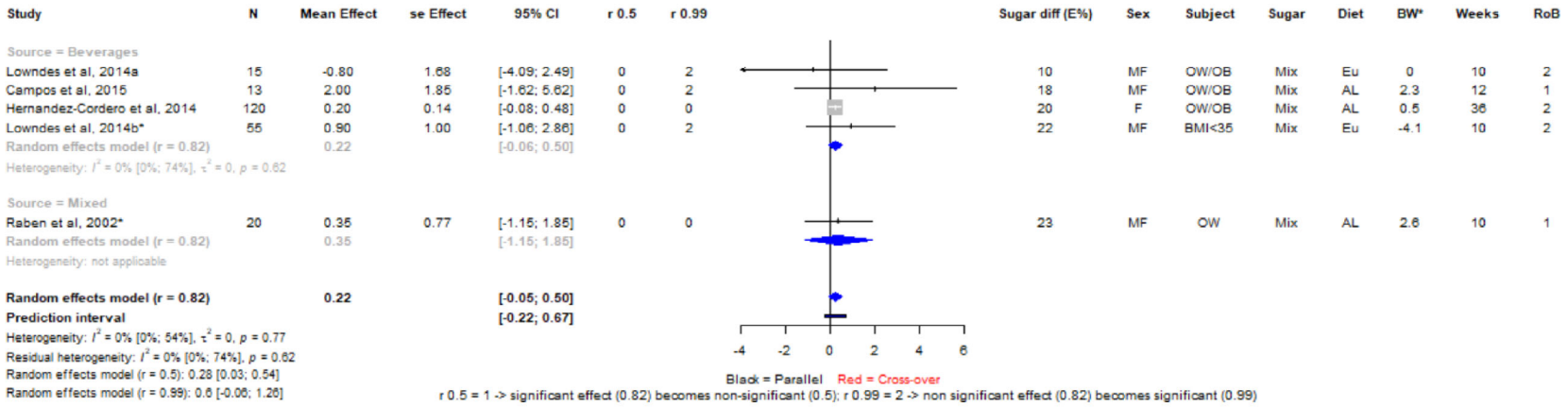


Figure G.1c: Effect of high vs low sugar intake on waist circumference (cm)



Footnote to Figure G1. * differences in BW change between high and low sugar intake, AL = add libitum; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Eu = eucaloric; F = females; GP = general population; H-TG = hyper-triglyceridemic; MF = males and females; Mix under Sugar = sugar mixtures; Mixed under Source = foods and beverages; N = average sample size per arm; OB = obese; OW = overweight; RoB = risk of bias (tier); r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement. Study duration is expressed in weeks.

Figure G.1d: Effect of high vs low sugar intake on body fat (%)

Figure G.2: Randomised controlled trials: effect of high vs. low sugar intake on measures of ectopic fat deposition

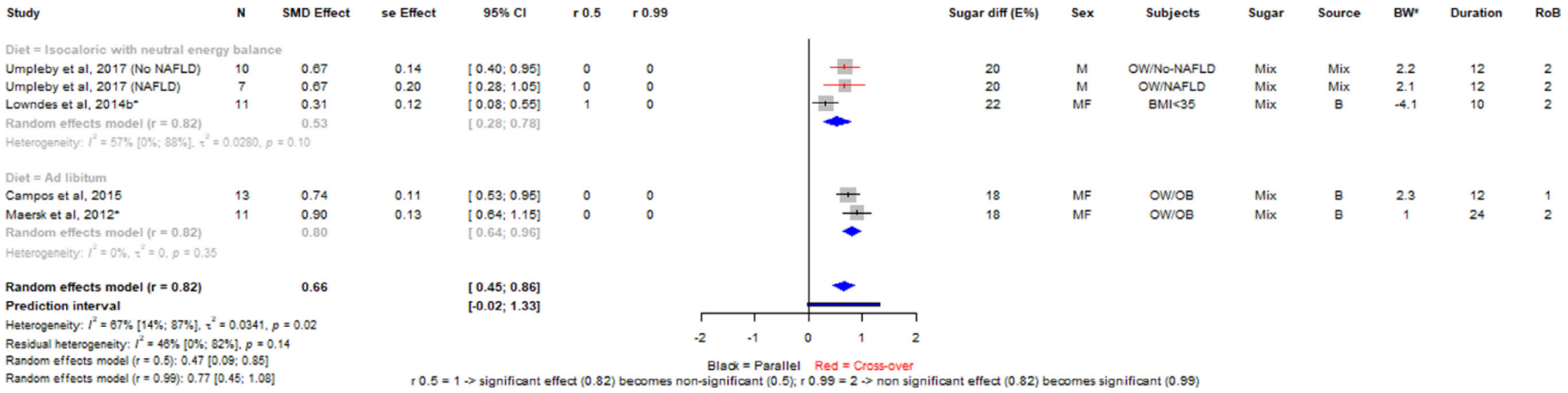
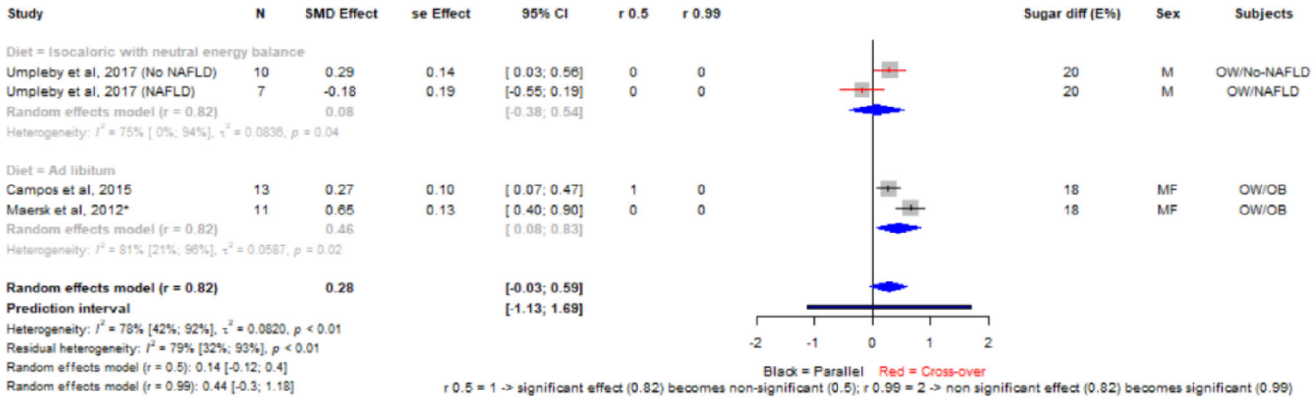


Figure G.2a: Effect of high vs low sugar intake on liver fat (standardized mean difference)



Footnote to Figure G2. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; OB = obese; OW = overweight; RoB = risk of bias (tier); r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; SMD = standardized mean difference. Study duration is expressed in weeks.

Figure G.2b: Effect of high vs low sugar intake on visceral adipose tissue (standardized mean difference)

Figure G.3: Randomised controlled trials: effect of fructose vs. glucose on measures of ectopic fat deposition

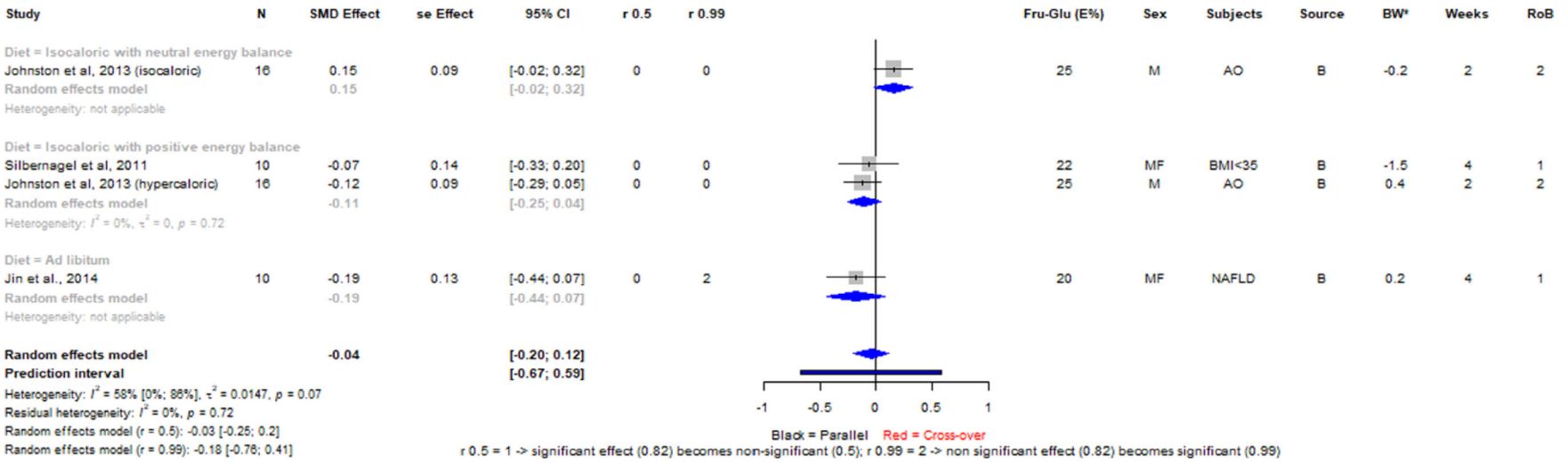
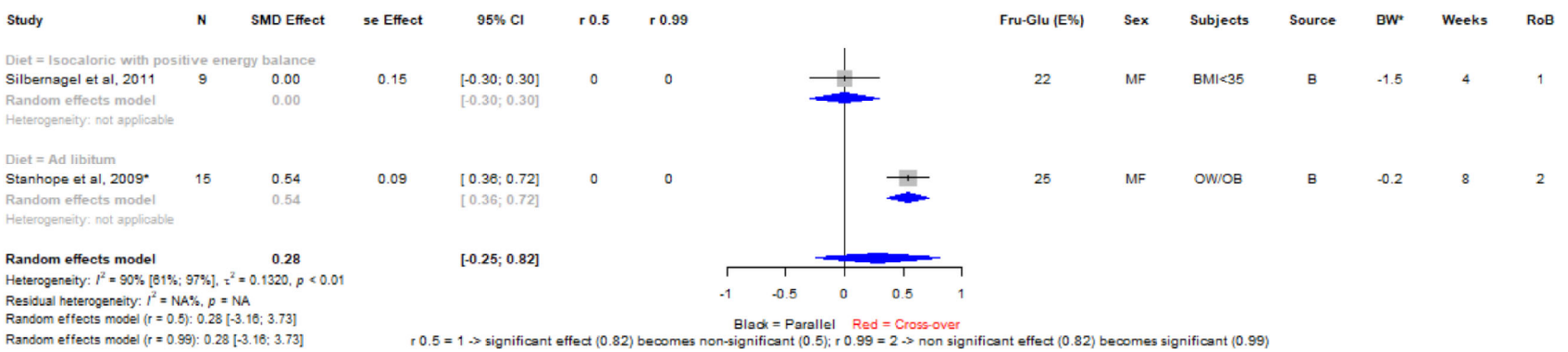


Figure G.3a: Effect of fructose vs glucose on liver fat (standardized mean difference)



Footnote to Figure G3. * differences in BW change between high and low sugar intake; AO = abdominal obesity; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Fru = fructose; Glu = glucose; M = males; MF = males and females; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier); SMD = standardized mean difference. Study duration is expressed in weeks.

Figure G.3b: Effect of fructose vs glucose on visceral adipose tissue (standardized mean difference)

Figure G.4: Randomised controlled trials: effect of high vs. low sugar intake on measures of glucose tolerance

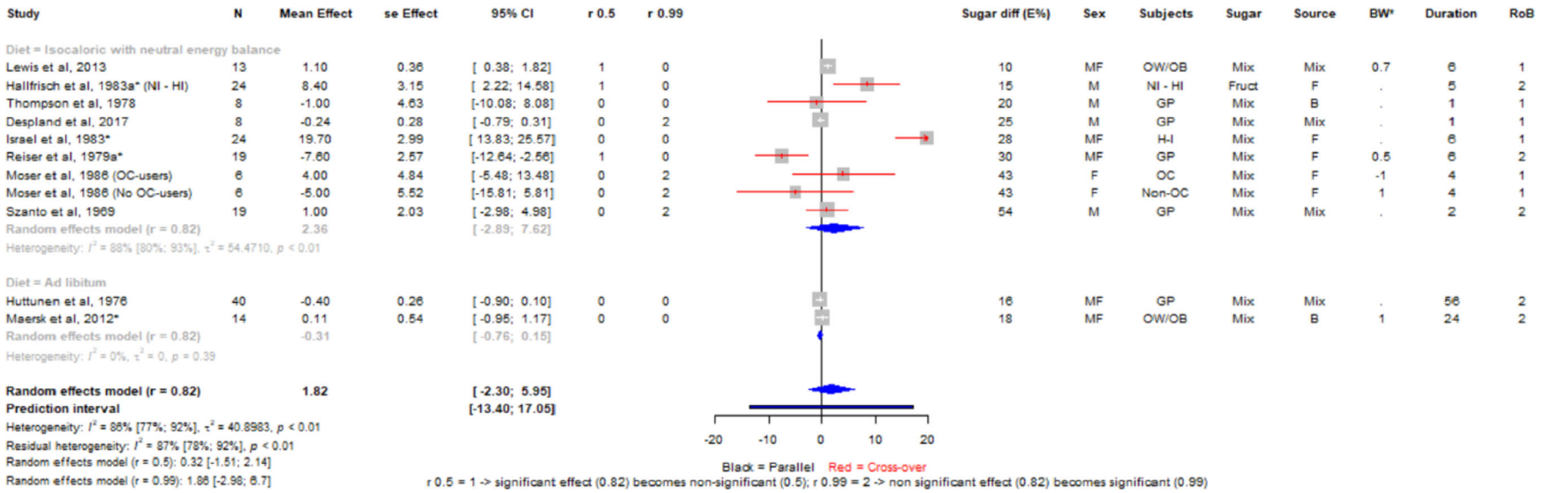


Figure G.4a: Effect of high vs low sugar intake on blood glucose at 120' during an OGTT (mg/dL)

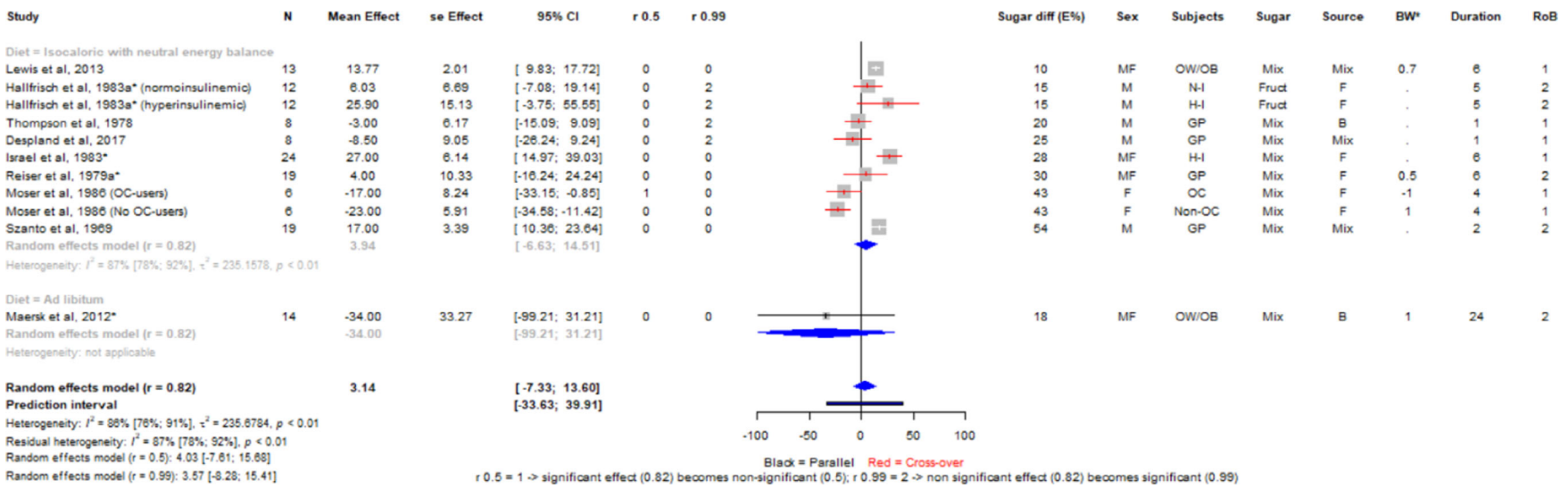
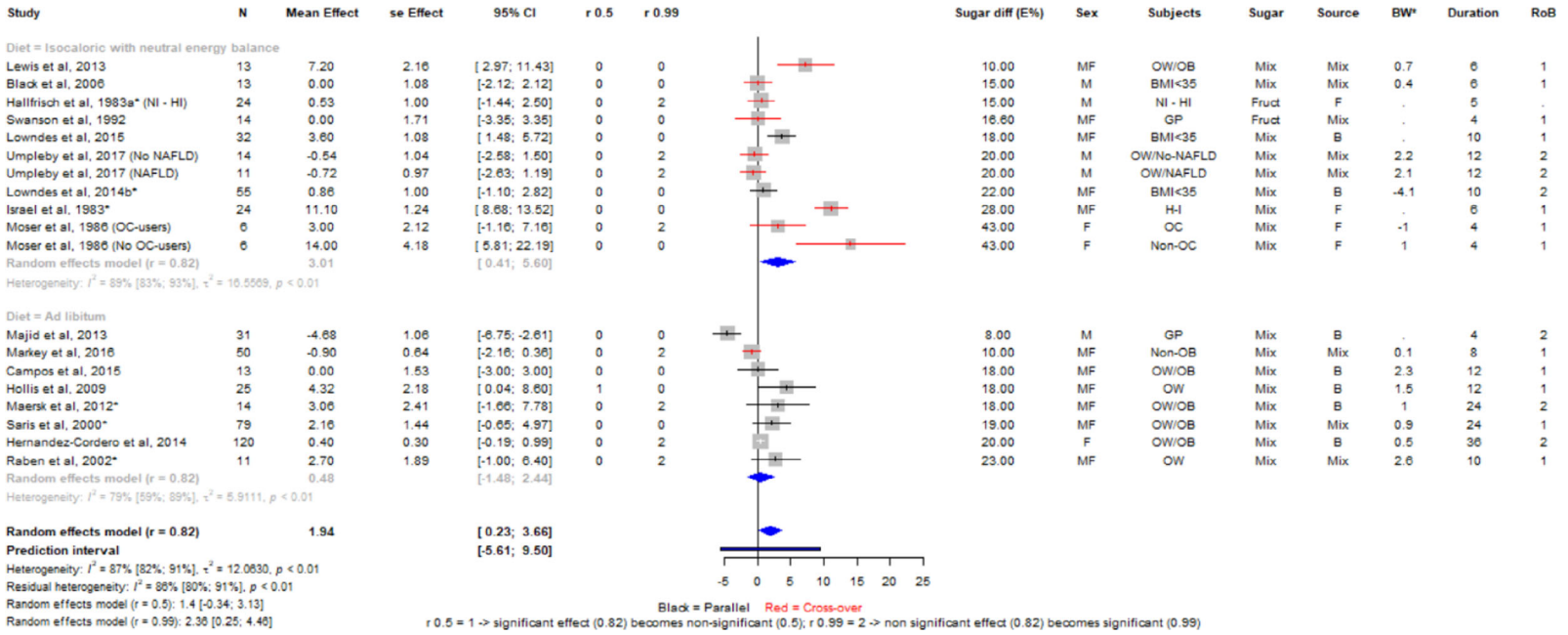


Figure G.4b: Effect of high vs low sugar intake on insulin at 120' during an OGTT (pmol/L)

Figure G.4c: Effect of high vs low sugar intake on fasting glucose (mg/dL)



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99	Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy balance														
Lewis et al, 2013	13	7.20	2.16	[2.97; 11.43]	0	0	10.00	MF	OW/OB	Mix	Mix	0.7	6	1
Black et al, 2006	13	0.00	1.08	[-2.12; 2.12]	0	0	15.00	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (NI - HI)	24	0.53	1.00	[-1.44; 2.50]	0	2	15.00	M	NI - HI	Fruct	F	.	5	.
Swanson et al, 1992	14	0.00	1.71	[-3.35; 3.35]	0	0	16.60	MF	GP	Fruct	Mix	.	4	1
Lowndes et al, 2015	32	3.60	1.08	[1.48; 5.72]	0	0	18.00	MF	BMI<35	Mix	B	.	10	1
Umpleby et al, 2017 (No NAFLD)	14	-0.54	1.04	[-2.58; 1.50]	0	2	20.00	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	-0.72	0.97	[-2.63; 1.19]	0	2	20.00	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al, 2014b*	55	0.86	1.00	[-1.10; 2.82]	0	0	22.00	MF	BMI<35	Mix	B	-4.1	10	2
Israel et al, 1983*	24	11.10	1.24	[8.68; 13.52]	0	0	28.00	MF	H-I	Mix	F	.	6	1
Moser et al, 1986 (OC-users)	6	3.00	2.12	[-1.16; 7.16]	0	2	43.00	F	OC	Mix	F	-1	4	1
Moser et al, 1986 (No OC-users)	6	14.00	4.18	[5.81; 22.19]	0	0	43.00	F	Non-OC	Mix	F	1	4	1
Random effects model (r = 0.82)		3.01		[0.41; 5.60]										
Heterogeneity: I^2 = 89% [83%; 93%], τ^2 = 16.5569, p < 0.01														
Diet = Ad libitum														
Majid et al, 2013	31	-4.68	1.06	[-6.75; -2.61]	0	0	8.00	M	GP	Mix	B	.	4	2
Markey et al, 2016	50	-0.90	0.64	[-2.16; 0.36]	0	2	10.00	MF	Non-OB	Mix	Mix	0.1	8	1
Campos et al, 2015	13	0.00	1.53	[-3.00; 3.00]	0	0	18.00	MF	OW/OB	Mix	B	2.3	12	1
Hollis et al, 2009	25	4.32	2.18	[0.04; 8.60]	1	0	18.00	MF	OW	Mix	B	1.5	12	1
Maersk et al, 2012*	14	3.06	2.41	[-1.66; 7.78]	0	2	18.00	MF	OW/OB	Mix	B	1	24	2
Saris et al, 2000*	79	2.16	1.44	[-0.65; 4.97]	0	0	19.00	MF	OW/OB	Mix	Mix	0.9	24	1
Hernandez-Cordero et al, 2014	120	0.40	0.30	[-0.19; 0.99]	0	2	20.00	F	OW/OB	Mix	B	0.5	36	2
Raben et al, 2002*	11	2.70	1.89	[-1.00; 6.40]	0	2	23.00	MF	OW	Mix	Mix	2.6	10	1
Random effects model (r = 0.82)		0.48		[-1.48; 2.44]										
Heterogeneity: I^2 = 79% [59%; 89%], τ^2 = 5.9111, p < 0.01														
Random effects model (r = 0.82)		**1.94**		**[0.23; 3.66]**										
Prediction interval				**[-5.61; 9.50]**										

Heterogeneity: I^2 = 87% [82%; 91%], τ^2 = 12.0630, p < 0.01
Residual heterogeneity: I^2 = 86% [80%; 91%], p < 0.01
Random effects model (r = 0.5): 1.4 [-0.34; 3.13]
Random effects model (r = 0.99): 2.36 [0.25; 4.46]

Figure G.4c1: Stratified by type of diet

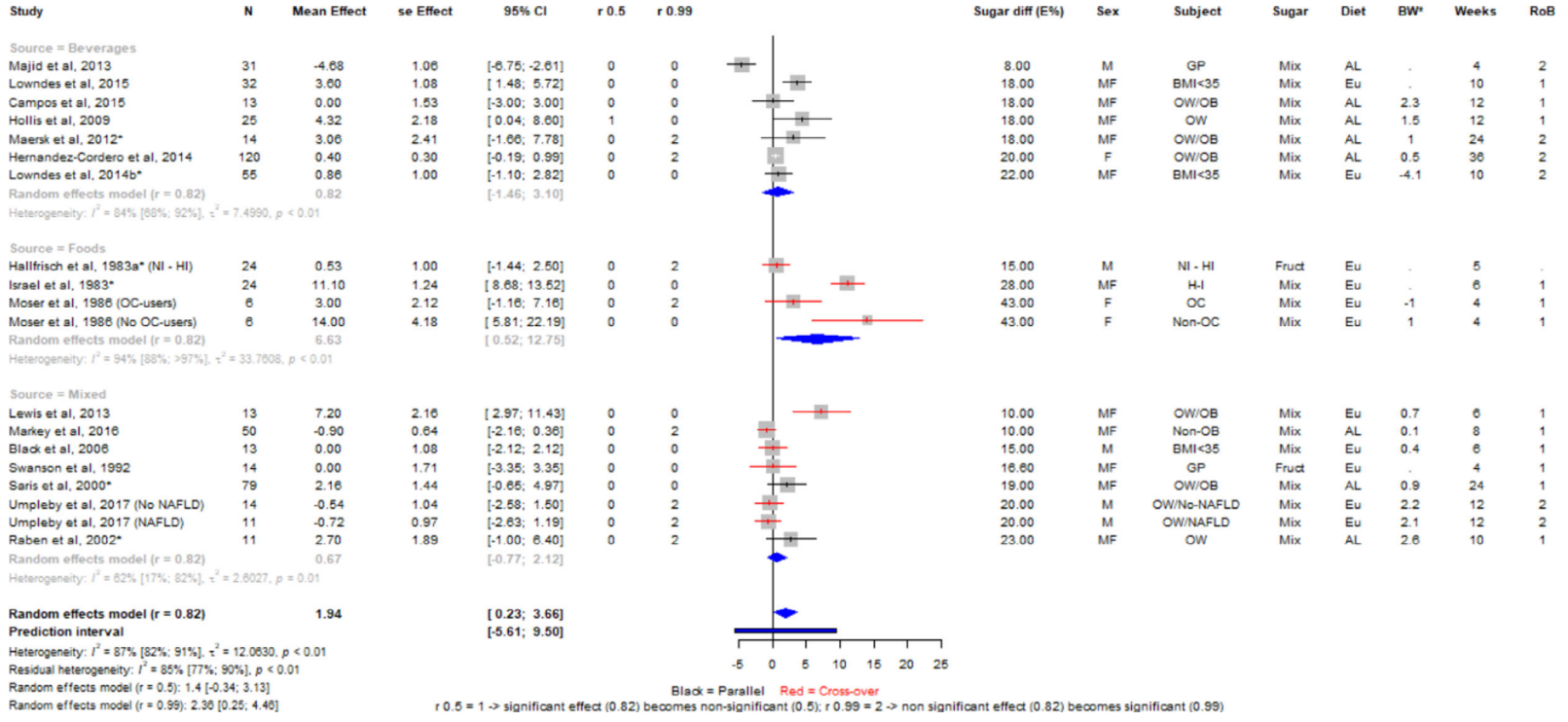
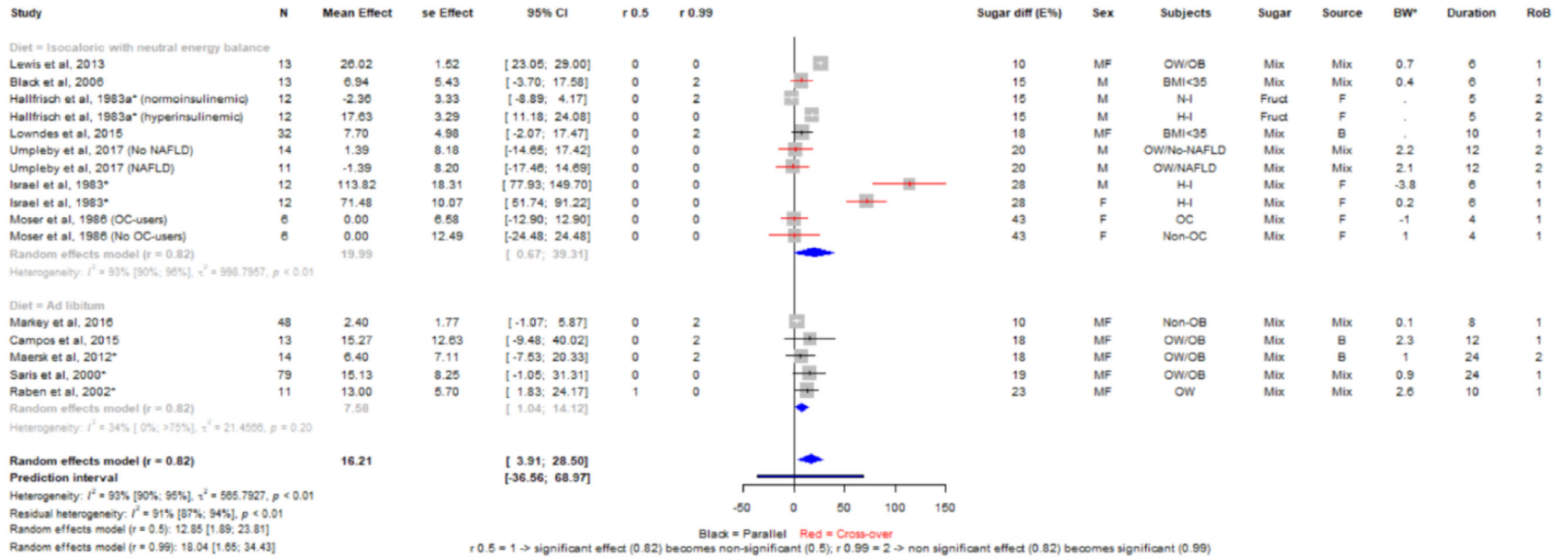


Figure G.4c2: Stratified by sugars source



Footnote to Figure G4. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Source = food; Fruct = fructose; GP = general population; H-I = hyperinsulinemia; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; N-I = normo-insulinemia; NAFLD = non-alcoholic fatty liver disease; OB = obese; OC = oral contraceptives; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.4d: Effect of high vs low sugar intake on fasting insulin (pmol/L)

Figure G.5: Randomised controlled trials: effect of fructose vs. glucose on measures of glucose tolerance

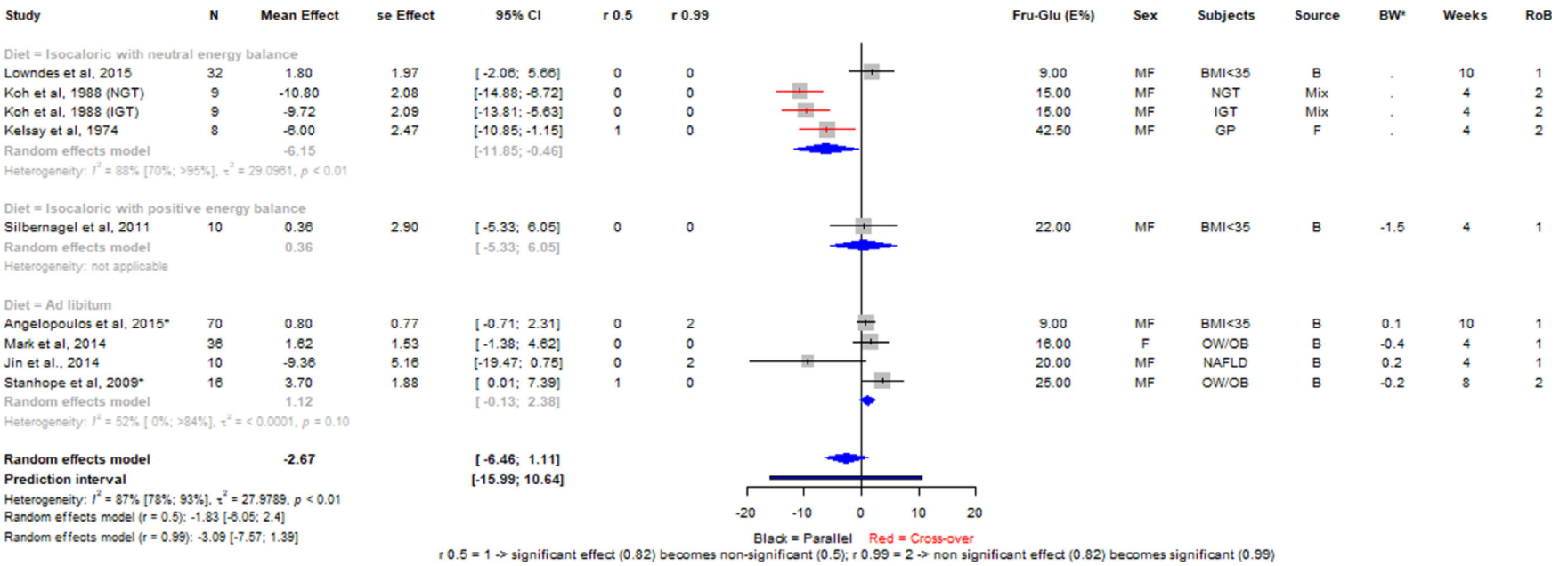
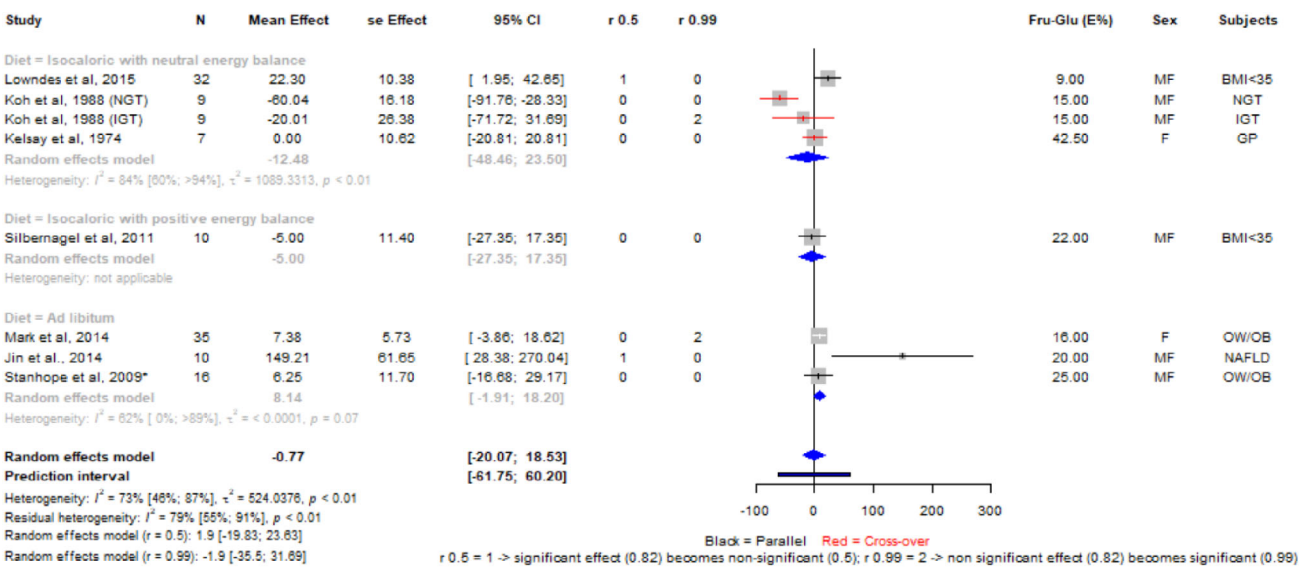


Figure G.5a: Effect of fructose vs glucose on fasting glucose (mg/dL)



Footnote to Figure G5. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Source = food; Fru = fructose; Glu = glucose; GP = general practitioner; IGT = impaired glucose tolerance; MF = males and females; Mix = foods and beverages; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose concentration; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.5b: Effect of fructose vs glucose on fasting insulin (pmol/L)

Figure G.6: Randomised controlled trials: effect of high vs. low sugar intake on blood lipids

Figure G.6a: Effect of high vs low sugar intake on total cholesterol (mg/dL)

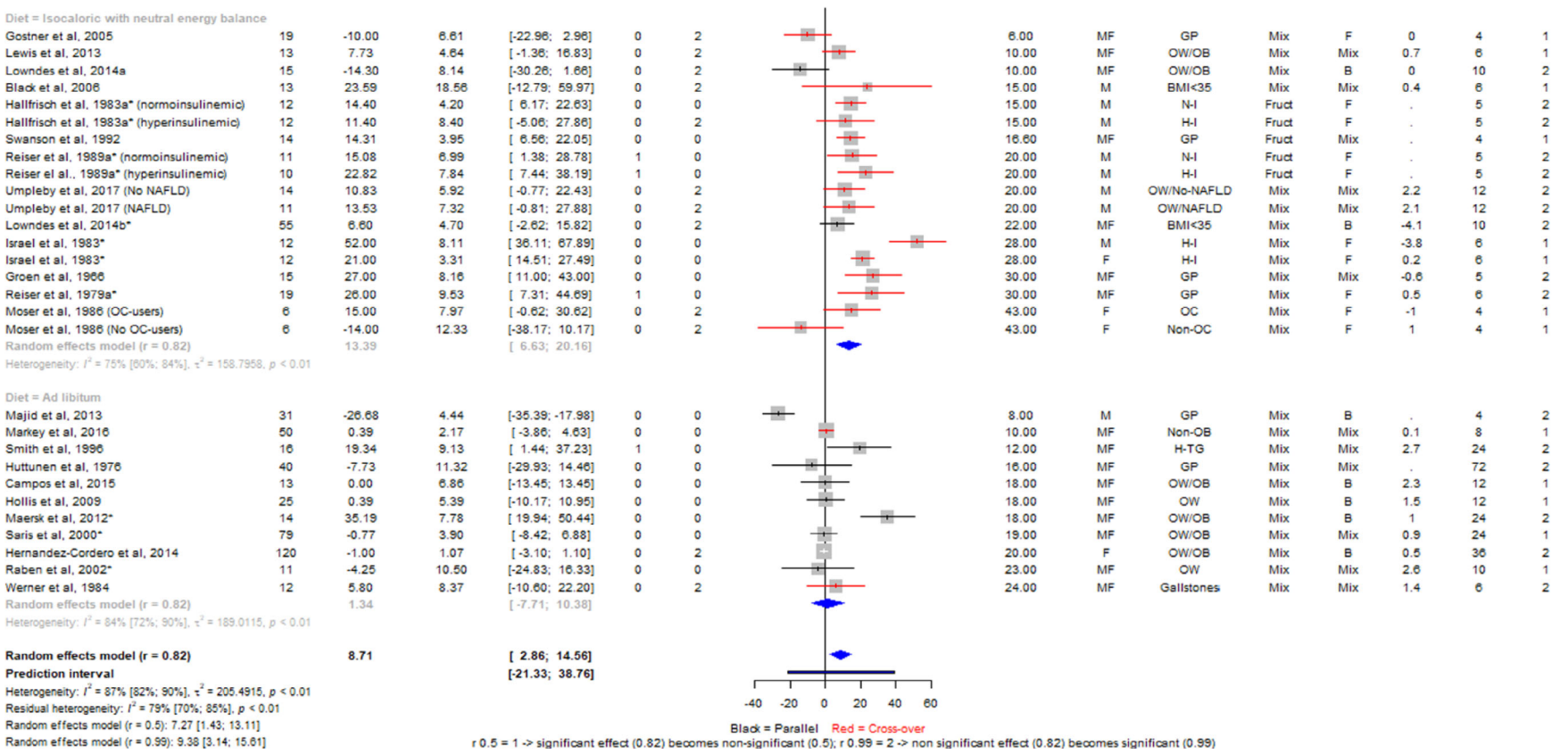


Figure G.6a1: Stratified by type of diet

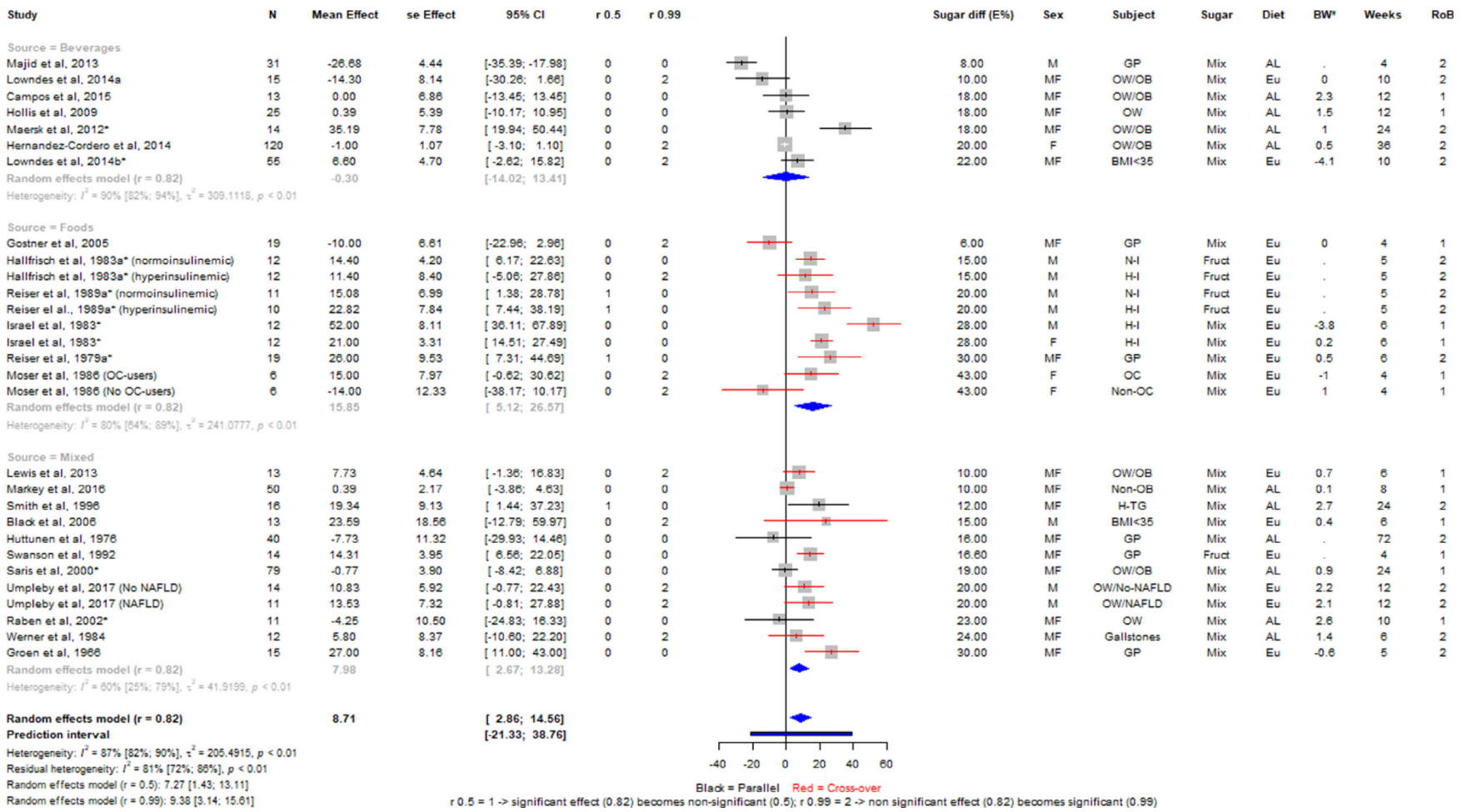


Figure G.6a2: Stratified by sugars source

Figure G.6b: Effect of high vs low sugar intake on LDL-cholesterol (mg/dL)

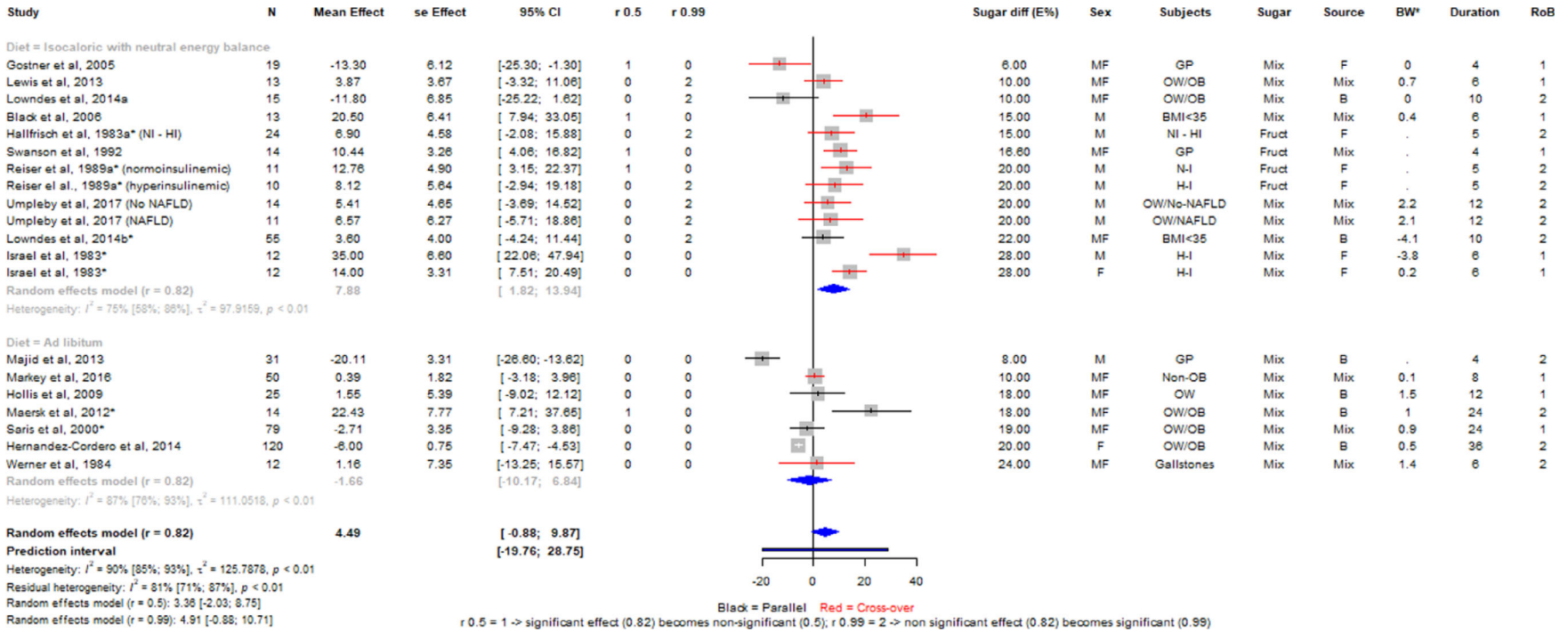


Figure G.6b1: Stratified by type of diet

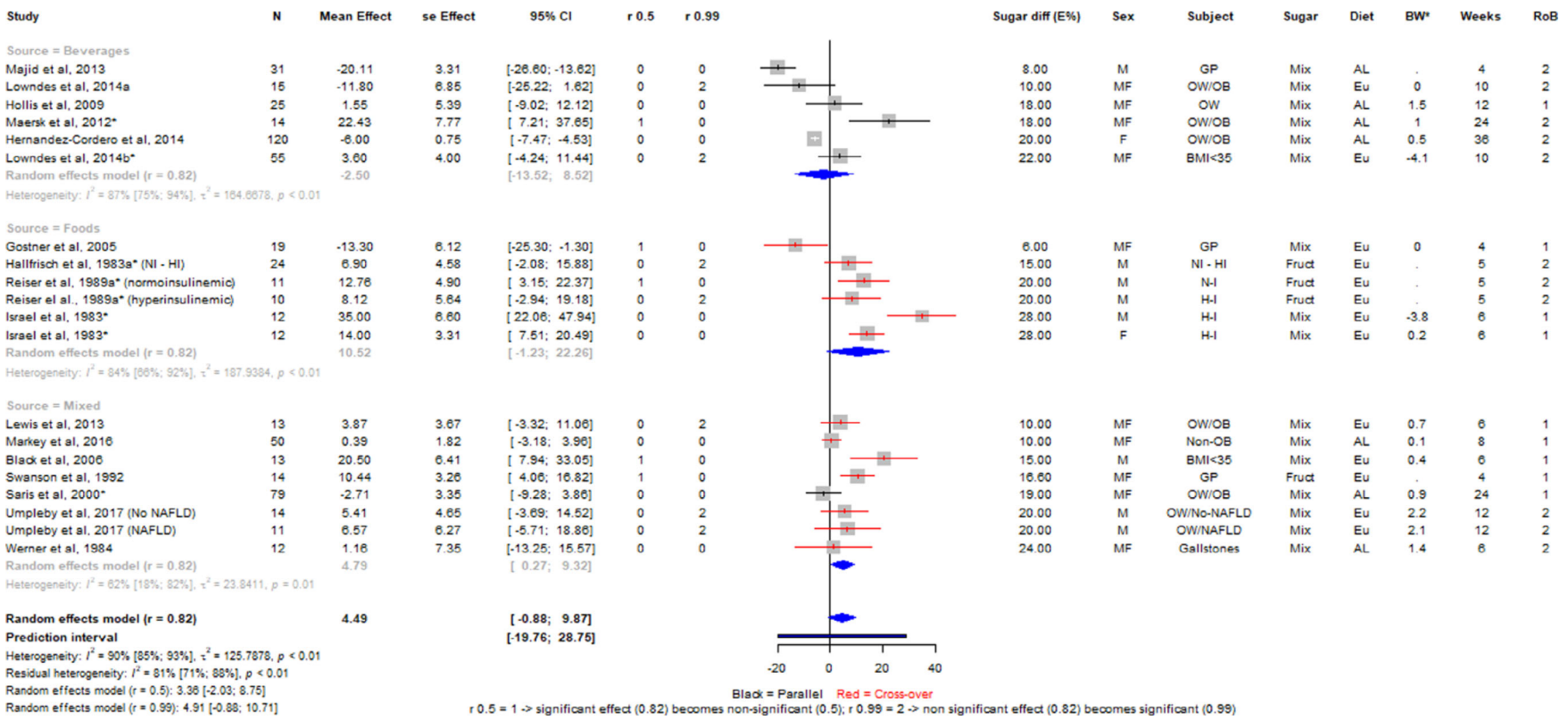


Figure G.6b2: Stratified by sugars source

Figure G.6c: Effect of high vs low sugar intake on HDL-cholesterol (mg/dL)

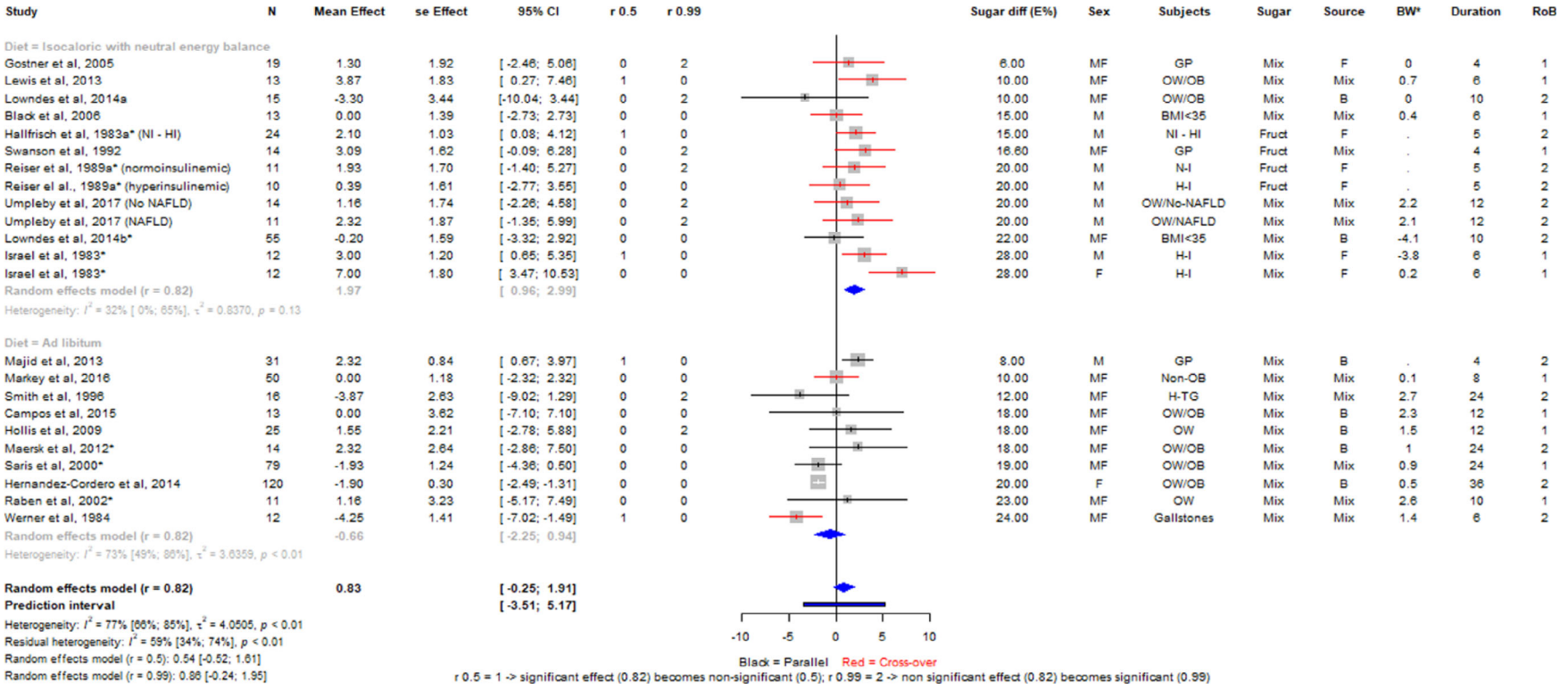


Figure G.6c1: Stratified by type of diet

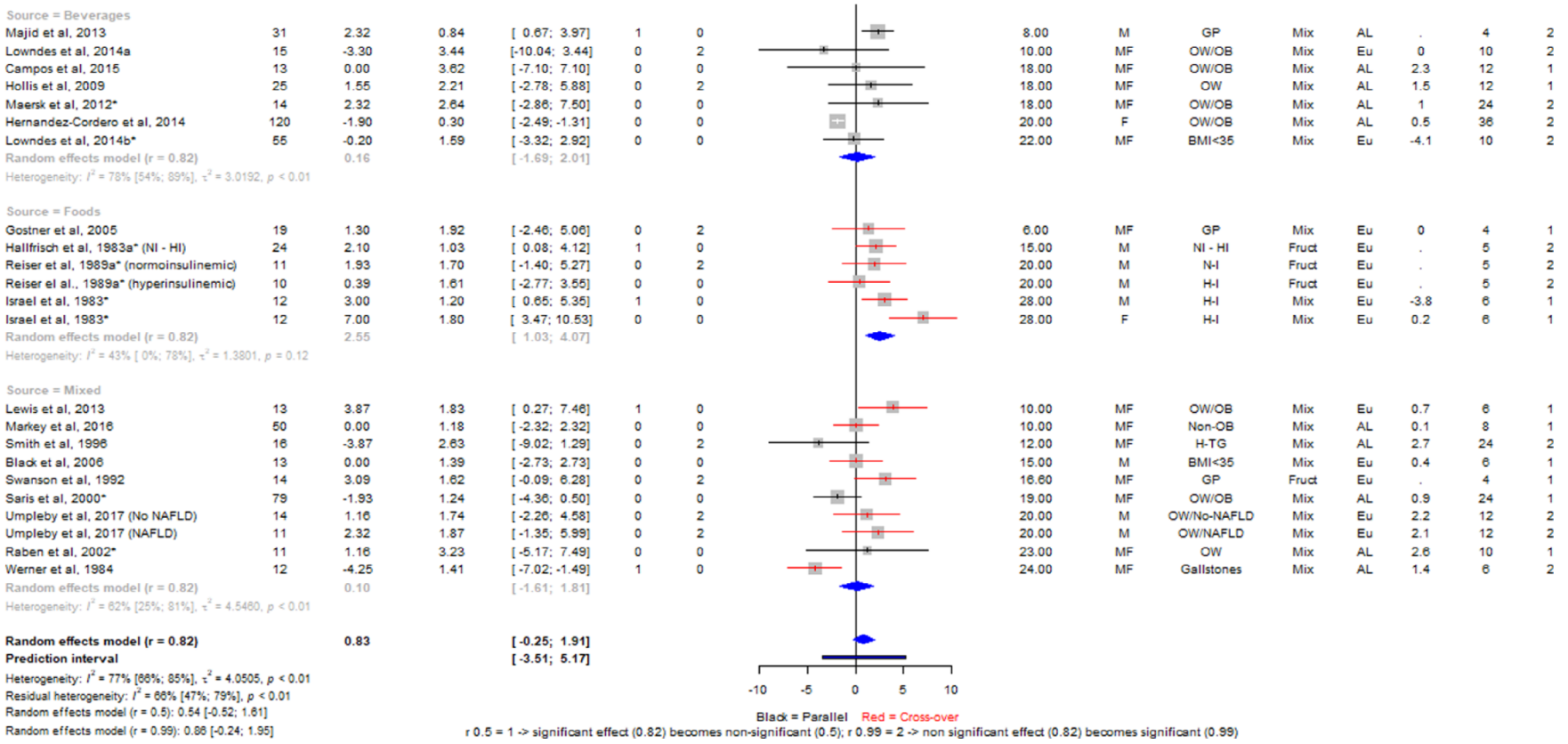
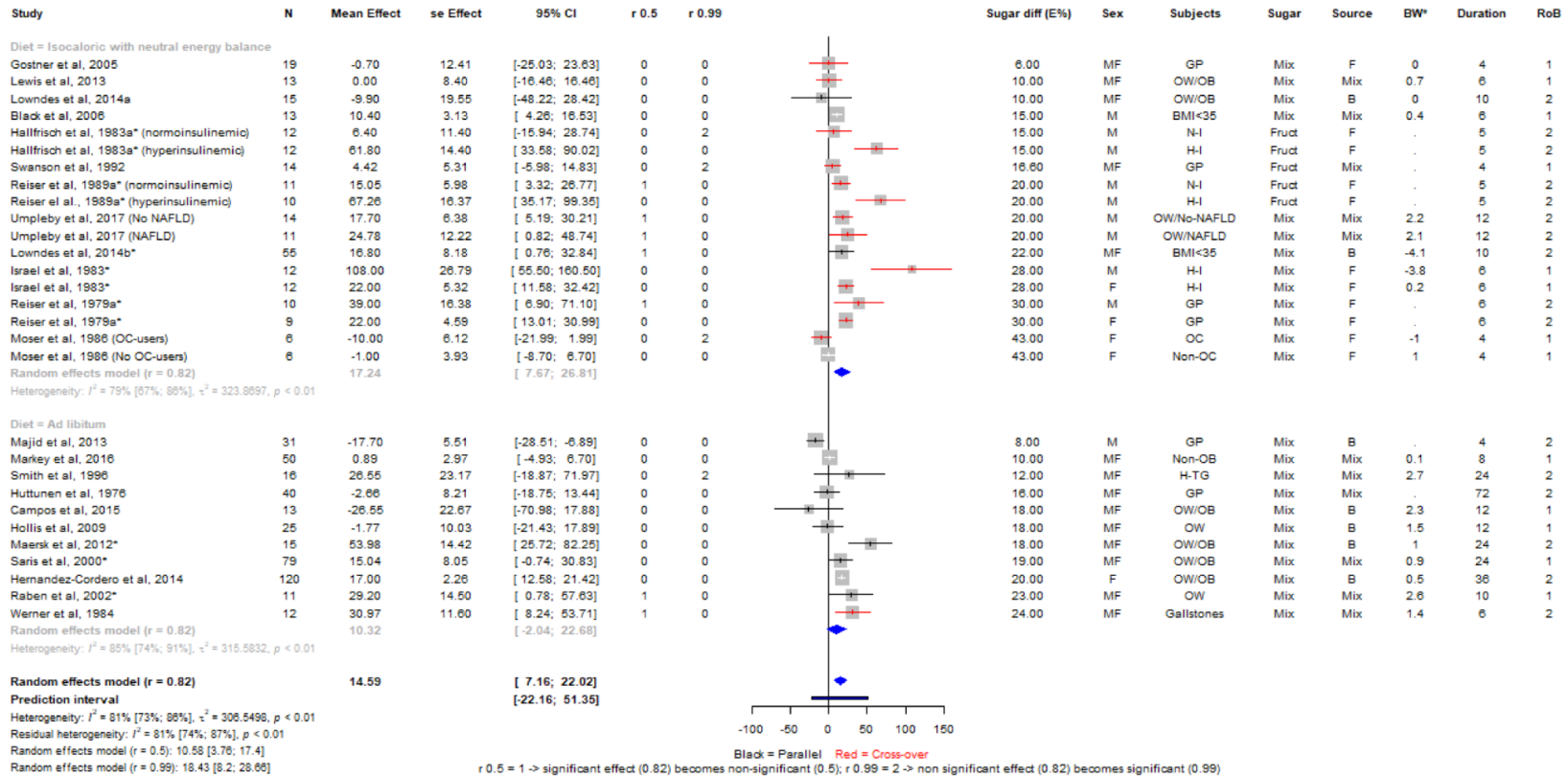


Figure G.6c2: Stratified by sugars source

Figure G.6d: Effect of high vs low sugar intake on fasting triglycerides (mg/dL)



Footnote to Figure G6. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Source = food; Fruct = fructose; GP = general practitioner; H-I = hyperinsulinemia; H-TG = hyper-triglyceridemic; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; N-I = normo-insulinemia; NAFLD = non-alcoholic fatty liver disease; OB = obese; OC = oral contraceptives; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.6d1: Stratified by type of diet

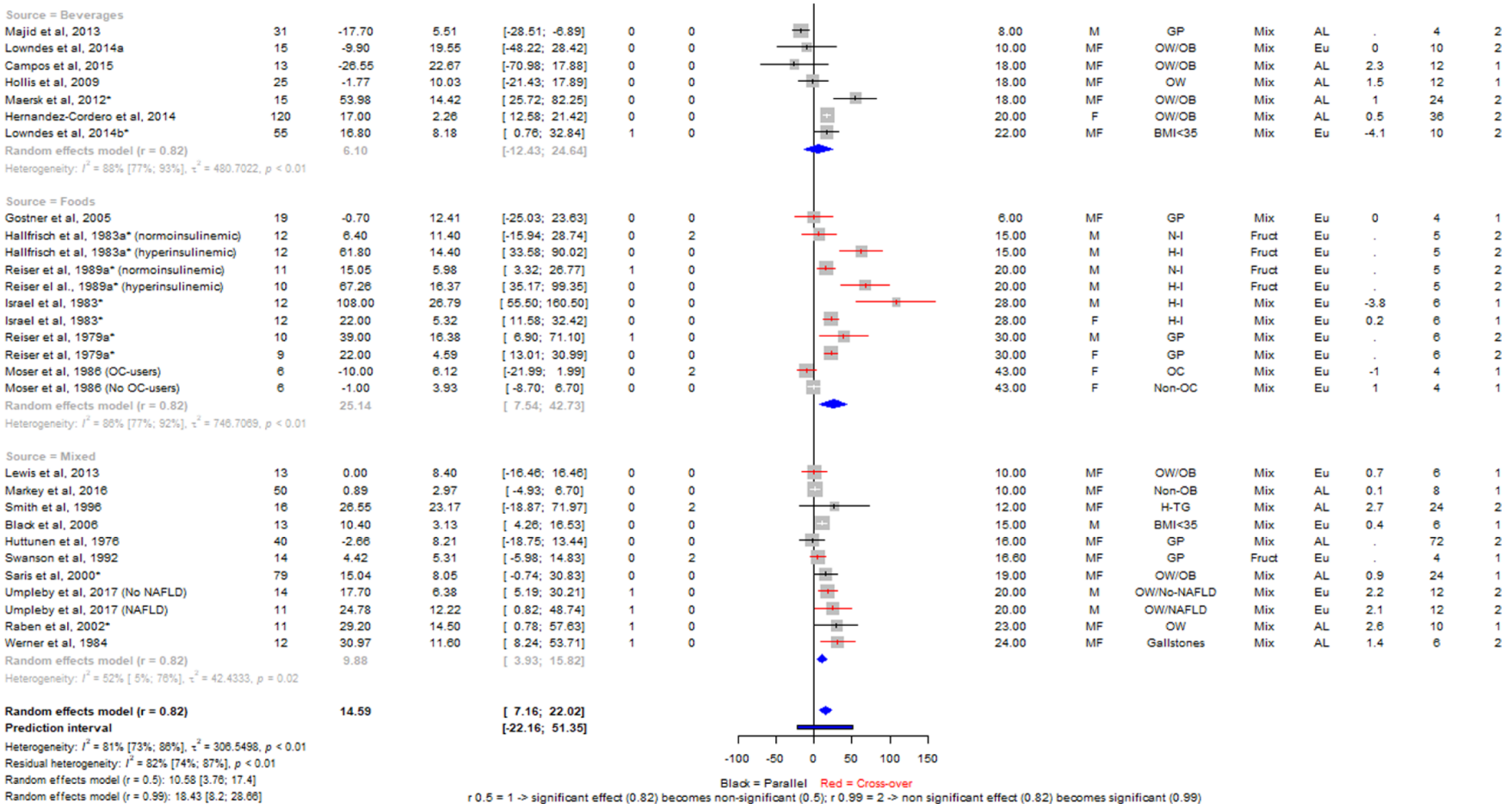


Figure G.6d2: Stratified by sugars source

Figure G.7: Randomised controlled trials: effect of fructose vs. glucose on blood lipids

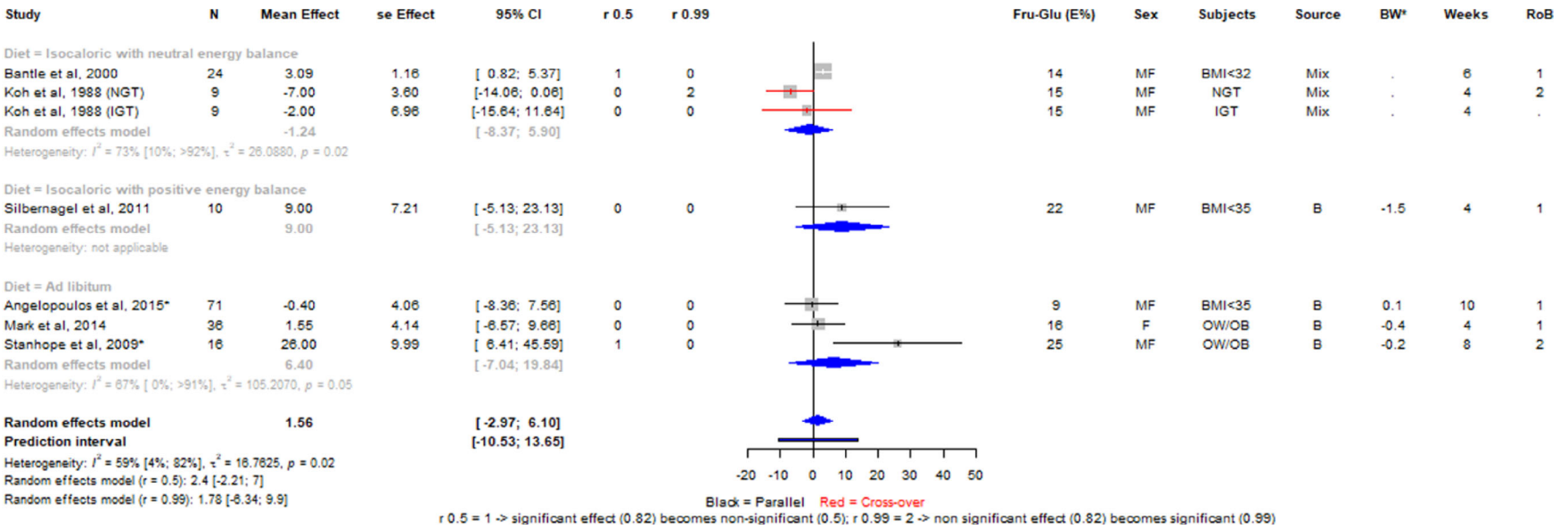


Figure G.7a: Effect of fructose vs glucose on total cholesterol (mg/dL)

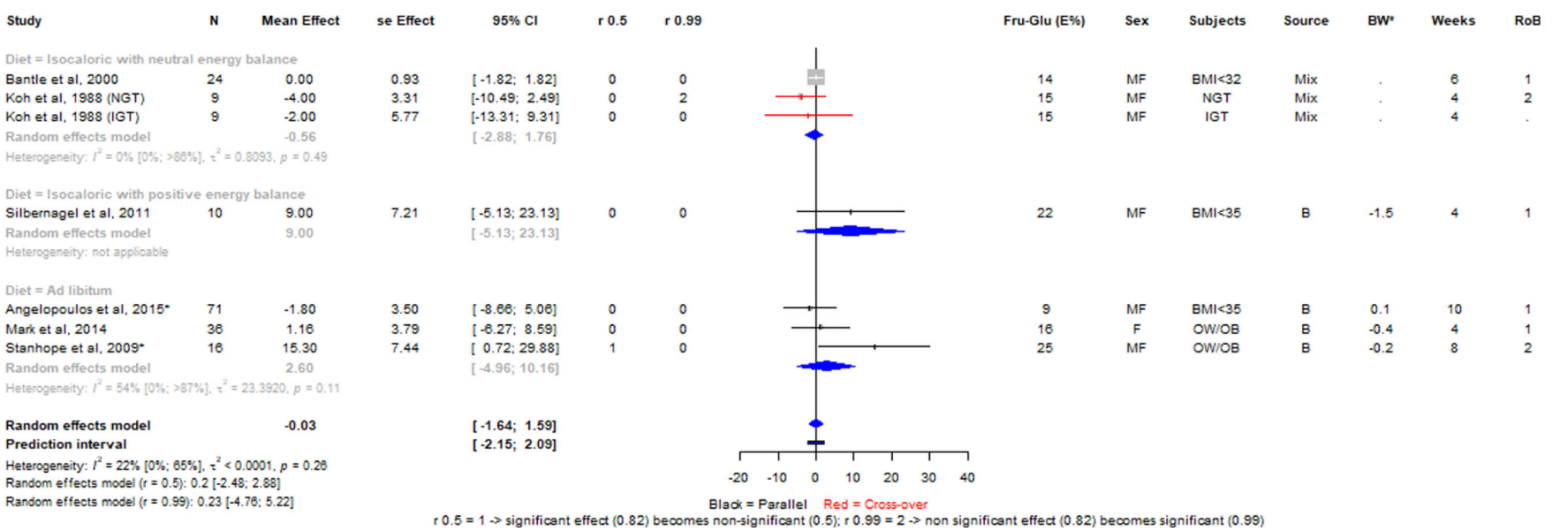


Figure G.7b: Effect of fructose vs glucose on LDL-cholesterol (mg/dL)

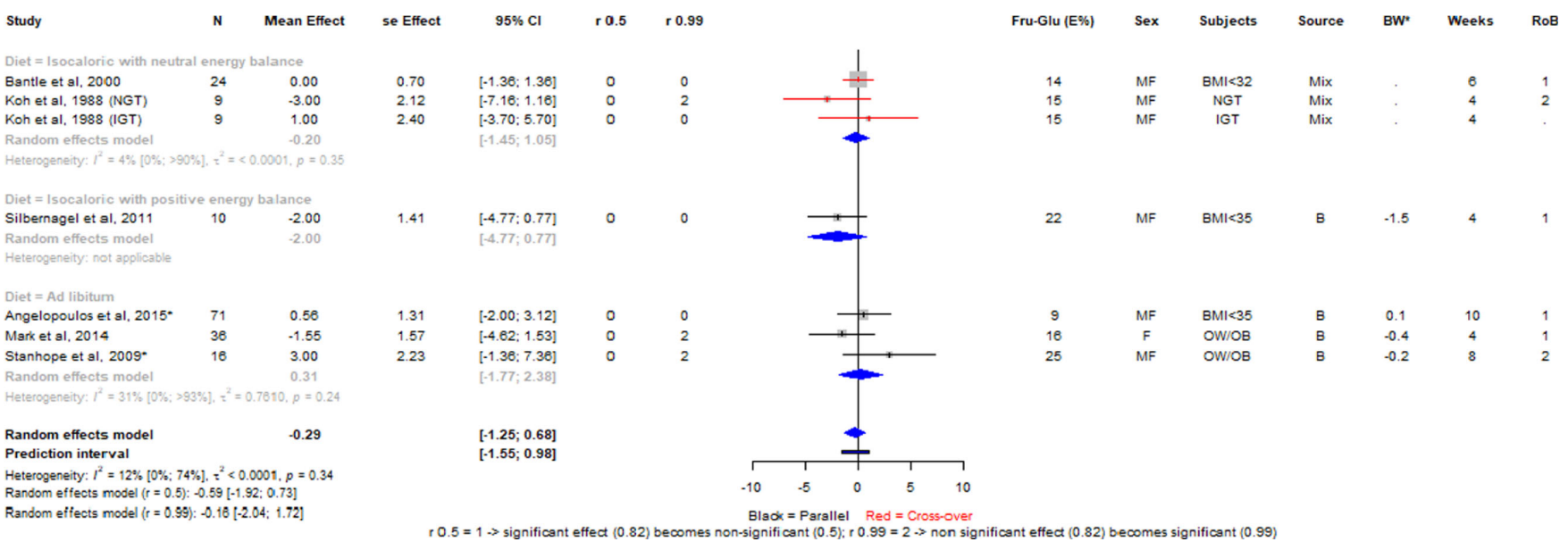
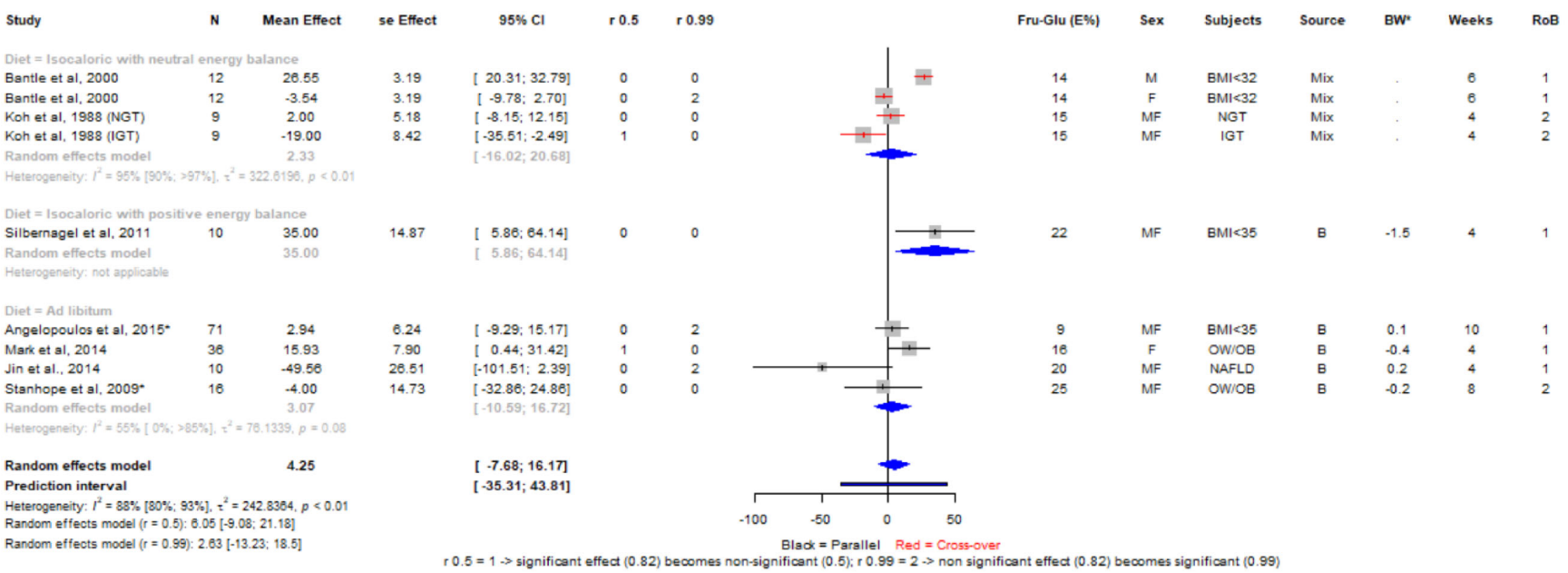


Figure G.7c: Effect of fructose vs glucose on HDL-cholesterol (mg/dL)



Footnote to Figure G7. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Source = food; Fru = fructose; Glu = glucose; HDL = high-density lipoprotein; IGT = impaired glucose tolerance; LDL = low-density lipoprotein; M = males; MF = males and females; Mix = foods and beverages; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose concentration; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.7d: Effect of fructose vs glucose on fasting triglycerides (mg/dL)

Figure G.8: Randomised controlled trials: effect of high vs. low sugar intake on blood pressure

Figure G.8a: Effect of high vs low sugar intake on systolic blood pressure (mmHg)

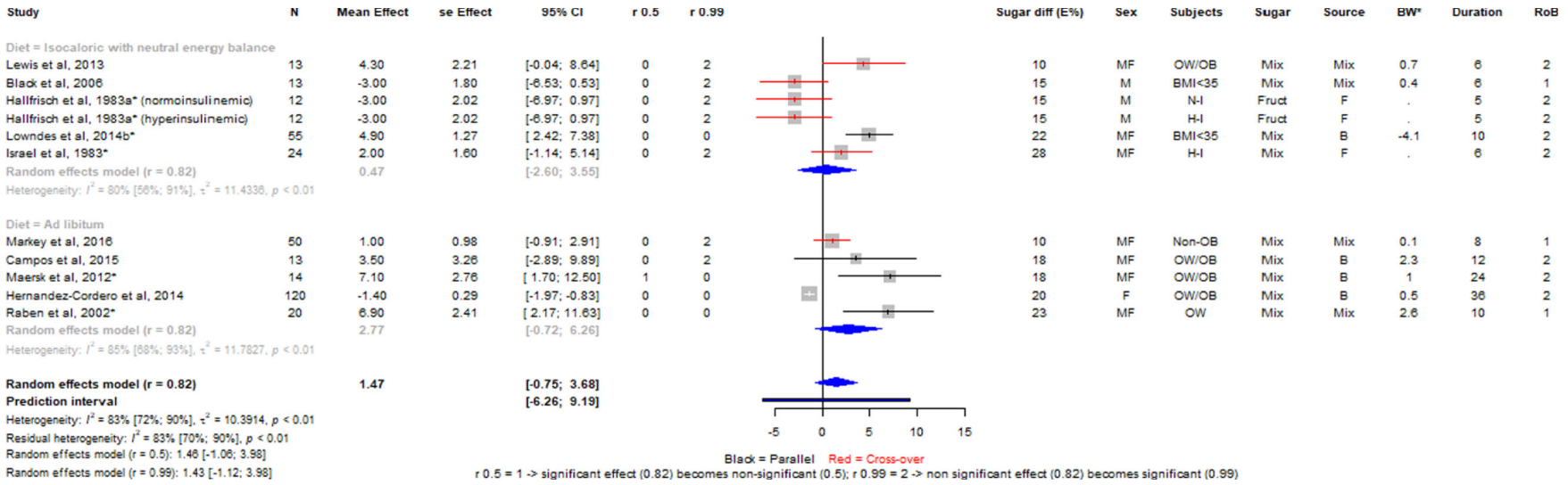


Figure G.8a1: Stratified by type of diet

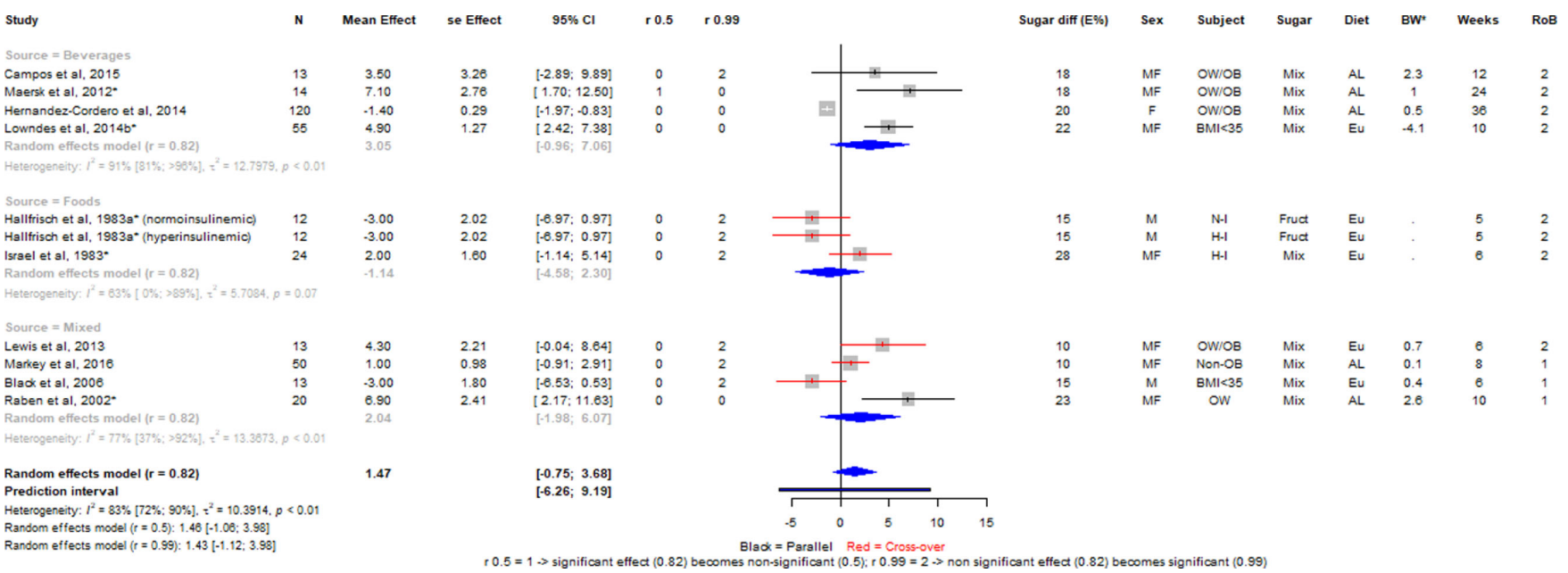
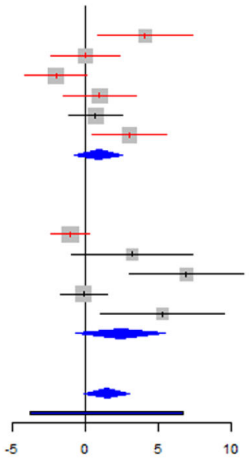


Figure G.8a2: Stratified by sugars source

Figure G.8b: Effect of high vs low sugar intake on diastolic blood pressure (mmHg)

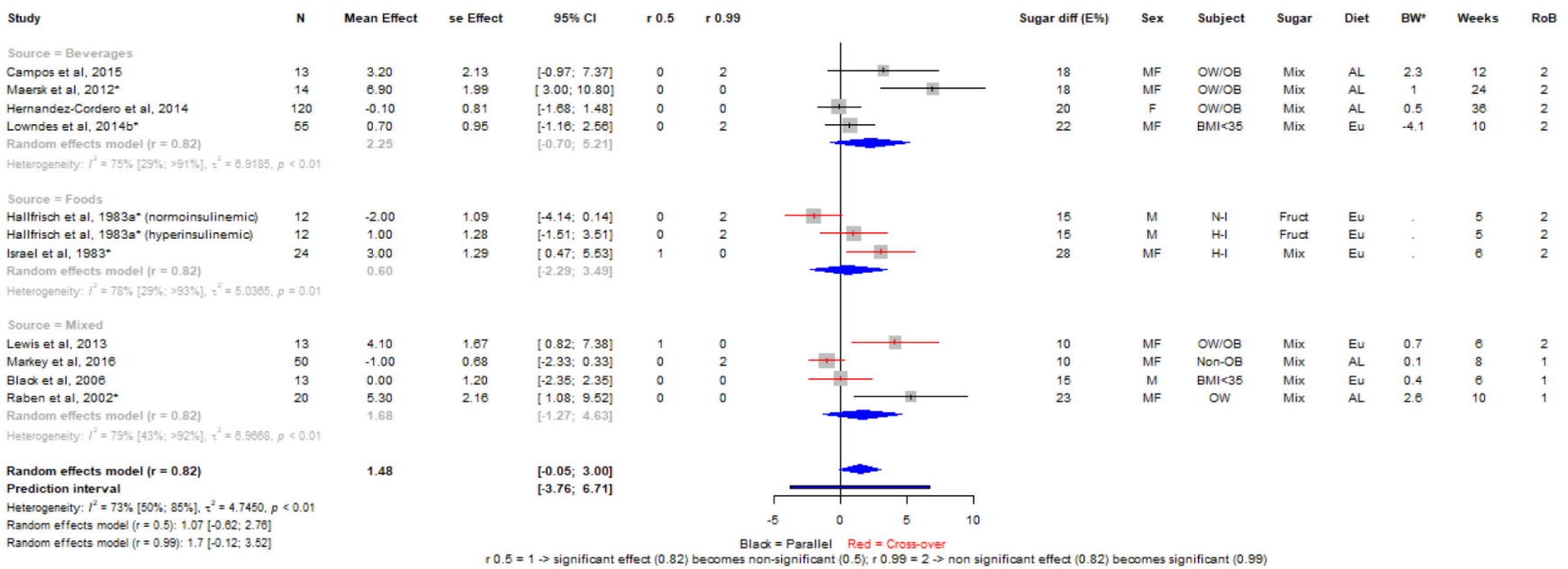
Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99	Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy balance														
Lewis et al, 2013	13	4.10	1.67	[0.82; 7.38]	1	0	10	MF	OW/OB	Mix	Mix	0.7	6	2
Black et al, 2006	13	0.00	1.20	[-2.35; 2.35]	0	0	15	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (normoinsulinemic)	12	-2.00	1.09	[-4.14; 0.14]	0	2	15	M	N-I	Fruct	F	.	5	2
Hallfrisch et al, 1983a* (hyperinsulinemic)	12	1.00	1.28	[-1.51; 3.51]	0	2	15	M	H-I	Fruct	F	.	5	2
Lowndes et al, 2014b*	55	0.70	0.95	[-1.16; 2.56]	0	2	22	MF	BMI<35	Mix	B	-4.1	10	2
Israel et al, 1983*	24	3.00	1.29	[0.47; 5.53]	1	0	28	MF	H-I	Mix	F	.	6	2
Random effects model (r = 0.82)		0.95		[-0.70; 2.60]										
Heterogeneity: I^2 = 64% [13%; 85%], τ^2 = 2.7122, p = 0.02														
Diet = Ad libitum														
Markey et al, 2016	50	-1.00	0.68	[-2.33; 0.33]	0	2	10	MF	Non-OB	Mix	Mix	0.1	8	1
Campos et al, 2015	13	3.20	2.13	[-0.97; 7.37]	0	2	18	MF	OW/OB	Mix	B	2.3	12	2
Maersk et al, 2012*	14	6.90	1.99	[3.00; 10.80]	0	0	18	MF	OW/OB	Mix	B	1	24	2
Hernandez-Cordero et al, 2014	120	-0.10	0.81	[-1.68; 1.48]	0	0	20	F	OW/OB	Mix	B	0.5	36	2
Raben et al, 2002*	20	5.30	2.16	[1.08; 9.52]	0	0	23	MF	OW	Mix	Mix	2.6	10	1
Random effects model (r = 0.82)		2.43		[-0.64; 5.49]										
Heterogeneity: I^2 = 82% [58%; 92%], τ^2 = 9.6755, p < 0.01														
Random effects model (r = 0.82)		**1.48**		**[-0.05; 3.00]**										
Prediction interval				**[-3.76; 6.71]**										
Heterogeneity: I^2 = 73% [50%; 85%], τ^2 = 4.7450, p < 0.01														
Residual heterogeneity: I^2 = 75% [53%; 87%], p < 0.01														
Random effects model (r = 0.5): 1.07 [-0.62; 2.76]														
Random effects model (r = 0.99): 1.7 [-0.12; 3.52]														



Black = Parallel Red = Cross-over

r 0.5 = 1 -> significant effect (0.82) becomes non-significant (0.5); r 0.99 = 2 -> non significant effect (0.82) becomes significant (0.99)

Figure G.8b1: Stratified by type of diet



Footnote to Figure G8. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F = females; F under Source = food; Fruct = fructose; H-I = hyperinsulinemia; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; N-I = normo-insulinemia; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.8b2: Stratified by sugars source

Figure G.9: Randomised controlled trials: effect of fructose vs. glucose on blood pressure

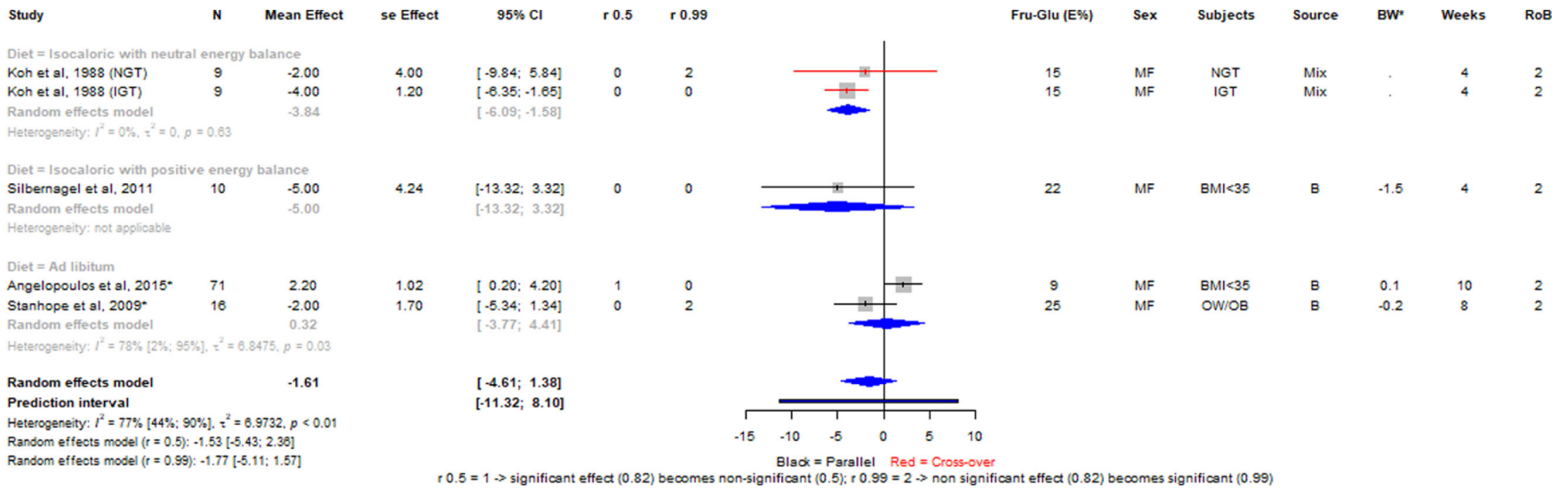
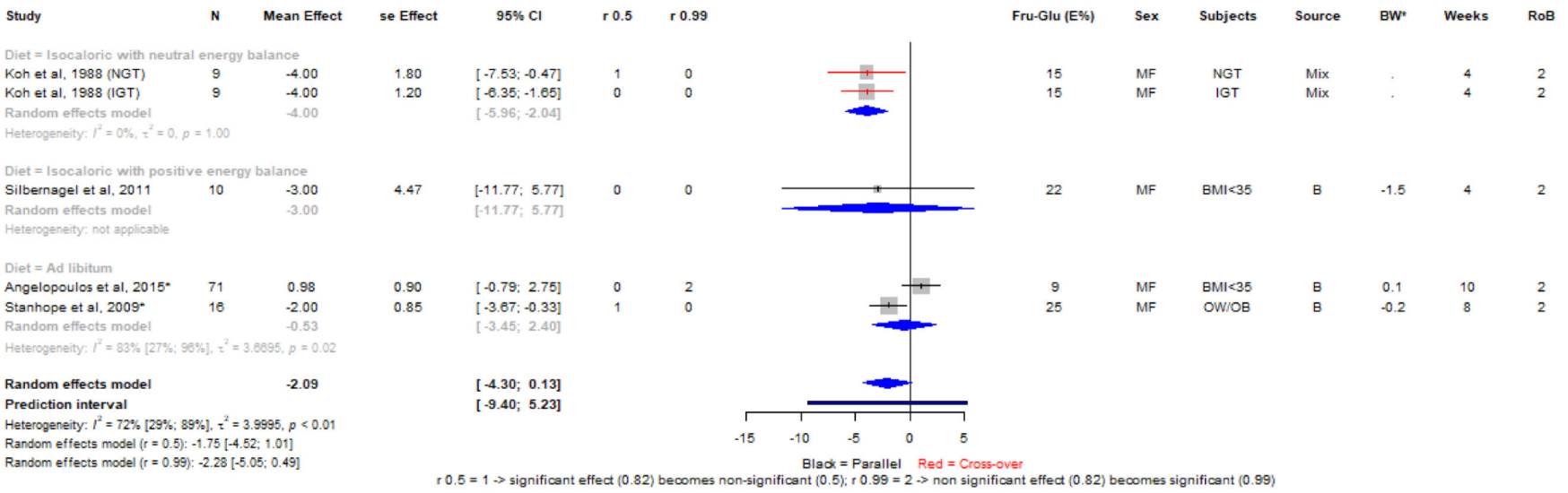


Figure G.9a: Effect of fructose vs glucose on systolic blood pressure (mmHg)



Footnote to Figure G9. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Fru = fructose; Glu = glucose; IGT = impaired glucose tolerance; MF = males and females; Mix = foods and beverages; N = average sample size per arm; NGT = normal glucose concentration; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.9b: Effect of fructose vs glucose on diastolic blood pressure (mmHg)

Figure G.10: Randomised controlled trials: effect of high vs. low sugar intake on uric acid (mg/dL)

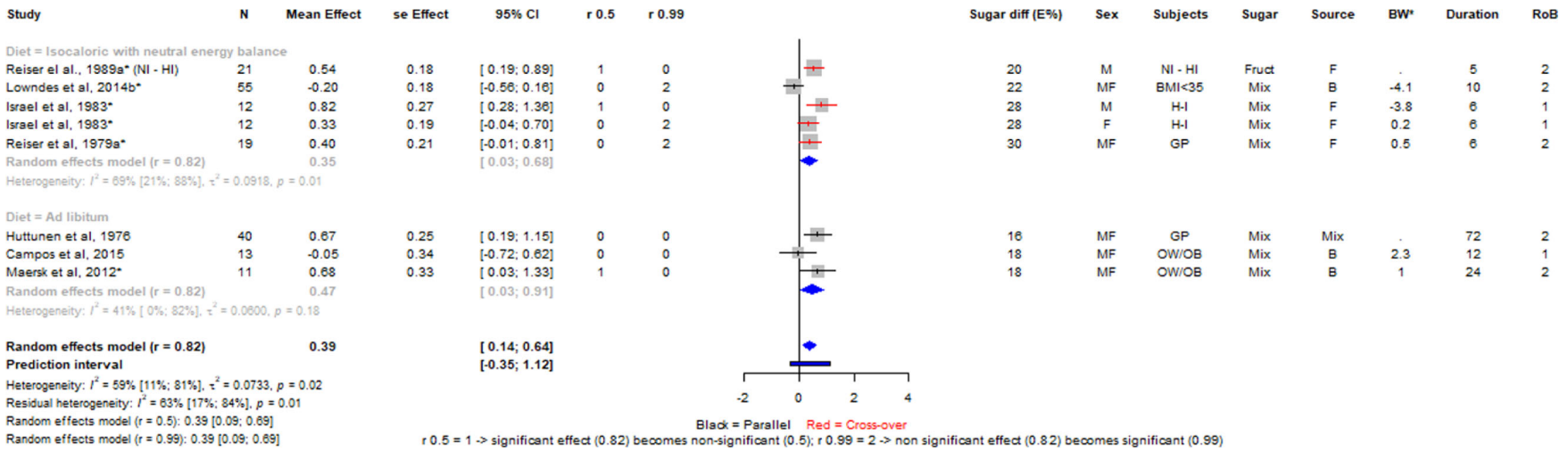
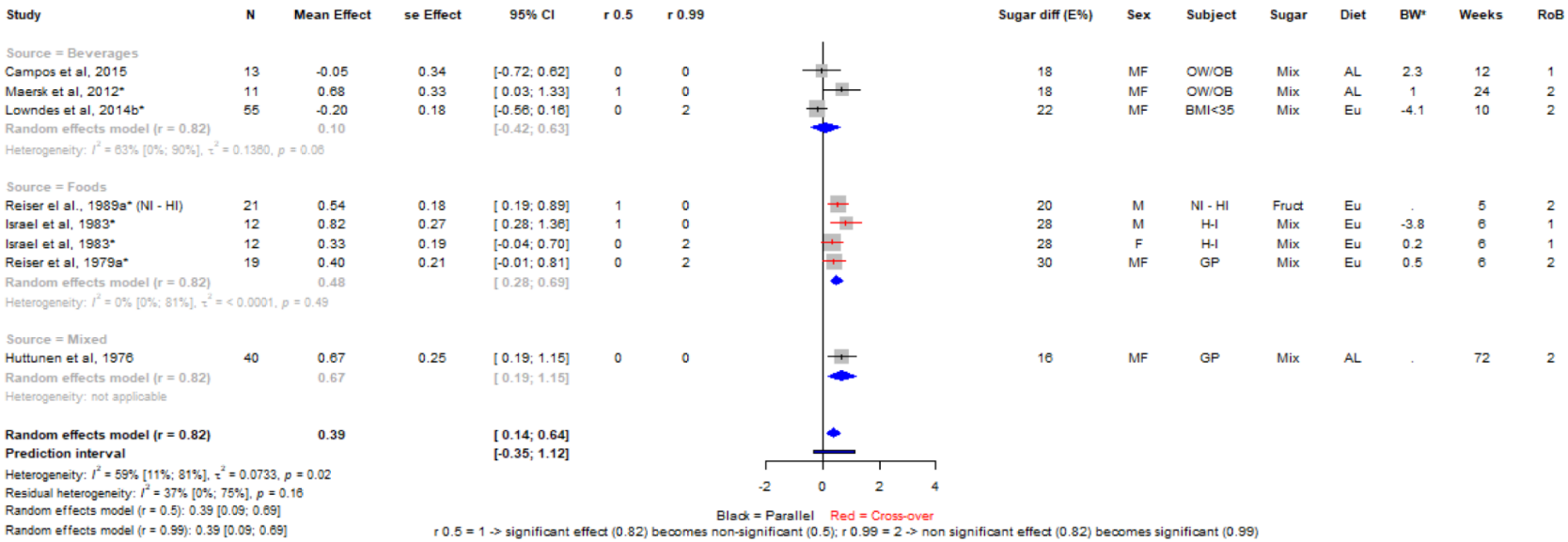
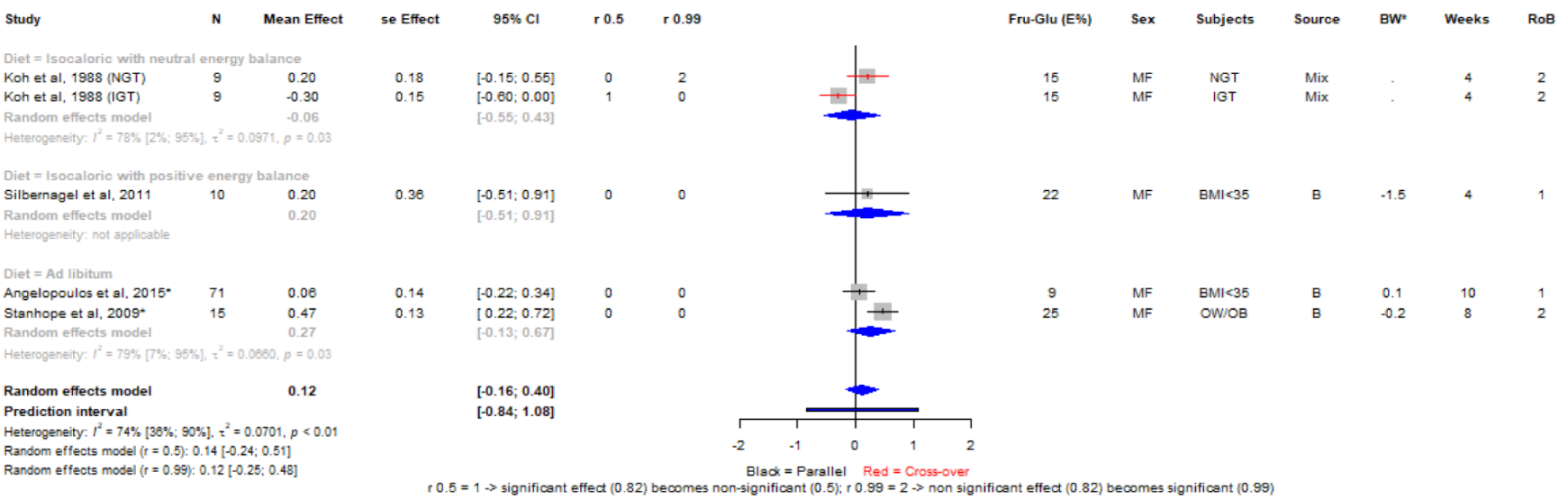


Figure G.10a: Stratified by type of diet



Footnote to Figure G10 a and b * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F = females; F under Source = foods; Fruc = fructose; GP = general practitioner; HI = hyperinsulinemia; M = males; MF = males and females; Mix = sugar mixtures; N = average sample size per arm; NI = normo-insulinemia; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.10b: Stratified by sugars source



Footnote to Figure G11 * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Fru = fructose; Glu = glucose; IGT = impaired glucose tolerance; MF = males and females; Mix = foods and beverages; N = average sample size per arm; NGT = normal glucose concentration; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.11: Randomised controlled trials: effect of fructose vs. glucose on uric acid (mg/dL)

Appendix H – Funnel plots. Intervention studies on metabolic diseases

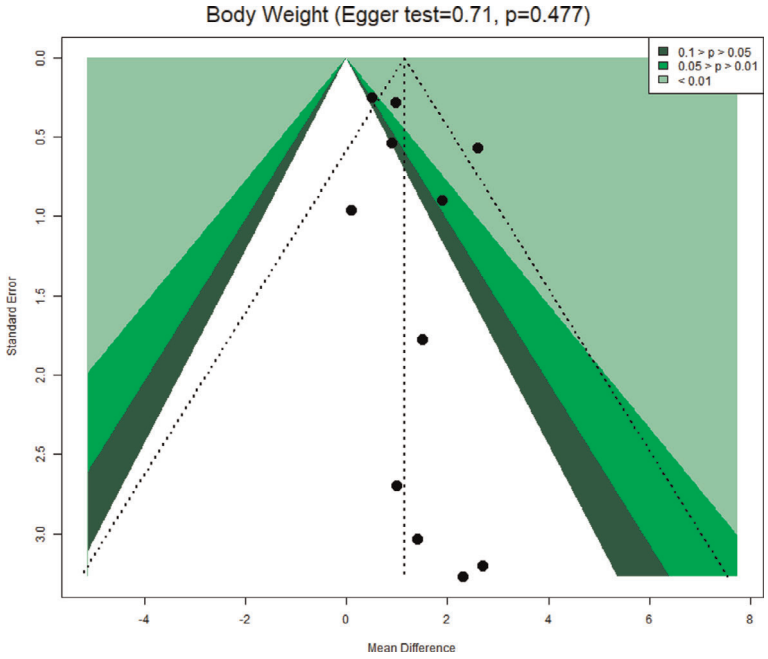


Figure H.1: RCTs on the effect of high vs. low sugar intake ad libitum on body weight

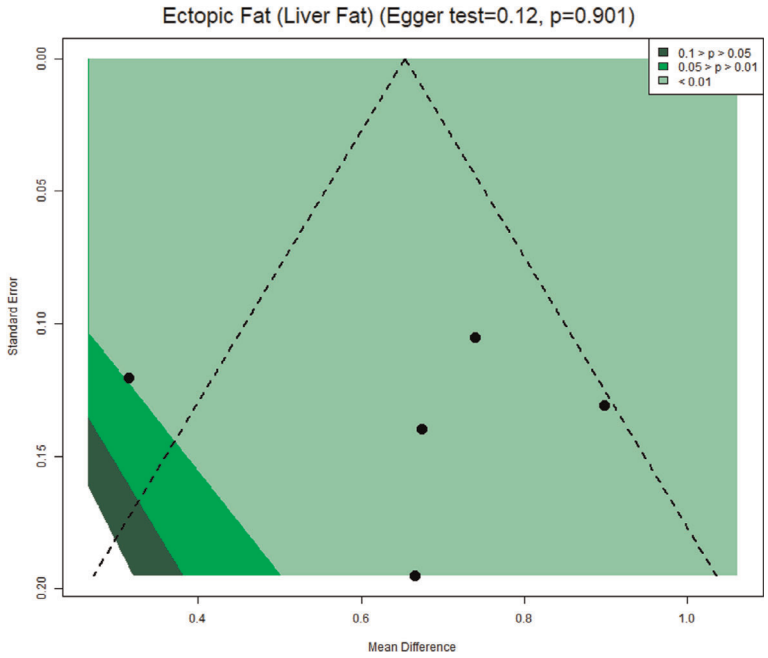


Figure H.2: RCTs on the effect of high vs. low sugar intake on liver fat

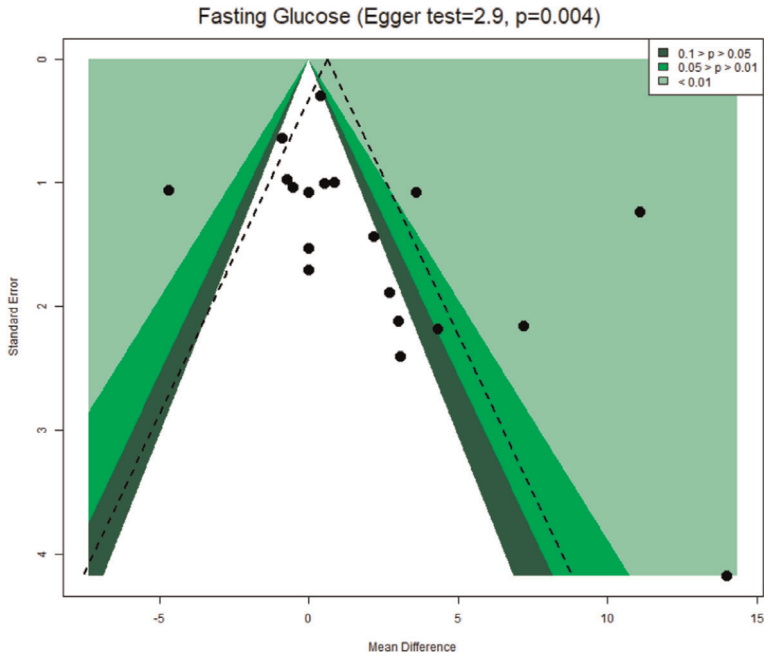


Figure H.3: RCTs on the effect of high vs. low sugar intake on fasting glucose

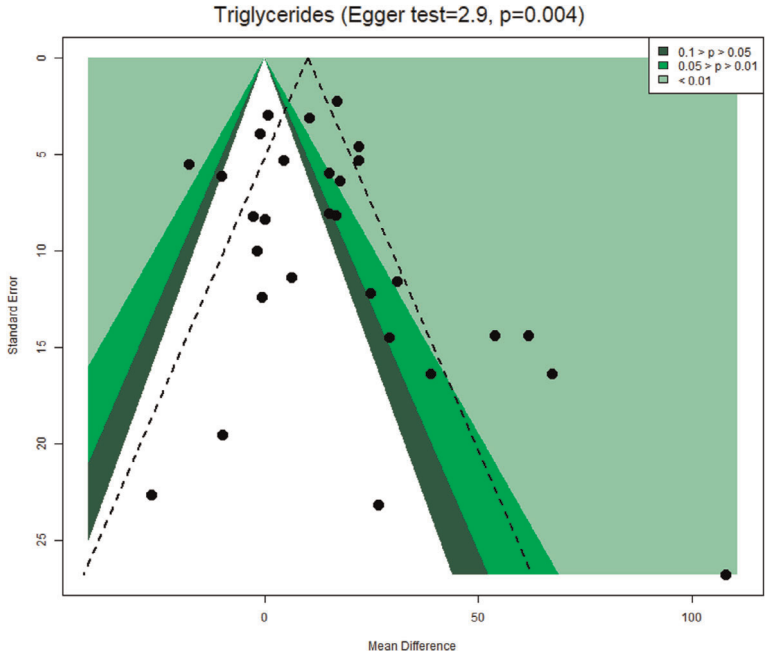


Figure H.4: Funnel plot. RCTs on the effect of high vs. low sugar intake on fasting triglycerides

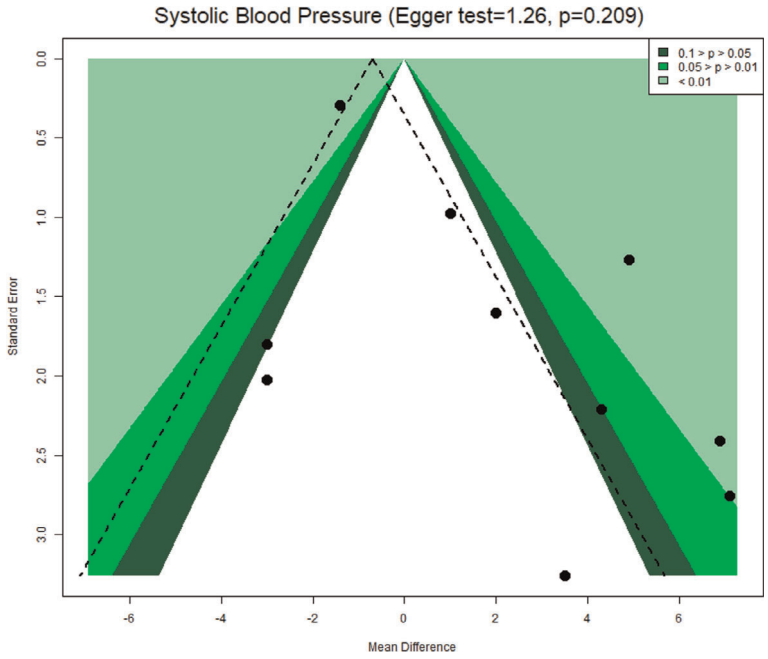


Figure H.5: Funnel plot. RCTs on the effect of high vs. low sugar intake on systolic blood pressure

Appendix I – Summary of risk of bias ratings for randomised controlled trials by type of design and endpoint

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Campos et al. (2015)_SSBs	+	NR	-	+	++	NR	++	++	2
Ebbeling et al. (2012)_SSBs	++	++	--	++	+	++	++	++	1
Ruyter et al. (2014)_ SSBs	++	++	+	+	++	++	++	++	1
Hernandez-Cordero et al. (2014)_SSBs	++	++	--	+	--	++	++	++	2
Hollis et al. (2009)_SSBs	+	NR	+	+	+	+	++	+	1
Maersk et al. (2012)*_SSBs	++	NR	--	--	+	--	++	+	2
Markey et al. (2016)	++	+	++	+	+	++	++	++	1
Saris et al. (2000)*	+	+	-	-	+	+	++	++	1
Raben et al. (2002)*	+	NR	-	++	+	++	++	+	1
Smith et al. (1996)	++	NR	--	-	+	NR	++	+	2
Werner et al. (1984)	+	NR	--	++	+	-	++	-	2

Figure I.1: Summary of Risk of Bias ratings for RCTs on the effect of high vs. low sugar intake on body weight

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Campos et al. (2015)_SSBs	+	NR	-	+	++	+	++	++	1
Lowndes et al. (2014b)*_SSBs	+	NR	-	-	+	+	++	-	2
Maersk et al. (2012)*_SSBs	++	NR	--	--	+	-	++	+	2
Umpleby et al. (2017)	++	++	NR	++	-	+	++	++	2

Figure I.2: Summary of Risk of Bias ratings for RCTs on the effect of high vs. low sugar intake on liver fat

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Black et al. (2006)	++	+	+	+	+	++	++	++	1
Campos et al. (2015)_SSBs	+	NR	-	+	++	-	++	++	1
Hallfrisch et al. (1983a)*	NR	NR	NR	++	+	+	-	+	2
Hernandez-Cordero et al. (2014)_SSBs	++	++	--	+	--	++	++	++	2
Hollis et al. (2009)_SSBs	+	NR	+	+	+	+	++	+	1
Israel et al. (1983)*	+	+	+	++	++	+	++	+	1
Lewis et al. (2013)	++	NR	NR	++	+	+	++	++	1
Lowndes et al. (2014b)*_SSBs	+	NR	-	-	+	+	++	-	2
Lowndes et al. (2015)_SSBs	++	++	+	+	+	+	++	+	1
Maersk et al. (2012)*_SSBs	++	NR	--	--	+	+	++	+	2
Majid et al. (2013)_SSBs	++	NR	--	++	+	++	++	-	2
Markey et al. (2016)	++	+	++	+	+	++	++	++	1
Moser et al. (1986)	+	+	+	++	++	+	++	+	1
Raben et al. (2002)*	+	NR	-	++	+	++	++	+	1
Saris et al. (2000)*	+	+	-	-	+	++	++	+	1
Swanson et al. (1992)	+	NR	NR	++	++	+	++	++	1
Umpleby et al. (2017)	++	++	NR	++	-	+	++	++	2

Figure I.3: Summary of Risk of Bias ratings for RCTs on the effect of high vs low sugar intake on fasting glucose

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Black et al. (2006)	++	+	+	+	+	++	++	++	1
Campos et al. (2015)_SSBs	+	NR	-	+	++	-	++	++	1
Gostner et al. (2005)	+	NR	+	++	++	+	++	+	1
Hallfrisch et al. (1983a)*	NR	NR	NR	++	+	+	-	+	2
Hernandez-Cordero et al. (2014)_SSBs	++	++	--	+	--	++	++	++	2
Hollis et al. (2009)_SSBs	+	NR	+	+	+	+	++	+	1
Huttunen et al. (1976)	--	--	--	++	+	+	++	-	2
Israel et al. (1983)*	+	+	+	++	++	+	++	+	1
Lewis et al. (2013)	++	NR	NR	++	+	+	++	++	1
Lowndes et al. (2014a)_SSBs	+	NR	-	+	+	+	++	++	1
Lowndes et al. (2014b)*_SSBs	+	NR	-	-	+	+	++	-	2
Maersk et al. (2012)*_SSBs	++	NR	--	--	+	+	++	+	2
Majid et al. (2013)_SSBs	++	NR	--	++	+	++	++	-	2
Markey et al. (2016)	++	+	++	+	+	++	++	++	1
Moser et al. (1986)	+	+	+	++	++	+	++	+	1
Raben et al. (2002)*	+	NR	-	++	+	++	++	+	1
Reiser et al. (1979a)*	-	NR	NR	+	+	+	++	++	2
Reiser et al. (1989a)*	NR	NR	+	+	++	++	++	+	2
Saris et al. (2000)*	+	+	-	-	+	++	++	+	1
Smith et al. (1996)	++	NR	--	-	+	+	++	+	2
Swanson et al. (1992)	+	NR	NR	++	++	+	++	++	1
Umpleby et al. (2017)	++	++	NR	++	-	+	++	++	2
Werner et al. (1984)	+	NR	--	++	+	+	++	-	2

Figure I.4: Summary of Risk of Bias ratings for RCTs on the effect of high vs. low sugar intake on fasting triglycerides

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Black et al. (2006)	++	+	+	+	+	++	++	++	1
Campos et al. (2015)_SSBs	+	NR	-	+	++	NR	++	++	2
Hallfrisch et al. (1983b)*	NR	NR	NR	++	+	-	-	+	2
Hernandez-Cordero et al. (2014)_SSBs	++	++	--	+	--	++	++	++	2
Israel et al. (1983)*	+	+	-	++	++	-	++	+	2
Lewis et al. (2013)	++	NR	NR	++	+	-	++	++	2
Lowndes et al. (2014b)*_SSBs	+	NR	-	-	+	-/NR	++	-	2
Maersk et al. (2012)*_SSBs	++	NR	--	--	+	--	++	+	2
Markey et al. (2016)	++	+	++	+	+	++	++	++	1
Raben et al. (2002)*	+	NR	-	++	+	+	++	+	1

Figure I.5: Summary of Risk of Bias ratings for RCTs on the effect of high vs. low sugar intake on systolic blood pressure

Reference	Randomisation	Allocation concealment	Blinding	Attrition	Exposure	Endpoint	Reporting	Other threats to interval validity	Tier
Angelopoulos et al. (2015)*_SSBs	+	NR	-	+	+	+	++	+	**1**
Silbernagel et al. (2011)_SSBs	++	++	+	++	+	++	++	++	**1**
Koh et al. (1988)	NR	NR	-	++	++	+	++	+	**2**
Stanhope et al. (2009)*_SSBs	NR	NR	++	+	++	++	++	+	**2**

Figure I.6: Summary of Risk of Bias ratings for RCTs on effect of fructose vs. glucose on uric acid

Appendix J – General characteristics of observational studies on metabolic diseases

Note: Under exposure(s) assessed, all the exposures used as independent variables in relation to the endpoints in the original publications are listed. Among these, the exposures used for this scientific assessment are in **bold** and those not considered for the assessment are *in italics*.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
AGAHLS Amsterdam Growth and Health Longitudinal Study The Netherlands Stoof et al. (2013) Mixed funding	N = 409 Children from two secondary schools in Amsterdam and the surrounding area Caucasian	13 year (mean) 52.1% females	**SSSD, SSFD, SSFJ** **SSSD, SSFD, TFJ**	Cross-check dietary history face-to-face interviews by a dietitian. Subjects were asked to recall the frequency of use and the amount of different foods and beverages during the previous month. No information on validation.	BMI Body fat Trunk fat
ALSPAC Avon Longitudinal Study of Parents and Children UK Johnson et al. (2007) Bigornia et al. (2015) Anderson et al. (2015) Cowin and Emmett (2001) Mixed funding	N = 15,247 General population living within a defined part of the country Caucasian	Birth 58.1% females	**Total sugars** **SSSD, SSFD** **100% FJs** *Carbohydrates* *Starch* *Protein* *Fat* *Milk* *Water* *PUFA* *SFA* *Vegetables* *Individual food items*	Three-day food diary covering 2 weekdays and 1 weekend day. Parents recorded their child's diet until the child reached age 10 year. SFFQ were also used at specified examinations, covering 43 items originally and growing to 68 items. FFQs had no portion size information included. No information on validation.	Body weight BMI WC Body fat NAFLD Blood lipids
ALSWH Australian Longitudinal Study on Women's Health Australia Looman et al. (2018) Public funding	N = 40,000 approximately Women from Australia's national health care system Caucasian	18–75 year Females	**Total sugars** **TFJ** *Carbohydrates* *LCD score* *Total dietary fibre* *Glycaemic index* *Glycaemic load* *Individual food groups/ items*	One self-administered SFFQ of 101 items – previous year. Portion sizes estimated with photo album. Two SFFQ completed but only the one done at baseline used for analysis. Validation for nutrients against 7-day food diaries of 63 women. Correlation coefficient of 0.78 for carbohydrates and 0.73 for total sugars.	GDM

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Amsterdam The Netherlands Weijs et al. (2011) Public Funding	N = 226 General population Caucasian	4–13 mo 46.7% females	**SSSD, SSFD, TFJ** *Animal protein*	Two-day food record (1 weekday and 1 weekend) of actual consumption in portions (translated into weight by standard portion sizes) or weighed. Parents were asked to subtract spilled or not consumed amounts. No information on validation.	Overweight
ARIC Atherosclerosis Risk in Communities Study USA Bomback et al. (2010) Paynter et al. (2006) Public funding	N = 15,792 General population 78.1% White, 21.9% African American	45–64 year 55.2% females	**SSSD** **SSSD, FD and all FJs** *ASSD* *Coffee*	One interview administered SFFQ of 66 items – previous year. Specified portion sizes (frequency). Two SFFQ completed but only the one done at baseline used for analysis. Validation against four one-week records with a sample of 173 women who answered the 1980 Nurses' Health Study questionnaire.[23] Sucrose Pearson correlation coefficients (0.71).	Hyperuricaemia T2DM
BMES Blue Mountain Eyes Study Australia Goletzke et al. (2013a) Public funding	N = 3,654 General population Caucasian	67 year (median) 62.7% females	**Total sugars** *Glycaemic index* *Glycaemic load* *Starch* *Fibre*	One self-administered SFFQ of 145 items – previous year. Validated against 4-day weighed food records collected on three occasions during 1 year (sub-sample of the cohort n = 79). Correlation coefficient of 0.62 for carbohydrates and for total sugars.	Blood lipids
BWHS Black Women's Health Study USA Boggs et al. (2013)	N = 59,001 African American women	21–69 year Females	**SSSD** **SSFD and SSFJ** **100% FJs** (orange and grapefruit)	One self-administered SFFQ of 68 items – previous year. Specified portion sizes (frequency).	Obesity T2DM

[23] Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH and Speizer FE, 1985. Reproducibility and validity of a semiquantitative food frequency questionnaire. American Journal of Epidemiology, 122.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Palmer et al. (2008) Public funding			*Individual food items*	Baseline SFFQ validated for nutrients against 3-day food diaries and three 24-h recalls.[24] Pearson correlation coefficients (95% CI) for carbohydrates: – SFFQ vs. mean of 3 24-h recalls (n = 408): Crude 0.09 (−0.03, 0.25); energy-adjusted 0.30 (0.18,0.41); energy-adjusted and deattenuated 0.48 (0.29, 0.66) – FFQ vs. mean of a 3-day diary (n = 245): crude 0.20 (0.04, 0.32); energy-adjusted 0.26 (0.05, 0.39); energy-adjusted and deattenuated 0.35 (0.08, 0.48) – FFQ vs. mean of combined recall and diary data (n = 408): crude 0.13 (−0.03, 0.25); energy adjusted 0.30 (0.18, 0.40); energy adjusted and deattenuated 0.43 (0.26, 0.53)	
Camden USA Lenders et al. (1997) Public funding	N = 594 Pregnant adolescents 61% Black 30% Hispanic 9% White	12–19 year Females	**Total sugars**	Three 24-h dietary recall (interviewer administered) analysed for energy intake and nutrients, including total sugars No information about validation.	Birth weight
CARDIA Coronary Artery Risk Development in Young Adults USA	N = 5,115 General population of 4 centres selected to balance subgroups of	18–30 year 53.5% females	**Sucrose** **SSSD, SSFD** **100% FJ** *Low-fat milk* *Whole fat milk*	One interview-administered SFFQ – previous month Validation against a second SFFQ and seven 24-h recalls (n = 128 young adults)[25]	T2DM HTN Abdominal obesity Glucose homeostasis (FI)

[24] Kumanyika SK, Mauger D, Mitchell DC, Phillips B, Smiciklas-Wright H and Palmer J, 2003. Relative validity of food frequency questionnaire nutrient estimates in the Black Women's Health study. Annals of Epidemiology, 13, 111–118.
[25] McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C and Caan B, 1991. The CARDIA dietary history: development, implementation and evaluation. Journal of American Diet Association, 91, 1104–1112.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Archer et al. (1998) Duffey et al. (2010) Folsom et al. (1996) Mixed funding	race, sex, education and age 52.6% Black, 47.4% White			Pearson correlation coefficients for total carbohydrates: White men 0.79 White women 0.89 Black men 0.43 Black women −0.22	Blood lipids
CoSCIS Copenhagen School Child Intervention Study Denmark Jensen et al. (2013) Mixed funding	N = 1,024 Children entering a public school in two suburbs of Copenhagen Caucasian	6 year (mean) 51.1% females	**SSSD** **SSSD, SSFD**	A 7-day food record administered by parents/ caregivers when the children were 6 and 9 years, respectively. No information on validation.	BMI Body fat
CTS California Teachers Study USA Pacheco et al. (2020)‡ Public funding	N = 133,477 Female teachers from California 87.3% Caucasian and 12.7% all other races	22–104 year Females	**SSSD** **SSFD** **SSSD, SSFD** *Sweetened bottled water or tea*	One self-administered SFFQ of 103 items – previous year. Validated against a sub-sample of CTS using another FFQ and 4 x 24 h dietary recalls.[26] Correlation coefficient for SFFQ vs. 24 h recalls was 0.7 for carbohydrates.	CVD CHD Stroke Revascularisation
Daily-D Daily-D Health Study USA Van Rompay et al. (2015) Public funding	N = 690 General population from Boston area schools 45% Caucasian, 13% Black, 18% Hispanic, 9% Asian and 15% multi-racial/other	8–15 year 50.8% females	**SSSD, SSFD**	Three SFFQs of 78 items – past week use to estimate mean SSBs intake over 12 months. Validation against 2 x 24 hrs dietary recall by telephone in a sample of 83 children aged 10–17 years.[27] Deattenuated adjusted correlations (whole sample) for E% from carbohydrates = 0.69.	Blood lipids

[26] Horn-Ross PL, Lee VS, Collins CN, Stewart SL, Canchola AJ, Lee MM, Reynolds P, Clarke CA, Bernstein L and Stram DO, 2008. Dietary assessment in the California Teachers Study: reproducibility and validity. Cancer Causes Control, 19, 595–603.
[27] Cullen KW, Watson K and Zakeri I, 2008. Relative reliability and validity of the Block Kids Questionnaire among youth aged 10 to 17 years. Journal of American Diet Association, 108, 862–866.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
DCH Diet, Cancer and Health Study Denmark Olsen et al. (2016) Mixed funding	N = 57,053 Inhabitants from Copenhagen and Aarhus counties Caucasian	50–64 year 49.4% females	**SSSD**	One self-administered SFFQ of 192 items – previous year. Validated against two 7-day diet records in a random sample of men and women from Copenhagen (aged 40–64 year).[28] Correlation coefficients for carbohydrates: 0.40 and 0.47 and for sucrose: 0.50 and 0.41, for men and women, respectively.	Body weight WC
DDHP Detroit Dental Health Project USA Lim et al. (2009) Mixed funding	N = 1,021 Low-income African American children from Detroit	3–5 year 51.6% females	**SSSD** **SSFD** **SSSD, SSFD**	One interview administered SFFQ (Block Kids Food Frequency Questionnaire) containing 75 questions and measuring intake of previous week. Validation against a similar cohort (age: 8.3 ± 0.3) of n = 129 that completed 3-day diaries (for 2 weekdays and 1 weekend day during a 7-day period.) Validity in the estimates of beverage intakes established for children aged 7–9y Spearman correlation coefficients (SFFQ vs. Diary)[29]: – SSSD+SSFD: 0.326 – Carbohydrate: 0.203	Overweight/obesity
DONALD Dortmund Nutritional and Anthropometric Longitudinally Designed Study Germany	N = > 1,300 General population from Dortmund Caucasian	birth 53.5% Females	**Free sugars** **SSSD, SSFD, SSFJ** **100% FJ** *Sugar from individual food groups* *Energy drinks*	3-day weighed dietary records (over 3 consecutive days). No information on validation.	BMIz-score Body fat Glucose homeostasis (HOMA-IR)

[28] Tjønneland A, Overvad K, Haraldsdottir J, Bang S, Ewertz M and Jensen OM, 1991. Validation of a semiquantitative food frequency questionnaire developed in Denmark. International Journal of Epidemiology, 20, 906–912.

[29] Teresa A, Marshall JM, Eichenberger G, Barbara B, Stumbo PJ and Levy SM, 2008. Relative validity of the Iowa Fluoride Study targeted nutrient semi-quantitative questionnaire and the Block Kids' Food questionnaire for estimating beverage, calcium, and vitamin D intakes by children. Journal of the American Dietetic Association, 108, 465–472.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Herbst et al. (2011) Libuda et al. (2008) Goletzke et al. (2013b) Public funding			*Carbohydrate* *Glycaemic index* *Glycaemic load* *Fibre* *Whole grain*		
ELEMENT Early Life Exposure in Mexico to Environmental Toxicants Mexico Cantoral et al. (2015) Public funding	N = 1,079 General population Hispanics	Birth 54% females	**SSSD, SSFD, SSFJ**	SFFQ of previous 3 months administered in each visit (8 visits, from when the child was 12mo to 5y in 6-months intervals). SFFQ included 116 foods grouped into 10 categories and beverages (natural juice, milk, sodas, commercial fruit drinks and flavoured water with sugar). Standard serving size used to obtain average daily intakes. SFFQ validated (24-h recall) with a random sample of women from medium to low socioeconomic status living in Mexico City. To assess the validity for carbohydrates of the questionnaire Pearson correlation coefficients between the average of 16 24-hour recalls and the first and second administration of the FFQ were calculated. – FFQ1 vs. 24-hr recall: Unadjusted 0.51; adjusted* 0.49; de-attenuated 0.52 – FFQ2 vs. 24-hr recall: Unadjusted 0.56; de-attenuated 0.57 – FFQ1 vs. FFQ2: Unadjusted 0.56; adjusted* 0[30] *adjusted for total energy intake At revisit (8 and 14y of age) SFFQ (ENSANUT 2006) was 'administered to the children who	Obesity Abdominal obesity

[30] HERNÁNDEZ-AVILA, Mauricio et al. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. **Salud Pública de México**, [S.l.], v. 40, n. 2, p. 133-140, mar. 1998. ISSN 1606-7916. Available online: https://saludpublica.mx/index.php/spm/article/view/6068/7081 [Accessed: 20 September 2019].

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
				were assisted – this instrument used a 1-week recall period and queried about the consumption of natural juices, commercial fruit drinks, flavoured water with sugar, tap water, sodas, diet sodas, whole fat milk, coffee and tea'.	
EPIC-Diogenes European Prospective Investigation into Cancer and Nutrition-Diet, Obesity and Genes project IT, UK, NL, DE, DK Romaguera et al. (2011) Public funding	N = 146,543 General population from 5 countries (8 sites) Caucasian	20–60 year 59.5% females	**SSSD** **TFJ** *Individual food items/ groups*	Country-specific self-administered SFFQs. Validation against 24-h dietary recalls or weighted food records.[31]	WC_{BMI}
EPIC-Interact European Prospective Investigation into Cancer and Nutrition-InterAct project DK, FR, DE, IT, NL, ES, SE, UK Sluijs et al. (2013) InterAct consortium (2013) Public funding	**N** = 29,238 Mainly general population Caucasian	35–70 year 62% females	**Total sugars** **SSSD, SSFD** **TFJ** *ASSD* *ASSD, SSSD, SSFD* *Glycaemic index* *Glycaemic load* *Digestible carbohydrates* *Starch*	One baseline assessment Quantitative dietary questionnaire with individual portion sizes: France, Spain, The Netherlands, Germany and Italy. SFFQ: Denmark, Naples (Italy), Sweden and the UK. Each dietary assessment tool was validated locally.[32] Validation against 24-h dietary recalls or weighted food records. Correlation coefficients varied from 0.40 in Denmark to 0.84 in Spain for men and from	T2DM

[31] Kaaks R and Riboli E, 1997. Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. European Prospective Investigation into Cancer and Nutrition. International Journal of Epidemiology, 26(Suppl 1), S15–S25.

[32] Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, Sneyd MJ, Key TJ, Roe L and Day NE, 1994. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. British Journal of Nutrition, 72, 619–643; Margetts BM and Pietinen P, 1997. European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. International Journal of Epidemiology, 26:S1–5. Available online: https://epic.iarc.fr/about/dietaryexposure.php

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
				0.46 in Malmo (Sweden) to 0.78 in Spain for women.	
EPIC-Morgen European Prospective Investigation into Cancer and Nutrition-Morgen cohort The Netherlands Burger et al. (2011) Public funding	N = 22,654 General population Caucasian	20–65 year 54.8% females	**Total sugars** *Glycaemic index* *Glycaemic load* *Carbohydrates* *Starch*	One self-administered SFFQ of 79 items–previous year. The questionnaire contained photographs of 21 foods in different sizes. For most other items, the consumption frequency was asked in number of specified units; for a few foods a standard portion size was assumed.[33] Validation against twelve 24-h recall. Person correlation for carbohydrate was 0.74 (men) and 0.76 (women)	CHD Stroke
EPIC-Multicentre European Prospective Investigation into Cancer and Nutrition- Multiple countries DK, DE, GR, FR, NL, UK, NO, ES, SE, IT Mullee et al. (2019)‡ Sieri et al. (2020)‡ Public funding	N = 521,330 General population Caucasian	35–70 year 71% females	**Total sugars** **SSSD, SSFD** *ASSD* *SSSD, SSFD, ASSD* *Glycaemic load* *Glycaemic index* *Carbohydrates* *Starch*	Self-administered SFFQ (no. of items varied depending on study location – up to 260 items) were used in all centres, except in Greece, Spain and Ragusa (Italy), where data were collected during personal interviews. In Malmö (Sweden), a combined SFFQ and 7-day dietary diary and diet interview was used. Validation methods varied on type of assessment method used at each site. Correlation coefficients were country specific, but range from 0.46 to 0.77 for soft or non-alcoholic drinks (in the Netherlands, France, Germany and Spain).	CVD CHD Stroke
EPIC-Norfolk European Prospective Investigation into Cancer and Nutrition-Norfolk cohort	N = 25,639 General population Caucasian	39–79 year 54% females	**Total sucrose** **Free glucose** **Free fructose** **SSSD, SSFD**	7-day diet diary (several completed throughout the year, for four years) and a self-administered SFFQ of 130-item. First day of diary completed as a 24-h recall with a trained interviewer.	WC BMI T2DM

[33] Ocké, MC, Bueno-de-Mesquita, HB, Goddijn, HE, Jansen, A, Pols, MA, van Staveren, WA & Kromhout, D. (1997). The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. International journal of epidemiology, 26 Suppl 1, S37–S48.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
UK Ahmadi-Abhari et al. (2014) Kuhnle et al. (2015) Public funding			**TFJ** *ASBs* *Sweetened tea or coffee* *Sweetened-milk beverages* *Starch* *Total carbohydrates* *Lactose* *Maltose*	The 7-day diet diary and the SFFQ were repeated at 18 months to ascertain details of changes in health since recruitment.[34] Validation was done for nutrients. (n = 300, subsample of the original Norfolk cohort) Pearson correlation coefficients for sugars: – 1st vs. 2nd diary: 0.75 – 1st vs. 2nd SFFQ: 0.67 – 1st diary vs. 1st SFFQ: 0.53 – 1st diary vs. 1st 24-h recall: 0.57	
EPICOR European Prospective Investigation into Cancer and Nutrition-Italian cohort Italy Sieri et al. (2010) Sieri et al. (2013) Public funding	N = 47,749 General population Caucasian	35–75 year 69% females	**Total sugars** *Carbohydrates* *Carbohydrates from high-GI food* *Carbohydrates from low-GI food* *Starch* *Glycaemic index* *Glycaemic load* *Fibre*	SFFQ – previous year. Three different types: One for northern and central Italian centres (self-administered), one for Ragusa (administered by trained interviewers) and one for Naples (administered by trained interviewers) Validation for food groups and sugar against 24-h recall and between questionnaires. Correlation coefficient for sugar: Men Q1-Q2 0.62; Q1-24-h 0.51. for women Q1-Q2 0.66; Q1-24-h 0.26[35]	CHD Stroke
EPIC-Utrecht European Prospective Investigation into Cancer and Nutrition-Utrecht cohort The Netherlands Beulens et al. (2007) Public funding	N = 17,357 Breast cancer screening participants Caucasian	49–70 year Females	**Total sugars** *Carbohydrates* *Polysaccharides* *Glycaemic load* *Glycaemic index*	SFFQ – previous year. 77 main food items. Portion sizes assessed for 28 items. Total of 178 foods. Validation against 12 24-h recalls. Spearman correlations were 0.76 for carbohydrates and 0.74 for fibre, and 0.78, 0.56, 0.69 and 0.70 for bread, fruit, sweets and potatoes, respectively	CVD CHD Stroke

[34] Bingham SA, Welch AA, McTaggart A, Mulligan AA, Runswick SA and Luben R. Nutritional methods in the European prospective investigation of cancer in Norfolk. Public Health Nutrition, 4, 847–858.
[35] Pisani P, Faggiano F, Krogh V, Palli D, Vineis P and Berrino F, 1997. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres International Journal of Epidemiology, 26(Suppl. 1), S152–S60.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
FMCHES Finnish Mobile Clinic Health Examination Survey Finland Montonen et al. (2007) Public funding	N = 51,522 General population Caucasian	40–69 year 47% females	**Total sugars** **Sucrose** **Fructose+glucose** **Free fructose** **Free glucose** **SSSD** *Lactose* *Maltose* *Honey and syrup* *Jam and marmalade* *SS berry juice* *Table sugar*	Dietary history interview[36] SFFQ of 100 food items and mixed dishes and administered by trained interviewers – previous year Validated against dietary history interviews repeated after 4–7 years. Intraclass correlation coefficient for carbohydrates: men 0.41, women 0.39	T2DM
Framingham-3Gen Framingham-Third Generation cohort USA Ma et al. (2016b) Haslam et al. (2020)‡ Public funding	**N** = 4,095 General population Caucasian	19–72 year 45% females	**SSSD, SSFD** **100% FJ** *ASSD* *LCSB*	SFFQ of 126 items – previous year Validation against 7-day diet record with 157 men. Correlation coefficient for SSBs was 0.51, 0.84 for sugar sweetened cola, 0.55 for other sweetened soft drinks and for diet soda 0.66.	Ectopic fat (VAT and VAT:SAAT ratio) Blood lipids
Framingham-Offspring Framingham-Offspring cohort USA Ma et al. (2016a) Pase et al. (2017) Haslam et al. (2020)‡ Public funding	N = 5,135 General population Caucasian	30–59 year 53.1% females	**SSSD, SSFD** **SSSD, SSFD, 100% FJ** **100% FJ** *ASSD* *LCSB*	Three self-administered SFFQ of 126 items – previous year Average of all available SFFQs until diagnosis of the outcome Validation against 7-day diet record with 157 men. Correlation coefficient for SSBs was 0.51, 0.84 for sugar sweetened cola, 0.55 for other sweetened soft drinks and for diet soda 0.66.	Glucose homeostasis (HOMA-IR) Prediabetes or T2DM (composite endpoint) Stroke Blood lipids

[36] Ja¨rvinen R, 1996. Epidemiological follow-up study on dietary antioxidant vitamins. Results from the Finnish Mobile Clinic Health Examination Survey. Helsinki: Social Insurance Institution, Studies in Social Security and Health 11.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
GeliS Germany Günther et al. (2019)‡ Public funding	N = 2,286 Pregnant women with a singleton pregnancy Caucasian	18–43 year Females	**SSSD** *Carbohydrates* *Saccharose* *Protein* *Fat* *Alcohol* *Caffeine* *Light drinks* *Vegetables* *Fruits* *Dairy products* *Meat* *Sweets and snacks* *Fast food*	Two (early and late pregnancy) self-administered SFFQs of 54 items – past month. Validated against two 24-h dietary recalls (in sample of 161 participants aged 18–80y). Correlation coefficient of 0.61 for non-alcoholic beverages for all participants and 0.59 for females only.[37]	Birthweight
Generation R Generation R Study The Netherlands Leermakers et al. (2015) Mixed funding	N = 9,749 General population Caucasian	1.08 year (median) 50.1% females	**SSSD, SSFD, TFJ**	A SFFQ of 211 items completed by primary caregiver – previous year. Validated against 3-day 24-h recalls carried out by trained nutritionists. Correlation coefficient of 0.4 for carbohydrates and of 0.76 for sugar-containing beverages.	Obesity
Girona Spain Funtikova et al. (2015) Public funding	N = 3,058 General population Caucasian	25–74 year 49% females	**SSSD** **100% FJ** *Whole milk* *Skim and low-fat milk*	Interview administered SFFQ administered at baseline and follow-up. 166-item food list including alcoholic and non-alcoholic beverages. Medium servings and units (slices, glass, teaspoons etc.) were specified for each food item. A subset of participants repeated the 72-h recall (n = 19) and the FFQ (n = 29) for repeatability analysis purposes.[38] Correlation coefficient for carbohydrates was 0.71.	Abdominal obesity

[37] Haftenberger M, Heuer T, Heidemann C, Kube F, Krems C and Mensink GBM, 2010. Relative validation of a food frequency questionnaire for national health and nutrition monitoring. Nutrition Journal, 9, 36.
[38] Schroder H, Covas MI, Marrugat J, Vila J, Pena A, Alcantara M and Masia R, 2001. Use of a three-day estimated food record, a 72-hour recall and a food-frequency questionnaire for dietary assessment in a Mediterranean Spanish population. Clinical Nutrition, 20, 429–437.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
GUTS Growing Up Today Study USA Field et al. (2003) Berkey et al. (2004) Mixed funding	N = 16,882 Offspring of participants from NHSII Majority (94.7%) Caucasian	9–14 year 55% females	**SSSD, SSFD** **100% FJ** *Milk* *ASSD* *Fruit* *Vegetables*	A self-administered SFFQ of 132 items -previous year.[39] Validated against three 24-h recalls.[40] Correlation coefficient for nutrients from the FFQ compared with three 24-h recalls was r = 0.54.	BMIz-score
GUTSII Growing Up Today Study-II USA Field et al. (2014) Study USA Bernstein et al. (2012) Choi and Curhan (2008) Choi et al. (2010) Cohen et al. (2012) de Koning et al. (2011) Forman et al. (2009) Muraki et al. (2013) Pan et al. (2013) Joshipura et al. (1999) Malik et al. (2019)‡ Public funding	N = 51,529 Health professional males (dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians) Majority (~90%+) Caucasian	40–75 year Males	**Total fructose** **Free fructose** **SSSD** **SSSD and FD** **100% FJ** *ASSD* *ASB* *Glycaemic index* *Glycaemic load* *Orange or apple FJ* *Orange or apple (fruit)* *Total whole fruit* *Individual fruits* *Whole-fat milk* *Low-fat milk* *Total coffee* *Sweetened cola* *Other sweetened soft drinks* *Carbonated beverages*	One self-administered[41] SFFQ of 131 items-previous year. Additional SFFQs carried out throughout follow-up. A second SFFQ was completed by a subsample of 127 men that participated in the validation study. Validation against two 7-day diet records. Correlation coefficients were 0.84 for colas, 0.74 for low-calorie colas and 0.55 for other carbonated sugar-sweetened beverages, 0.88 low-fat milk and 0.75–0.89 fruit juice	Body weight CVD CHD Stroke Gout HTN T2DM

[39] Rockett HRH, Wolf AM and Colditz GA, 1995. Development and reproducibility of a food frequency questionnaire to assess diet of adolescents. Journal of American Diet Association, 95, 336–340.
[40] Rockett HRH, Breitenbach M and Frazier AL, 1997. Validation of a youth/adolescent food frequency questionnaire. Preventive of Medicine, 26, 808–816.
[41] Feskanich D, Rimm EB and Giovannucci EL, 1993. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. Journal of American Diet Association, 93, 790–796.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
			Non-carbonated beverages *Water* *Tea* *Vitamin C*		
HPP Harvard Pooling Project of Diet and Coronary Disease (ARIC, ATBC, HPFS, IWHS, WHS, NHS80, NHS86) USA Keller et al. (2020)‡ Public funding	N = 284,345 Health professionals and general population Majority Caucasian	≥ 35 year 76.1% females	**SSSD, SSFD** *Fruit juice* *Caffeinated coffee* *Total coffee* *Tea* *Low fat milk* *Whole fat milk* *Total milk* *ASB*	SFFQ at baseline – no further information on amount of items. No information on validation.	CHD
HSS-DK Healthy Start Study-Denmark Denmark (Zheng et al., 2015) Mixed funding	N = 552 Children who had a high predisposition for future overweight based on specific criteria Caucasian	2–6 year 45% females	**SSSD, SSFD, TFJ** *Water* *Milk* *ASB*	A 4-day dietary record completed by parents (covering weekdays and weekends). No information on validation.	Body weight BMIz-score
HSS-USA Healthy Start Study-USA USA Crume et al. (2016) Public funding	N = 1,410 Pregnant women White 54.81% Hispanic 24.62% Black 14.71% Other 5.87%	> 16 year Females	**Total sugars** *Total fat* *SFA* *Unsaturated fat* *MUFA* *PUFA* *Carbohydrates* *Protein*	Repeated (8x) 24-h dietary recall. No information on validation.	Birth weight
Inter99 Inter99 study	N = 13,016	30–60 year 49.3% females	**SSSD**	One self-administered SFFQ of 198 items – previous year.	Body weight WC

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Denmark Olsen et al. (2016) Mixed funding	Inhabitants from Copenhagen county Caucasian			Validated against 28-day diet history.[42] Correlation coefficients for carbohydrate: crude 0.45 and 0.46 (men and women, respectively); adjusted for total for total energy intake 0.51 and 0.46 (men and women, respectively).	
JPHC Japan Public Health centre-based Study Cohort Japan Eshak et al. (2012) Eshak et al. (2013) Public funding	N = 43,149 General population Asian	40–59 year 52.13% females	**SSSD, SSFD, SSFJ** **100% FJ** *Vegetable juice*	Self-administered FFQ: 1990, 44 items – previous month; 1995 and 2000, 147 foods – previous year. Validation: 1990 and 1995 FFQ, validated against four 7-day weighed dietary records (DR) over one year. Correlation coefficient for SSSD, FD and SFJ: – 1990 SFFQ vs. four 7-day DR was 0.29 for men and 0.31 for women – 1995 SFFQ vs. four 7-day DR was 0.35 for men and 0.41 for women – 1990 SFFQ vs. 1995 SFFQ was 0.52 for men and 0.51 for women Correlation coefficient for 100% FJ: – 1990 SFFQ vs. four 7-day DR was 0.17 for men and for women – 1990 SFFQ vs. 1995 SFFQ was 0.22 for men and 0.33 for women.	CHD Stroke T2DM
KoCAS Korean Child–Adolescent Cohort Study South Korea	N = 811 Children from four schools from city of Gwacheon	9–10 year 48.3% females	**Total sugars** **Free sugars from beverages** *Milk sugar* *Fruit sugar*	A three-day (two weekdays, one weekend day) food record – with parental assistance. No information on validity.	BMIz-score Body fat

[42] Toft U, Kristoffersen L, Ladelund S, Bysted A, Jakobsen J, Lau C, Jorgensen T, Borch-Johnsen K and Ovesen L, 2008. Relative validity of a food frequency questionnaire used in the Inter99 study. European Journal of Clinical Nutrition, 62, 1038–1046.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Hur et al. (2015) Public funding	Asian		*Other sources sugar*		
KoGES Korean Genome and Epidemiology Study South Korea Kang and Kim (2017) Kwak et al. (2018) Public funding	N = 10,030 General population Asian	> 30 year 54% females	**SSSD**	Two SFFQ of 103 items – previous year Validation against four 3-day dietary recall for 1 year of each participant (adherence of 85%).[43] Pearson's correlation coefficient for carbohydrate: Crude model: – Dietary recall vs. SFFQ1 was 0.27 – Dietary recall vs. SFFQ2 was 0.42 Sex, age and energy-adjusted: – Dietary recall vs. SFFQ1 was 0.37 – Dietary recall vs. SFFQ2 was 0.54 Sex, age, energy-adjusted and de-attenuated (corrected for within-person variation): – Dietary recall vs. SFFQ1 was 0.49 – Dietary recall vs. SFFQ2 was 0.64	Abdominal obesity Blood lipids T2DM HTN
MDCS Malmo Diet Cancer Study Sweden Ericson et al. (2018) Sonestedt et al. (2012) Sonestedt et al. (2015) Warfa et al. (2016)	N = 28,098 General population Caucasian	44–74 year 62% females	**Added sugars** **Sucrose** **SSSD** **100% FJ** *Carbohydrates* *Fat* *Protein* *Fibre*	Interview-based: 7-day food record combined with SFFQ of 168-items of previous year + diet history interview for checks Validation against 18-day weight food records collected over one year (n = ca. 100 aged 50–69 randomly extracted from Malmö's computerised population registry).	T2DM CVD CHD Stroke

[43] Ahn Y, Kwon E, Shim JE, Park MK, Joo Y and Kimm K, 2007. Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. European Journal of Clinical Nutrition, 61, 1435–1441.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Public funding			*Milk* *ASSD* *Sweets* *Cakes and biscuits* *Cakes and pastries* *Tea* *Coffee* *Chocolates* *Fruits and berries* *Vegetables* *Processed meat* *Whole grains* *Refined grains* *Potatoes* *Sugar and sweets* *Sugar and jam*	Energy-adjusted Person correlation coefficient for sugars: 0.60 for men and 0.74 for women.	
MIT-GDS Massachusetts Institute of Technology Growth and Development Study USA Phillips et al. (2004) Mixed funding	N = 196 Premenarcheal girls from Cambridge, MA 75% Caucasian, 14% Black and 11% other	8–12 year Females	**SSSD** *Candy* *Chips* *Baked goods* *Ice-cream*	Self-administered SFFQ of 116 items – previous year. Validation against four one-week records with a sample of 173 women who answered the 1980 Nurses' Health Study questionnaire.[44] Correlation coefficient for sucrose of 0.71.	BMIz-score BF
MoBA Norwegian Mother and Child Cohort Study Norway Grundt et al. (2017)	N = 75,075 mother-child dyads Pregnant women Caucasian	Mean age per intake category: 27.9 – 30.7 year Females	**SSSD** *ASSD*	Self-administered SFFQ of 255 food items – since the beginning of the pregnancy[45] Validated with a 4-day weighed food diary and one 24-h urine collection and blood sample (n = 119)	Birth weight

[44] Willett WC, Sampson L and Stampfer MJ, 1985. et Reproducibility and validity of a semiquantitative food frequency questionnaire. American Journal of Epidemiology, 122, 51–65.
[45] Brantsæter AL, Haugen M, Alexander J and Meltzer HM, 2008. Validity of a new food frequency questionnaire for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). Maternal and Child Nutrition, 4, 28–43.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Public funding				Spearman correlation coefficient for added sugars of SFFQ vs. food diary: 0.36 Energy-adjusted correlation coefficient for added sugars of SFFQ vs. food diary: 0.29	
MONICA Monitoring Trends and Determinants of Cardiovascular Disease Denmark Olsen et al. (2016) Public funding	N = 4,581 Inhabitants from Copenhagen county Caucasian	30–60 years 52.1% females	**SSSD**	7-day dietary record; information provided on the mean weight of 19 frequently consumed foods. Entries were expressed at estimated, or preferably weighted, grams. No information on validation.	Body weight
MOVE MOVE project USA Carlson et al. (2012) Public funding	N = 271 Children with history of parental obesity 39% Caucasian, 48% Latino, 13% other	6–7 year 56% females	**SSSD, SSFD** **100% FJ** *High fat foods* *Fruit and vegetables* *Fast food/restaurants*	One SFFQ administered by parents – no information on number of items. No data on validation against reference method – unclear validity.	BMIz-score BF
Mr and Ms OS Mr and Ms OS project of Hong Kong China Liu et al. (2018) Public funding	N = 4,000 General population Asian	≥ 6.5 year 50.2% females	**Added sugars** **Free sugars** *Added sugars from cereals/milk/sweets*	One self-administered SFFQ of 329 items (in which sugar intakes were estimated from 130 food items) – previous year. Validated by the basal metabolic rate calculation and the 24-h sodium/creatinine and potassium/creatinine analysis.[46]	Body weight BMI Body fat CVD
MTC Mexican Teachers' Cohort	N = 27,992 Female teachers	≥ 25 year Females	**SSSD** *ASSD*	Two self-administered SSFQ of 139 items – previous year.	Body weight WC

[46] Woo J, Leung SSF, Ho SC, Lam TH and Janus ED, 1997. A food frequency questionnaire for use in the Chinese population in Hong Kong: description and examination of validity. Nutrition Research, 17, 1633–1641.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Mexico Stern et al. (2017) Unclear funding	Hispanic			Validated against another FFQ and four 4-day 24-hour recalls.[47] Correlation coefficient between the SFFQ and the average of sixteen 24-h recalls (de-attenuated) was 0.52 for carbohydrates.	
NGHS National Lung, Heart and Blood Institute's Growth and Health Study USA Lee et al. (2014) Lee et al. (2015) Striegel-Moore et al. (2006) Unclear funding	N = 2,379 Non-Hispanic Caucasian and African American girls with racially concordant parents from 3 sites 51% Caucasian and 49% Black	9–10 year Females	**Total sugars** **Added sugars** **SSSD** **SSFD** **100% FJ** *Natural sugar* *Milk* *Coffee/tea*	An annually (10x) collected 3-day food record (2 weekdays and 1 weekend day). Validated against observation of a sub-sample of 60 participants. Correlation coefficient 0.78 for carbohydrates.	BMIz-score Body weight WC Blood lipids
NHS Nurses Health Study USA Bernstein et al. (2012) Choi and Curhan (2008) Choi et al. (2010) Cohen et al. (2012) Forman et al. (2009) Muraki et al. (2013) Pan et al. (2013) Joshipura et al. (1999) Malik et al. (2019)‡ Public funding	N = 121,770 Female nurses Majority (~93%+) Caucasian	30–55 year Females	**Total Fructose** **Free fructose** **SSSD** **100% FJ** **SSSD, SSFD** *ASSD* *ASB* *Lactose* *Sugar-sweetened cola* *Carbonated beverages* *Non-carbonated beverages* *Vitamin C* *Total whole fruit*	Six self-administered SFFQ of 61 foods – previous year (number of SFFQs varied per outcome assessed due to different lengths of follow). Additional SFFQs carried out throughout follow-up. Validation for food source against two 7-day diet records. Correlation coefficients were 0.84 for cola-type soft drinks (SSSD and ASSD combined), 0.36 for other carbonated soft drinks, 0.84 for orange juice and 0.56 for fruit punch.	Body weight CVD Stroke Gout HTN T2DM

[47] Hernández-Avila M, Romieu I and Parra S, 1998. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. Salud Publica Mex, 40, 133–140.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
			Individual fruits *Water* *Coffee* *Tea* *Low-fat milk* *Whole-fat milk* *Other sweetened soft drinks* *Glycaemic index* *Glycaemic load* *Orange or apple FJ* *Orange or apple (fruit)*		
NHS-II Nurses Health Study-II USA Chen et al. (2009b) Cohen et al. (2012) Forman et al. (2009) Chen et al. (2012) Muraki et al. (2013) Pan et al. (2013) Schulze et al. (2004) Public funding	N = 116,671 Female nurses Majority (~90%+) Caucasian	24–44 year Females	**Total fructose** **100% FJ** **SSSD, SSFD** *ASSD* *Total whole fruit* *Individual fruits* *Carbonated beverages* *Non-carbonated beverages* *Vitamin C* *Water* *Coffee* *Tea* *Low-fat milk* *Whole-fat milk*	Three self-administered SFFQ of 133 items – previous year Validation against two 7-day diet records Correlation coefficients for cola-type soft drinks (including diet) 0.84; other carbonated soft drinks 0.36; orange juice 0.84; and fruit punch 0.56.	Body weight GDM HTN T2DM
NIH-AARP National Institutes of Health-American Association for Retired Persons Diet and Health Study	N = 567,169 General population from 6 states ~ 93% White, 3% African-American, 2%	50–71 year 41.7% females	**Total sugars** **Added sugars** **Total sucrose** *Added sucrose* **Total fructose**	Self-administered SFFQ of 124 items – past year Validated with four 24-h dietary recall interviews (in subjects of the EATS study, a nationally representative sample of men and women aged 20–79 year).[48]	CVD

[48] Millen A, Midthune D, Thompson F, Kipnis V and Subar A, 2005. The National Cancer Institute Diet History Questionnaire: Validation of Pyramid Food Servings. American Journal of Epidemiology, 163, 279–288. https://doi.org/10.1093/aje/kwj031

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
USA Tasevska et al. (2014b) Public funding	Hispanic, 2% Asian/ Other		*Added free fructose*	Correlation coefficients (deattenuated and energy-adjusted) for added sugars: 0.79 for women and 0.68 for men.	
NSHDS Northern Sweden Health and Disease Study Sweden Winkvist et al. (2017) Mixed funding	N = 40,066 General population Caucasian	30–60 year 52.2% females	**Sucrose**	Two self-administered SFFQ of 64 items– previous year. Validated against 10x 24-h dietary recalls in a random subsample (n = 99) Vasterbotten county cardiovascular disease (CVD) study.[49] Correlation coefficients for sucrose de-attenuated: 0.65 for men and 0.37 for women.	BMI Blood lipids
PHHP Pawtucket Heart Health Program USA Parker et al. (1997) Public funding	N = 1,081 General population 94% Caucasian	18–64 year 62.2% females	**Sucrose** *Total fat* *Animal fat* *Vegetable fat* *Protein* *Carbohydrate* *Cholesterol* *Caffeine* *Saccharin* *Individual food items*	One self-administered SFFQ – previous year. Validated against one FFQ and 4x 7-day diet records (covering 1 year) for women (subsample of NHS) and for men against one FFQ and 2 one-week diet records (subsample of HPFS). Correlation coefficient for sucrose for women of 0.37 and for men for carbohydrates (deattenuated) 0.65 and 0.73.	Body weight
PHI Planet Health Intervention USA Ludwig et al. (2001) Public funding	N = 780 Children from four communities in the Boston metropolitan area	11–12 year 48% females	**SSSD, SSFD**	Self-administered (under supervision of trained personnel) SFFQ of 131 items – past year Validation in a similar cohort of 261 children and adolescents (9 to 18y) that completed three 24-h recalls and two FFQ (1 year apart). Correlation coefficients for carbohydrates:	Obesity

[49] Johansson I, Hallmans G, Wikman A, Biessy C, Riboli E and Kaaks R, 2002. Validation and calibration of food-frequency questionnaire measurements in the Northern Sweden Health and Disease cohort. Public Health Nutrition, 5, 487–496.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
	64% white, 15% Hispanic, 14% Afro-American, 8% Asian, 8% American Indian or other			– Mean 24-h recalls vs. mean FFQ: unadjusted 0.37; adjusted 0.40; de-attenuated 0.46 – Mean 24-h recalls vs. 2nd FFQ: unadjusted 0.38; adjusted 0.41; de-attenuated 0.47.[50]	
Project Viva USA Sonneville et al. (2015) Mixed funding	N = 2,128 Infants from eight urban and suburban obstetric offices in Massachusetts 70.3% Caucasian, 11.7% Black, 3.7% Hispanic, 3.1% Asian and 11.2% other	1 year 49.8% females	**100% FJ** *Water*	Two SFFQ of 103 items administered by the parents or guardian – past month. Validated against three 24-h dietary recalls (2x weekdays and 1x weekend).[51] Correlation coefficient of 0.52 for carbohydrates.	BMIz-score
QUALITY Quebec Adipose and Lifestyle InvesTigation in Youth USA Wang et al. (2014) Public funding	N = 630 General population from Quebec with at least one biological parent that had obesity and/or abdominal obesity Caucasian	8–10 year 44.5% females	**Added sugars**	Three 24-h dietary recalls on non-consecutive days of the week, including one weekend day. Completed by registered dietician. No information on validation.	Body weight BMI WC Body fat Glucose homeostasis (FG, FI, HOMA-IR, Matsuda-ISI)
REGARDS Reasons for Geographic and Racial Differences in Stroke study USA	N = 30,183 General population Caucasian 68.9%, African-America 31.1%	≥ 45 year 40.7% females	**SSSD, SSFD** **SSSD, SSFD, 100% FJ** **100% FJ**	Self-administered SFFQ of 98 items – past year Validation with three 4-day diet records (sample of 260 females from Women's Health Trial) Correlation coefficient of 0.51 for carbohydrates.	CHD

[50] Rockett H, Breitenbach M and Frazier A, 1997. Validation of a Youth/Adolescent Food Frequency Questionnaire. Preventive Medicine 26, 808–816.
[51] Blum R, Wei E and Rockett H, 1993. Validation of a food frequency questionnaire in native American and Caucasian children 1 to 5 years of age. Journal of Maternal Child Health, 3, 167–172.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Collin et al. (2019)‡ Public funding					
SCES Sidney Childhood Eye Study Australia Gopinath et al. (2013) Gopinath et al. (2012) Mixed funding	N = 2,353 Schoolchildren from Sydney 61.1% Caucasian, 19.5% East Asian, 4% Middle Eastern, 15.4% Other	12 year 49.2% females	**Total sugars** **Added sugars** **Fructose** *Glycaemic index* *Glycaemic load* *Carbohydrates* *Fibre* *Fruits*	One self-administered SFFQ of 120 items – previous year. Validated against four 24-h food records in children aged 9–16y.[52] The de-attenuated, energy-adjusted Pearson correlation coefficient for total sugars was 0.41.	BMI WC Body fat Blood pressure
SCHS Singapore Chinese Health Study Singapore Rebello et al. (2014) Public funding	N = 63,257 General population of Chinese adults living in Singapore Asian	45–74 year 56% females	**Total sugars** *Carbohydrates* *Starch* Dietary fibre *Vegetables* *Fruits* Rice Noodles	Interview administered SFFQ of 165 items– past year. with serving sizes reported as number based or coloured photographs representing the 15th, 50th and 85th percentiles of the portion size. Validated with 24-h dietary recall interviews (sub-group of n = 1022) Correlation coefficients for carbohydrate intake for Cantonese 0.37 and 0.32 (men and women, respectively) and for Hokkien 0.58 and 0.56 (men and women, respectively).	CHD
Seven Countries The Netherlands, Finland Feskens et al. (1995) Public funding	N = 2,589 General population Caucasian	50–70 year Males	**Total sugars**	Cross-check dietary history method at baseline and end of follow-up and at 10-year follow-up habitual food consumption pattern and checklist of foods. No validation for the method used in the study.	Dynamic glucose homeostasis (OGTT)

[52] Watson JF, Collins CE, Sibbritt DW, Dibley MJ and Garg ML, 2009. Reproducibility and comparative validity of a food frequency questionnaire for Australian children and adolescents. International Journal of Behaviour Nutrition Physcian Action, 6, 62.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
SUN Seguimiento Universidad de Navarra Spain Barrio-Lopez et al. (2013) Donazar-Ezcurra et al. (2018) Sayon-Orea et al. (2015) Fresan et al. (2017) Public funding	N = 21,678 University graduates, mainly health professionals Caucasian	> 18 year 69% females	**SSSD** **SSSD, SSFD** **100% FJ** **TFJ** SSFD SSFD, SSFJ, 100%	Self-reported SFFQ of 136 items – previous year. Four 4-day diet (n = 147)[53] Pearson correlation coefficient for carbohydrates: – Q1 vs. mean 4-day records: unadjusted 0.40; adjusted (for total caloric intake) 0.36; de-attenuated 0.40. – Q2 vs. mean 4-day records: unadjusted 0.44; adjusted (for total caloric intake) 0.42; de-attenuated 0.46.	GDM HTN Body weight T2DM
Takayama Japan Nagata et al. (2019)‡ Public funding	N = 34,018 General population Asian	≥ 35 year 54.1% females	**Total sugars** **Total fructose** *Added sugars* *Glucose*	One self-administered SFFQ of 169 items – previous year. Validated in subsamples in this population by comparing twelve 1-day diet records kept over a 1-year period.[54] Spearman's correlation coefficients between the questionnaire and twelve 1-day diet records kept over a 1-year period for intakes of total sugars, glucose, fructose, sucrose, maltose and lactose were 0·28, 0·46, 0·51, 0·48, 0·35 and 0·85, respectively, in men (n 17) and 0·68, 0·80, 0·46, 0·56 and 0·71, respectively, in women (n 20).	CVD
TLGS Teheran Lipid and Glucose Study	N = 15,005 General population	≥ 3 year 56.7% females	**Total fructose** **SSSD, SSFD, TFJ** **SSSD, SSFD, SSFJ**	Three interview-administered SFFQ of 168 items – previous year Validation against twelve 24-h recall (n = 132).[55]	Abdominal obesity WC

[53] Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S and Willett WC, 1993. Development and validation of a food frequency questionnaire in Spain. International Journal of Epidemiology, 22.
[54] Shimizu H, Ohwaki A and Kurisu Y, 1999. Validity and reproducibility of a quantitative food frequency questionnaire for a cohort study in Japan. Japan Journal of Clinical Oncology, 29, 38–44.
[55] Asghari G, Rezazadeh A, Hosseini-Esfahani F, Mehrabi Y, Mirmiran P and Azizi F, 2012. Reliability, comparative validity and stability of dietary patterns derived from an FFQ in the Tehran Lipid and Glucose Study. British Journal of Nutrition, 108, 1109–1117.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Iran Bahadoran et al. (2017) Mirmiran et al. (2015) Public funding	Caucasian		*Added fructose* *Natural fructose*	Spearman correlation coefficient for carbonated drinks: – SFFQ2 vs. 24-h recall: 0.43 (crude), 0.40 (energy adjusted) – SFFQ2 vs. SFFQ3: 0.50 (crude), 0.23 (energy adjusted) Spearman correlation coefficient for sugars, sweets and desserts: – SFFQ2 vs. 24-h recall: 0.52 (crude), 0.37 (energy adjusted) – SFFQ2 vs. SFFQ3: 0.40 (crude), 0.34 (energy adjusted)	Glucose homeostasis (FI, HOMA-IR) Blood lipids Blood pressure HTN T2DM CVD
Toyama Japan Sakurai et al. (2014) Public funding	N = 2,275 Male employees of a factory Asian	35–55 year Males	**SSSD** *ASSD*	Self-administered diet history questionnaire including SFFQ of 110 items– previous month Validation against 3-day diet record (n = 47 women from a similar cohort)[56] Pearson correlation coefficient for carbohydrates: 0.48 (crude); 0.46 (energy adjusted); 0.48 (energy adjusted and de-attenuated).	T2DM
WAPCS Western Australia Pregnancy Cohort (Raine) Study Australia	N = 2,868 Offspring from mothers from the Raine study	14 year 48.2% females	**SSSD, SSFD and SSFJ**	SFFQ of previous year completed in every follow-up by primary caregiver – 212 food items (individual foods, mixed dishes and beverages).[57]	BMI WC Blood lipids Blood pressure

[56] Sasaki S, Yanagibori R and Amano K, 1998. Self-administered diet history questionnaire developed for health education: a relative validation of the Test-Version by comparison with 3-day diet record in women. Journal of Epidemiology, 8, 203–215.

[57] Ambrosini GL, de Klerk NH and O'Sullivan TA, 2009. The reliability of a food frequency questionnaire for use among adolescents.Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP and Agurs-Collins T, 1999. Measurement characteristics of the Women's Health Initiative Food Frequency Questionnaire. Annals of Epidemiology, 9, 178–187. Ambrosini GL, Oddy WH and Robinson M, 2009. Adolescent dietary patterns are associated with lifestyle and family psycho-social factors.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Ambrosini et al. (2013) Unclear funding	Caucasian			Serving sizes measured in household units (cups, spoons, slices, etc.) Validation against 3-day food record. Pearson's correlation coefficient of total sugars: 0.29 ($p < 0.001$)[58]	Glucose homeostasis (FI, FG and HOMA-IR)
WHI Women's Health Initiative USA Auerbach et al. (2017) Auerbach et al. (2018) Huang et al. (2017) Tasevska et al. (2018) Public funding	N = 122,970 Postmenopausal women enrolled into the WHI Observational Study (n = 93,676) and the comparison arm of the Dietary Modification Clinical Trial (n = 29,294) ~ 84% Caucasian, 7.6% Black, Hispanic/ Latino 4% and 3% Asian/Pacific	50–79 year Females	**Total sugars** **100% FJ** **SSSD** **SSFD** **SSSD, SSFD and TFJ** *ASB* *Whole fruit*	SFFQ of 122 items – previous 3 months Validated with: four 24-h dietary recalls conducted by trained staff; and four self-completed food records (n = 113 in 1995). Correlation coefficients for carbohydrates was 0.41 (unadjusted), 0.63 (energy-adjusted), 0.67 (de-attenuated)[59]	T2DM CVD CHD Stroke Heart failure CABG PCI HTN Body weight
WHS Women's Health Study USA Janket et al. (2003) Public funding	N = 39,876 Women (health professionals) whom participated in a RCT on low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer	≥ 45 year Females	**Total sugars** **Sucrose** **Free fructose** **Free glucose** **SSSD** *Lactose* *Starch* *Jam and marmalade* *Maltose* *SS berry juice*	SFFQ of 131 items – previous year The SFFQ used was the same as for HPFS and NHS, validation described previously. Also validated against a diet record in a similar group of women. Correlation coefficient for energy-adjusted carbohydrates ranged from 0.59 to 0.73.	T2DM

[58] Ambrosini GL, de Klerk NH and O'Sullivan TA, 2009. The reliability of a food frequency questionnaire for use among adolescents.
[59] Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP and Agurs-Collins T, 1999. Measurement characteristics of the women's health initiative food frequency questionnaire. Annals of Epidemiology, 9, 178–187.

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
	94.8 White, 2.3% African American, 1.1% Hispanic, 1.4% Asian/Pacific Islander, 0.3% American Indian/Alaskan Native, and 0.1% more than one race.				
Dental caries					
Finnish Cohort Finland Bernabé et al. (2016) Public funding	N = 6,335 General population Caucasian	30–89 year 56% females	**Total sugars**	SFFQ of 128 food items and mixed dishes – previous year. SFFQ only administered at baseline. Standard portion size assigned to each FFQ item and specified with natural units. The overall frequency of sugars intake (times/day) was estimated by adding the weighted responses for 15 sugary food items The amount of sugars intake (g/day) was estimated by multiplying the food consumption frequency by fixed portion sizes. Validated against a 3-day food record (n = 294; 137 men and 157 women).[60]	DMFT
IFS Iowa Fluoride Study Chankanka et al. (2011) USA	N = 608 General population 94% Caucasian, 6% Other	5–9 year 55% females	**Total sugars** **SSSD** **100% FJ** *Milk* *Powder-sugared beverages*	3-day food diaries (2 weekdays, 1 weekend day) were obtained every 1.5 to 6 months during the study period. Intakes were averaged for each child to reflect sugar intakes from 5 to 8 years of age.[61]	Caries increment

[60] Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J and Pietinen P, 2006. Validity of a food frequency questionnaire varied by age and body mass index. Journal of Clinical Epidemiology, 59, 994–1001.

[61] Marshall TA, Broffitt B, Eichenberger-Gilmore J, Warren JJ, Cunningham MA and Levy SM, 2005. The roles of meal, snack, and daily total food and beverage exposures on caries experience in young children. Journal of Public Health Dentrics, 65, 166–73. [PubMed: 16171262].

Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
Public funding			*ASSD* *Water* *Individual food items*		
Michigan cohort USA Burt et al. (1988) Burt and Szpunar (1994) Szpunar et al. (1995) Unclear funding	N = 747 General population from three towns with non-fluoridated water supply	10–15 year 47.9% females	**Total sugars**	Dietary interviews – 3 times two 24-h diet recalls administered for the previous day. Included weekdays and weekends and covered seasonal variations during the study period. Models provided to assess quantities Intake data from all the interviews for the same child over the 3-year follow-up were averaged.	DMFS DMFS (AP) DMFS (FS)
STRIP-1 Special Turku Coronary Risk Factor Intervention Project Finland Ruottinen et al. (2004) Unclear funding	N = 1,066 Children attending well-baby clinics of the city of Turku, where the fluoride concentration in drinking water is 0.3 ppm Caucasian	13 months 31% females	**Sucrose**	3-day food records (at 13 months) and 4-day food records (thereafter every 6 months until 7 years of age, every 2 years thereafter in the intervention group and every year in the control group until 10 years of age. Records included one weekend day and were reviewed by nutritionist at next visit.	$d_3$mft, $d_3$mft+D_3MFT D_3MFT scores
STRIP-2 Special Turku Coronary Risk Factor Intervention Project Finland Karjalainen et al. (2001) Karjalainen et al. (2015) Unclear funding	N = 1,066 Children attending well-baby clinics of the city of Turku, where the fluoride concentration in drinking water is 0.3 ppm Caucasian	3 year 45.8% females	**Sucrose**	4-day food records at 3, 6, 9, 12 and 16 years of age. Records included one weekend day and were reviewed by nutritionist at next visit.	D3MFT scores d3mft

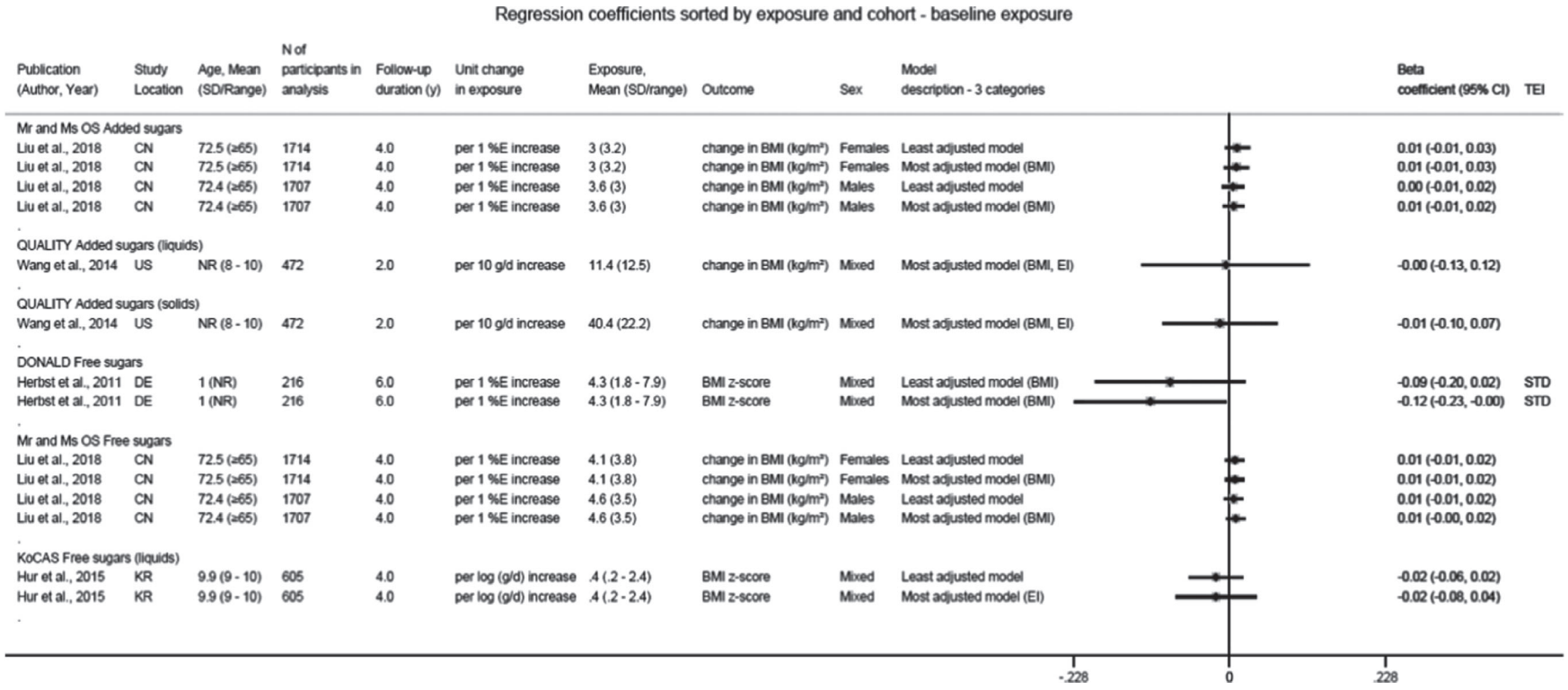
Cohort Country References Funding	Population (original cohort)	Age (years) Gender	Exposure(s) assessed	Exposure assessment, time coverage and validation	Endpoints
UK cohort United Kingdom Rugg-Gunn et al. (1984) Rugg-Gunn et al. (1987) Public funding	N = 466 Children in their final 2 years of middle school from the area of south Northumberland Caucasian	11.5 year (mean) 52.4% females	**Total sugars** *Individual food items* *Starch*	5 times 3-day food diaries (3 consecutive days) in the 2 years of the study (total of 15 days of dietary intake). All days of the week covered. Children were instructed to record all foods and beverages consumed, the amounts and the time of the day in which these were consumed. Interview the day of completion to check quantities and uncertainties. Food models and graduated cups used for quantification of the amount.	DMFS DMFT DFS DFS(FS) DFS (SS) DFS (AP)
VA-DLS Department of Veterans Affairs-Dental Longitudinal Study USA Kaye et al. (2015) Public funding	N = 687 U.S Veterans from greater Boston area	47–90 year Males	**Total sugars** **SSSD** *Starch* *DASH adherence score* *DASH vegetable score* *DASH total grain score* *DASH sweets score*	Repeated administration of an expanded self-administered 131-item SFFQ at each visit. Average dietary variables were computed from all SFFQs after the first root surface was exposed until edentulism or the end of the study for analyses of root caries increment. Validation against two 7-day diet records administered 6 months apart[62,63]. The SFFQ was administered twice to 127 men at one-year interval.	Root caries increment

ASBs, artificially sweetened beverages; ASSD, artificially sweetened soft drinks; BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; D3MFT, decayed into dentine, missing and filled permanent teeth; d3mft, decayed into dentine, missing and filled primary teeth; DFS: decayed, filled surfaces; DFS (AP), approximal surfaces; DFS (FS), pit and fissure surfaces; DFS (SS), free smooth surfaces; DMFS: decayed, missing and filled surfaces; DMFT: decayed, missing and filled permanent teeth; dmft: decayed, missing and filled primary teeth; FD, fruit drinks; FG, fasting glucose; FI, fasting insulin; FJ, fruit juice; GI, glycaemic index; GL, glycaemic load; GDM, gestational diabetes mellitus; HOMA, homeostatic model of assessment; HTN, hypertension; IR, insulin resistance; LCDS, Low-carbohydrates diet score; LCSB, low-calorie sweetened beverage; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acid; RCT, randomised control trial; SAT, subcutaneous adipose tissue; SFA, saturated fatty acid; SFFQ, semiquantitative food frequency questionnaire; SSBs, sugar-sweetened beverages, SSFDs, sugar-sweetened fruit drinks, SSFJs, sugar-sweetened fruit juices, SSSDs, sugar-sweetened soft drinks, T2DM, type 2 diabetes mellitus; TFJ, total fruit juice; VAT, visceral adipose tissue; WC, waist circumference; WC_{BMI}, waist circumference regressed on body mass index.
‡: Study identified through the update of the literature search.

[62] Rimm EB, Giovannucci EL and Stampfer MJ, 1992. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. American Journal of Epidemiology, 135, 1114–1126.
[63] Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993;93:790–796.

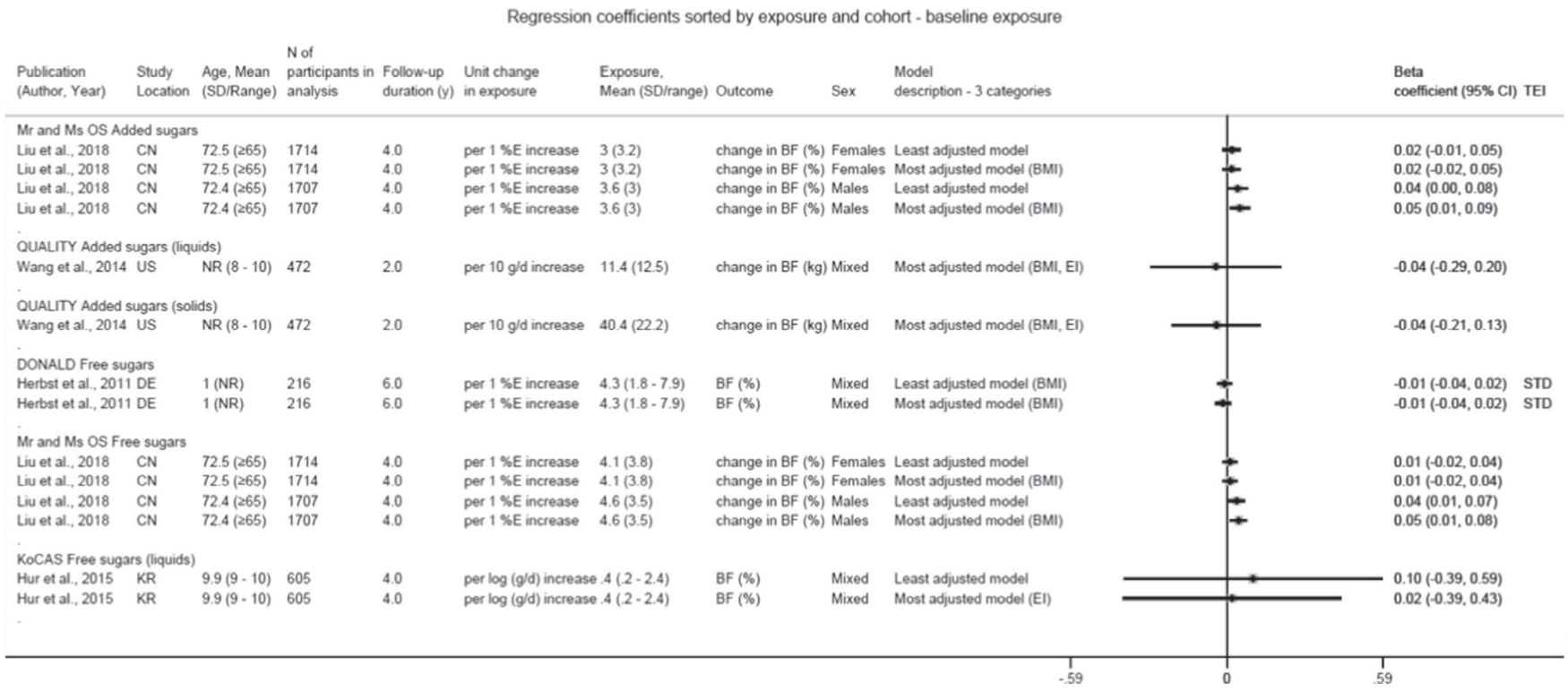
Appendix K – Forest plots. Observational studies on metabolic diseases

Figure K.1: Intake of added and free sugars and continuous variables related to the risk of obesity and abdominal obesity



Note: STD = Standardised for Total Energy Intake.
EPIC-Norfolk (Kuhnle et al., 2015) and PHHP (Parker et al., 1997) excluded.

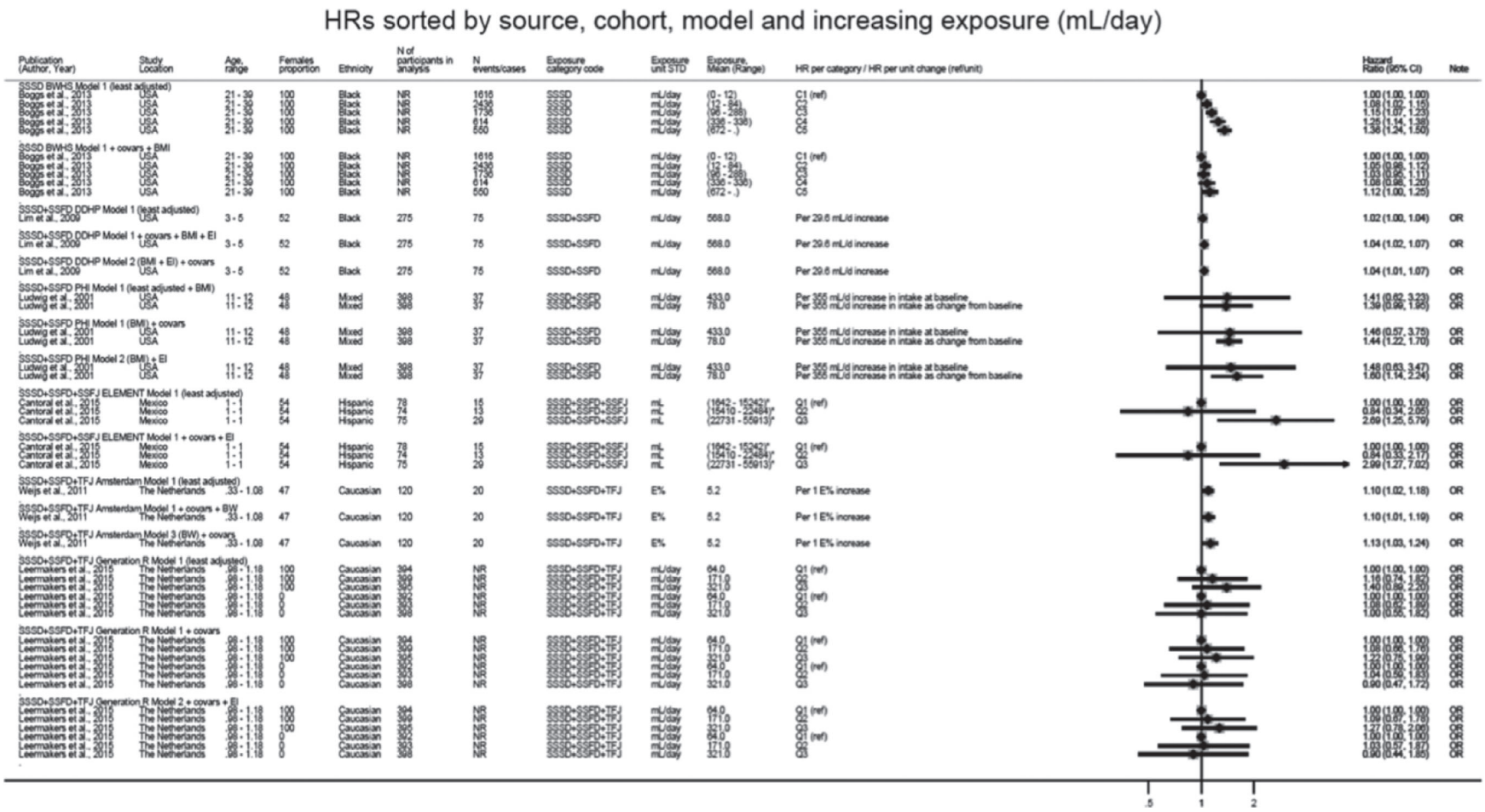
Figure K.1a: Intake of added and free sugars at baseline and measures of body mass index



Note: STD = Standardised for Total Energy Intake.

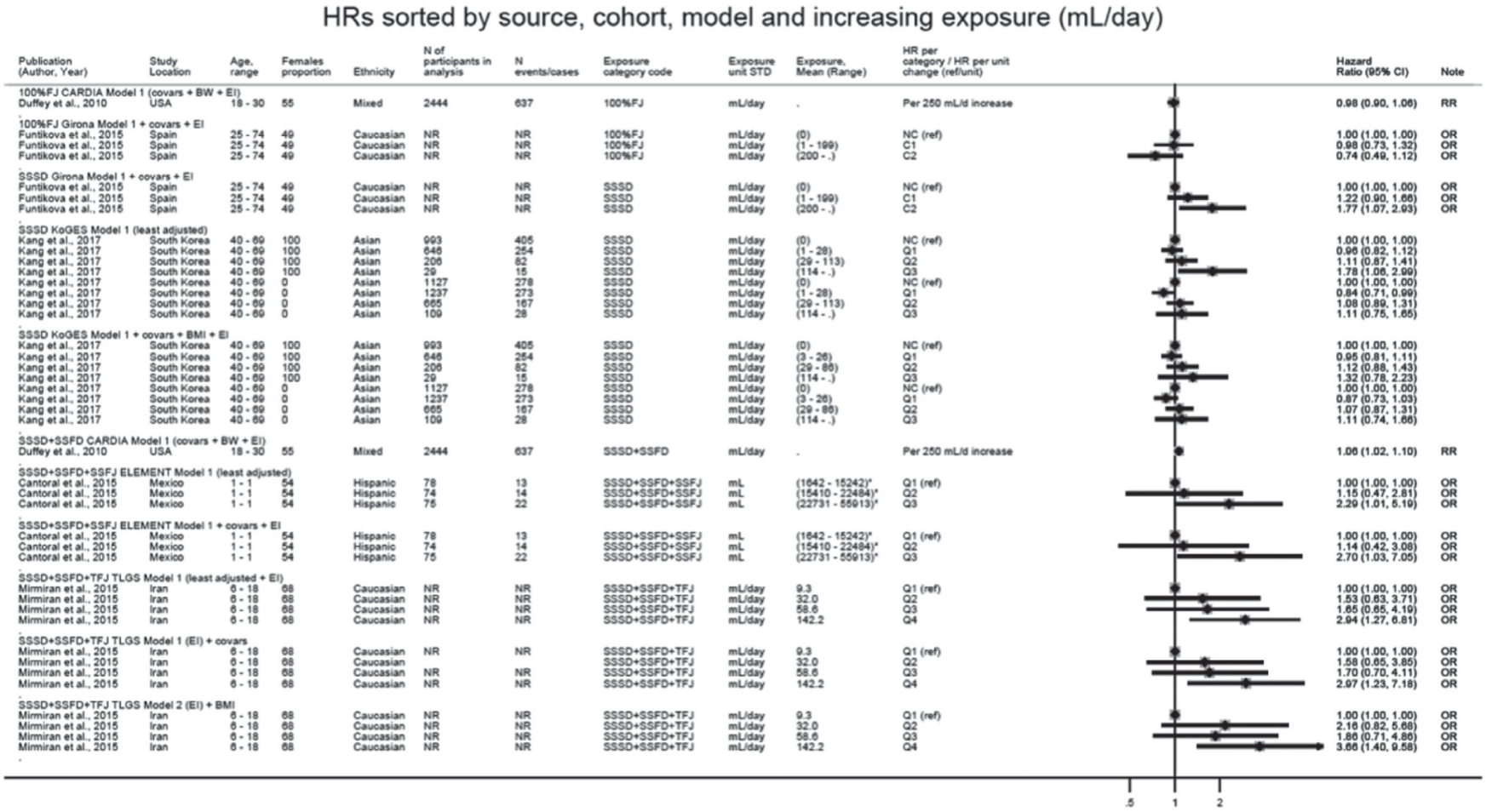
Figure K.1b: Intake of added and free sugars at baseline and measures of body fat

Figure K.2: Intake of SSBs and Fruit Juices and incidence of overweight/obesity and abdominal obesity



Note: * = cumulative exposure; RR = Rate Ratio; OR = Odds Ratio.

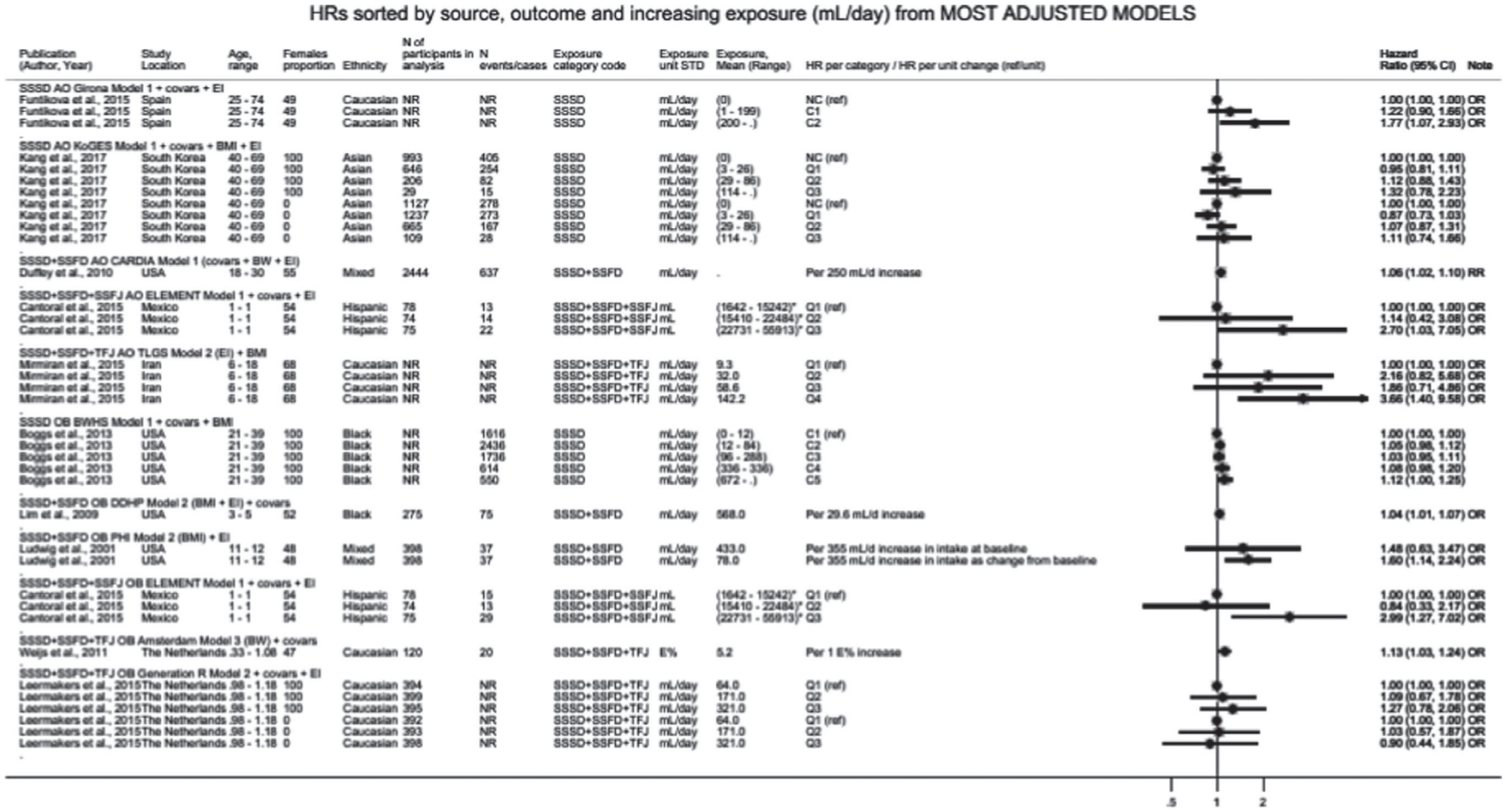
Figure K.2a: Intake of SSBs at baseline and incidence of overweight/obesity



Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethnicity	N of participants in analysis	N events/cases	Exposure category code	Exposure unit STD	Exposure, Mean (Range)	HR per category / HR per unit change (ref/unit)	Hazard Ratio (95% CI)	Note
100%FJ CARDIA Model 1 (covars + BW + EI)												
Duffey et al., 2010	USA	18 - 30	55	Mixed	2444	637	100%FJ	mL/day	.	Per 250 mL/d increase	0.98 (0.90, 1.06)	RR
100%FJ Girona Model 1 + covars + EI												
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	100%FJ	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	OR
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	100%FJ	mL/day	(1 - 199)	C1	0.98 (0.73, 1.32)	OR
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	100%FJ	mL/day	(200 - .)	C2	0.74 (0.49, 1.12)	OR
SSSD Girona Model 1 + covars + EI												
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	SSSD	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	OR
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	SSSD	mL/day	(1 - 199)	C1	1.22 (0.90, 1.66)	OR
Funtikova et al., 2015	Spain	25 - 74	49	Caucasian	NR	NR	SSSD	mL/day	(200 - .)	C2	1.77 (1.07, 2.93)	OR
SSSD KoGES Model 1 (least adjusted)												
Kang et al., 2017	South Korea	40 - 69	100	Asian	993	405	SSSD	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	646	254	SSSD	mL/day	(1 - 28)	Q1	0.96 (0.82, 1.12)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	206	82	SSSD	mL/day	(29 - 113)	Q2	1.11 (0.87, 1.41)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	29	15	SSSD	mL/day	(114 - .)	Q3	1.78 (1.06, 2.99)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	1127	278	SSSD	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	1237	273	SSSD	mL/day	(1 - 28)	Q1	0.84 (0.71, 0.99)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	665	167	SSSD	mL/day	(29 - 113)	Q2	1.08 (0.89, 1.31)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	109	28	SSSD	mL/day	(114 - .)	Q3	1.11 (0.75, 1.66)	
SSSD KoGES Model 1 + covars + BMI + EI												
Kang et al., 2017	South Korea	40 - 69	100	Asian	993	405	SSSD	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	646	254	SSSD	mL/day	(3 - 28)	Q1	0.95 (0.81, 1.11)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	206	82	SSSD	mL/day	(29 - 86)	Q2	1.12 (0.88, 1.43)	
Kang et al., 2017	South Korea	40 - 69	100	Asian	29	15	SSSD	mL/day	(114 - .)	Q3	1.32 (0.78, 2.23)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	1127	278	SSSD	mL/day	(0)	NC (ref)	1.00 (1.00, 1.00)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	1237	273	SSSD	mL/day	(3 - 26)	Q1	0.87 (0.73, 1.03)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	665	167	SSSD	mL/day	(29 - 86)	Q2	1.07 (0.87, 1.31)	
Kang et al., 2017	South Korea	40 - 69	0	Asian	109	28	SSSD	mL/day	(114 - .)	Q3	1.11 (0.74, 1.66)	
SSSD+SSFD CARDIA Model 1 (covars + BW + EI)												
Duffey et al., 2010	USA	18 - 30	55	Mixed	2444	637	SSSD+SSFD	mL/day	.	Per 250 mL/d increase	1.06 (1.02, 1.10)	RR
SSSD+SSFD+SSFJ ELEMENT Model 1 (least adjusted)												
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	78	13	SSSD+SSFD+SSFJ	mL	(1642 - 15242)*	Q1 (ref)	1.00 (1.00, 1.00)	OR
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	74	14	SSSD+SSFD+SSFJ	mL	(15410 - 22484)*	Q2	1.15 (0.47, 2.81)	OR
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	75	22	SSSD+SSFD+SSFJ	mL	(22731 - 55913)*	Q3	2.29 (1.01, 5.19)	OR
SSSD+SSFD+SSFJ ELEMENT Model 1 + covars + EI												
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	78	13	SSSD+SSFD+SSFJ	mL	(1642 - 15242)*	Q1 (ref)	1.00 (1.00, 1.00)	OR
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	74	14	SSSD+SSFD+SSFJ	mL	(15410 - 22484)*	Q2	1.14 (0.42, 3.08)	OR
Cantoral et al., 2015	Mexico	1 - 1	54	Hispanic	75	22	SSSD+SSFD+SSFJ	mL	(22731 - 55913)*	Q3	2.70 (1.03, 7.05)	OR
SSSD+SSFD+TFJ TLGS Model 1 (least adjusted + EI)												
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	9.3	Q1 (ref)	1.00 (1.00, 1.00)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	32.0	Q2	1.53 (0.63, 3.71)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	58.6	Q3	1.65 (0.65, 4.19)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	142.2	Q4	2.94 (1.27, 6.81)	OR
SSSD+SSFD+TFJ TLGS Model 1 (EI) + covars												
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	9.3	Q1 (ref)	1.00 (1.00, 1.00)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian			SSSD+SSFD+TFJ	mL/day	32.0	Q2	1.58 (0.65, 3.85)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	58.6	Q3	1.70 (0.70, 4.11)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	142.2	Q4	2.97 (1.23, 7.18)	OR
SSSD+SSFD+TFJ TLGS Model 2 (EI) + BMI												
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	9.3	Q1 (ref)	1.00 (1.00, 1.00)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	32.0	Q2	2.16 (0.82, 5.68)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	58.6	Q3	1.86 (0.71, 4.86)	OR
Mirmiran et al., 2015	Iran	6 - 18	68	Caucasian	NR	NR	SSSD+SSFD+TFJ	mL/day	142.2	Q4	3.66 (1.40, 9.58)	OR

Note: in Funtikova et al. (2015) total N analysed = 1479, total N of events = 336; in Duffey et al. (2010) exposure = average across years 0 and 7; NC (ref) = non-consumers; * = cumulative exposure; RR = Rate Ratio; OR = Odds Ratio.

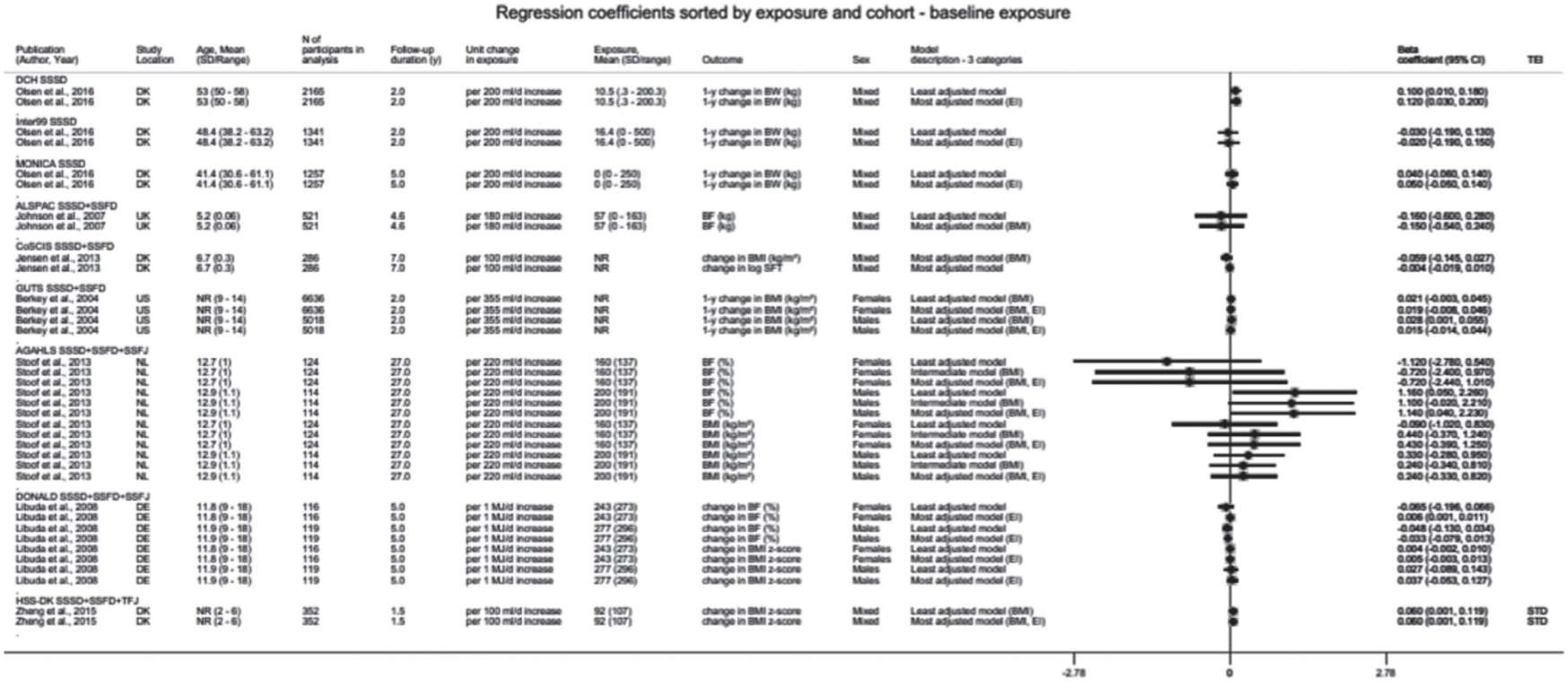
Figure K.2b: Intake of SSBs at baseline and Fruit juices and incidence of abdominal obesity



Note: * = cumulative exposure; NC (ref) = non-consumers; RR = Rate Ratio; OR = Odds Ratio

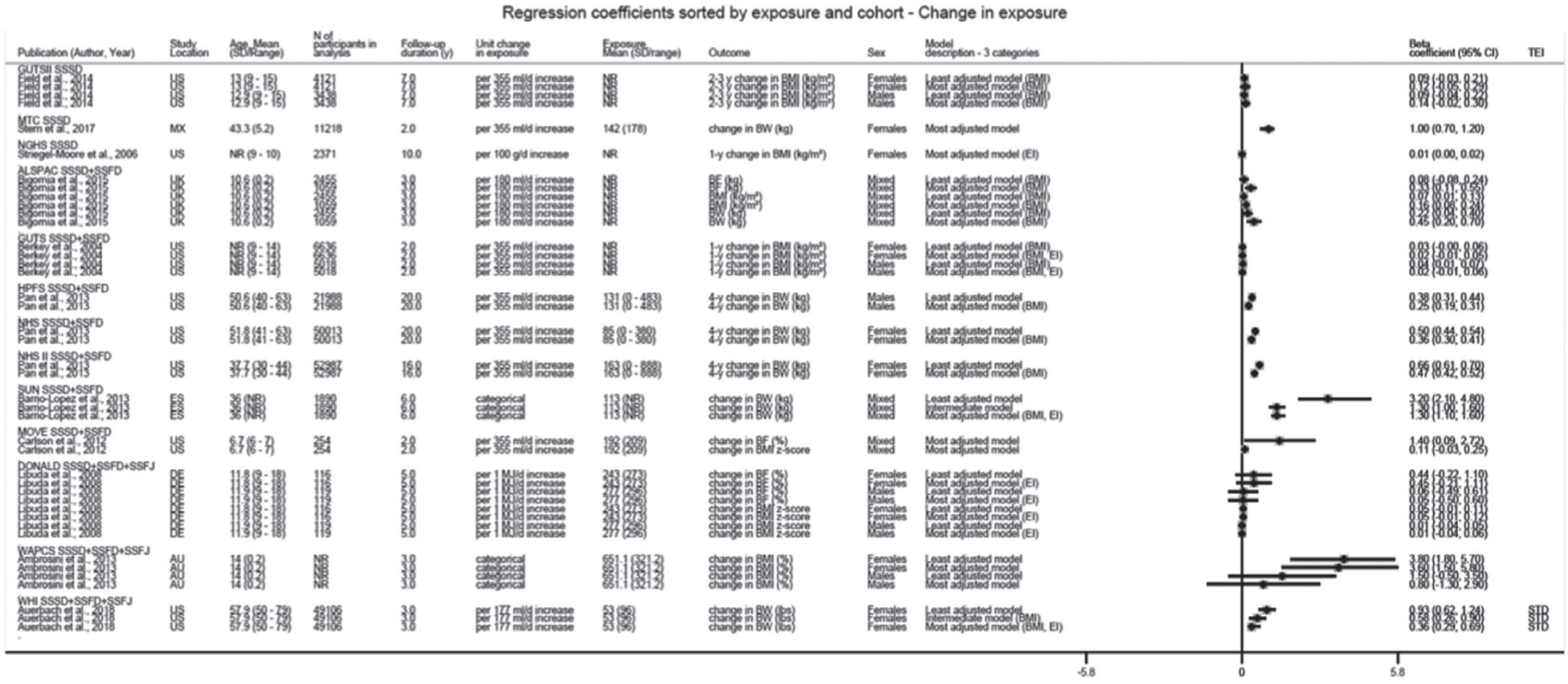
Figure K.3: Intake of SSBs at baseline and incidence of overweight/obesity and abdominal obesity

Figure K.4: Intake of SSBs and continuous variables related to the risk of obesity and abdominal obesity



Note: STD = Standardised for Total Energy Intake.
MIT-GDS (Phillips et al., 2014) and Framingham-3Gen (Ma et al., 2016) excluded.

Figure K.4a: Intake of SSBs at baseline and measures of body weight, body mass index and body fat



Note: STD = Standardised for Total Energy Intake; Ambrosini et al. (2013) and Barrio-Lopez et al. (2013) = only coefficients from highest categories (categorical analysis).

Figure K.4b: Change in intake of SSBs and measures of body weight, body mass index, and body fat

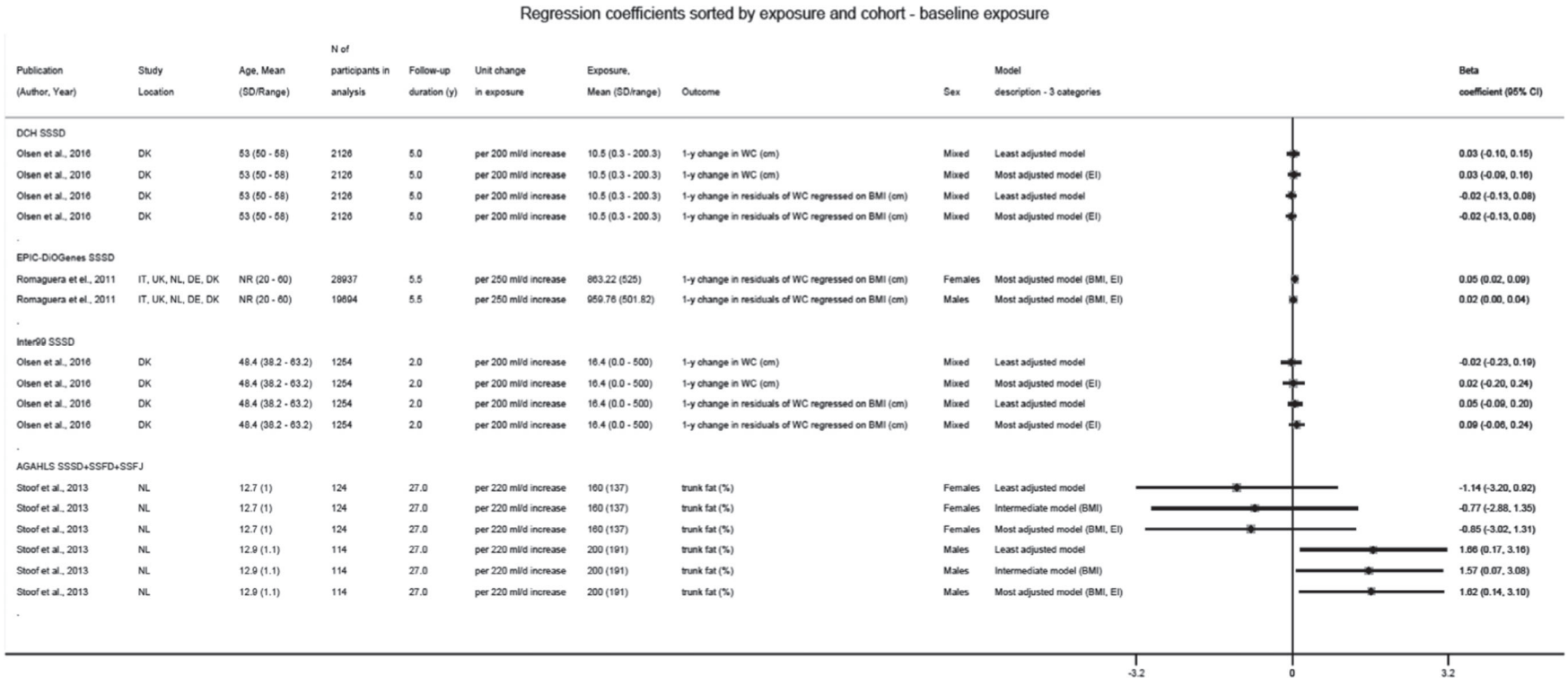


Figure K.4c: Intake of SSBs at baseline and measures of waist circumference and abdominal fat

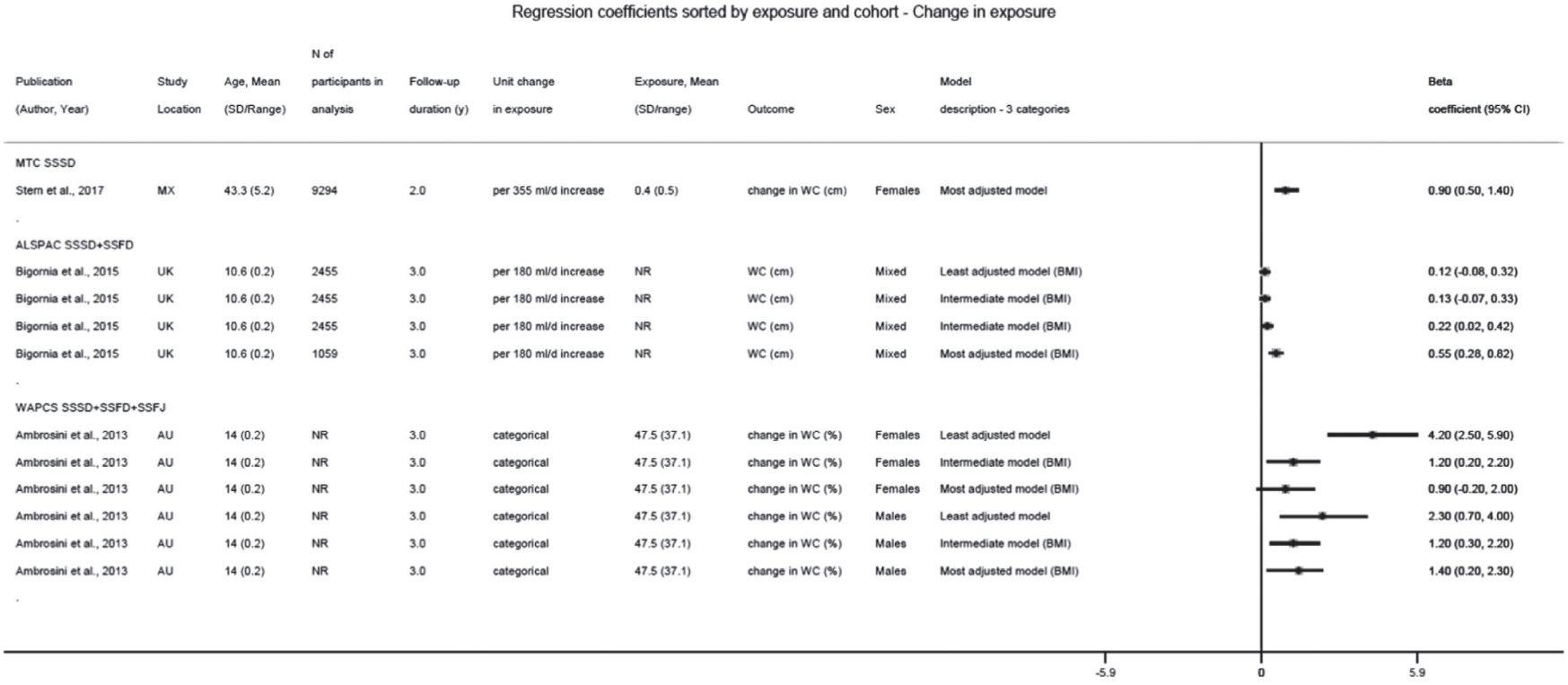
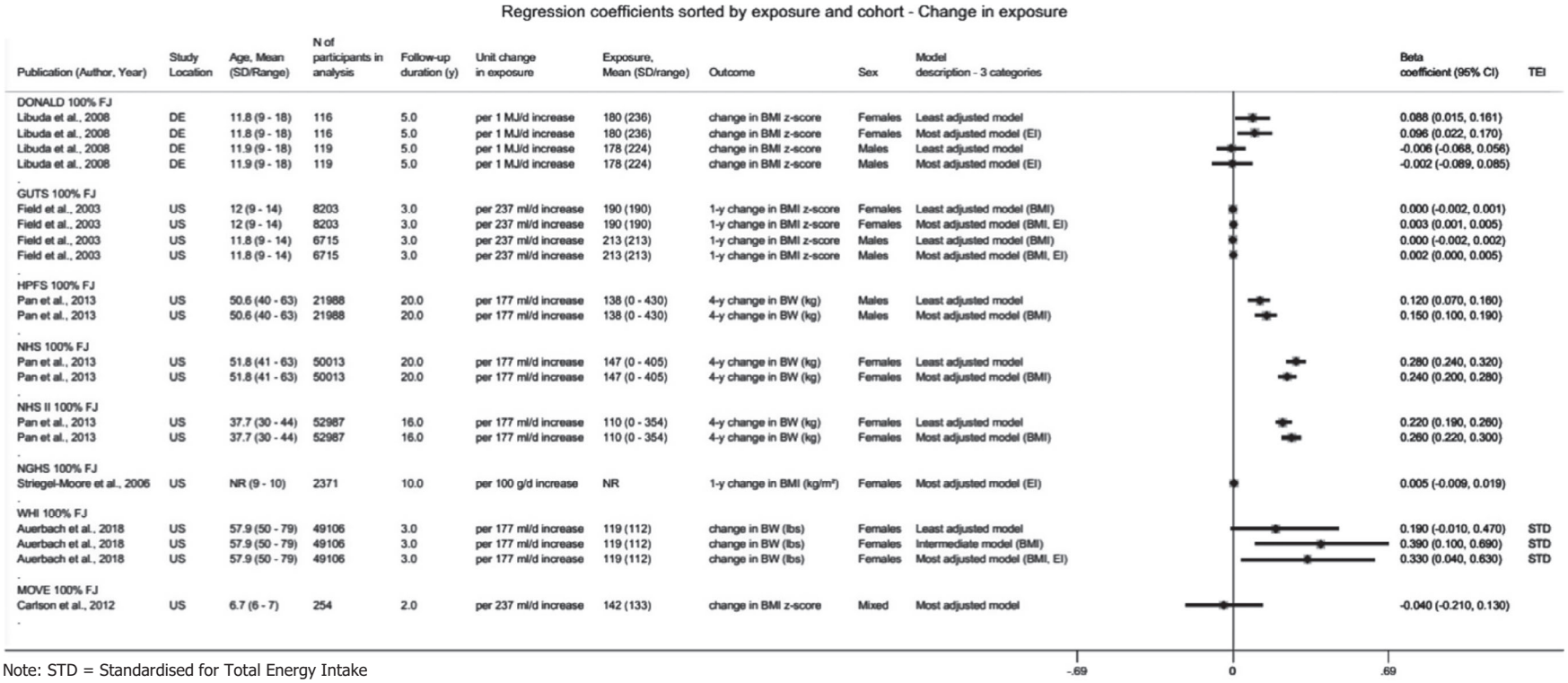


Figure K.4d: Change in intake of SSBs and measures of waist circumference and abdominal fat



Note: STD = Standardised for Total Energy Intake

Figure K.5: Change in intake of Fruit juices and measures of body weight and body mass index

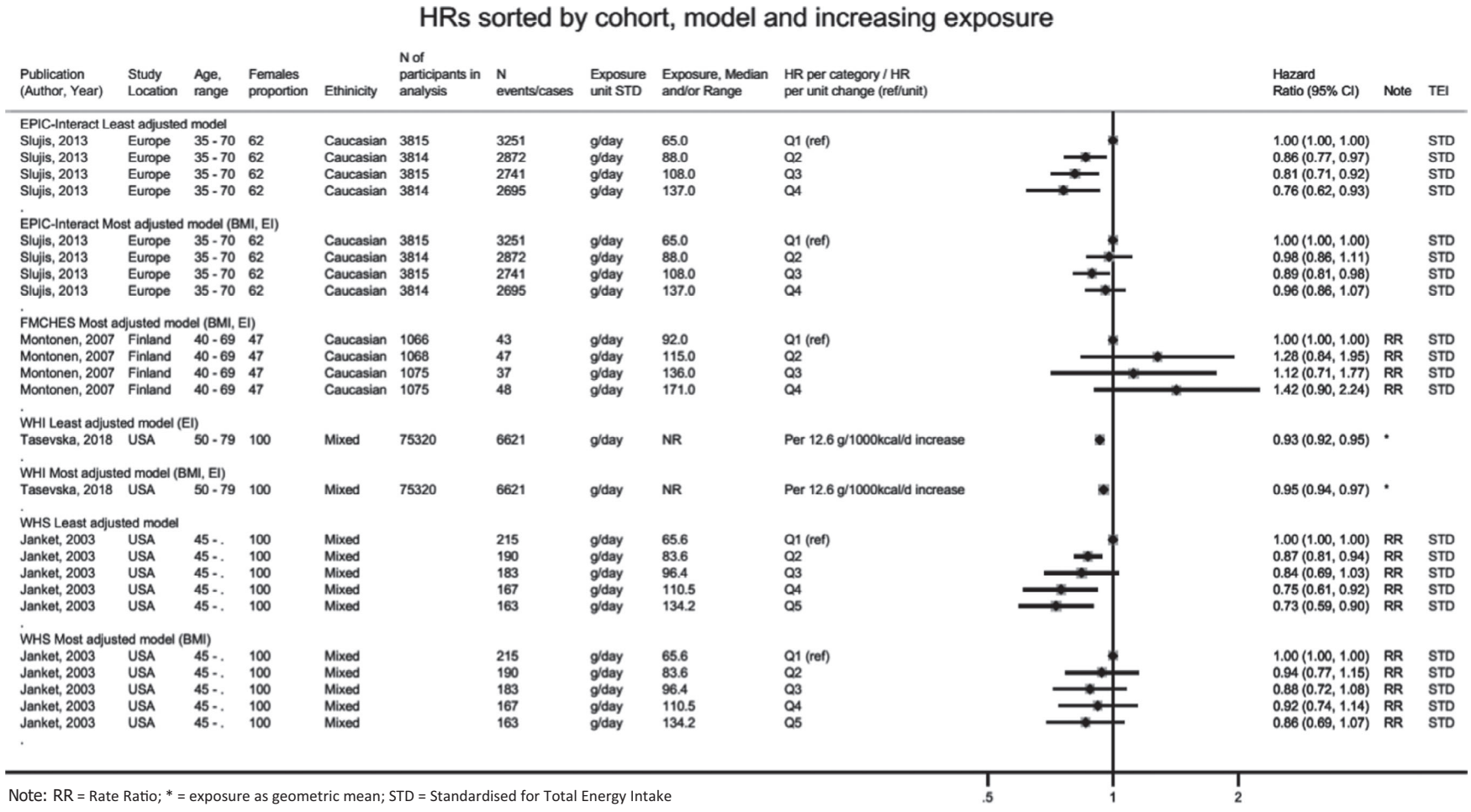


Figure K.6: Intake of total sugars and incidence of type 2 diabetes mellitus

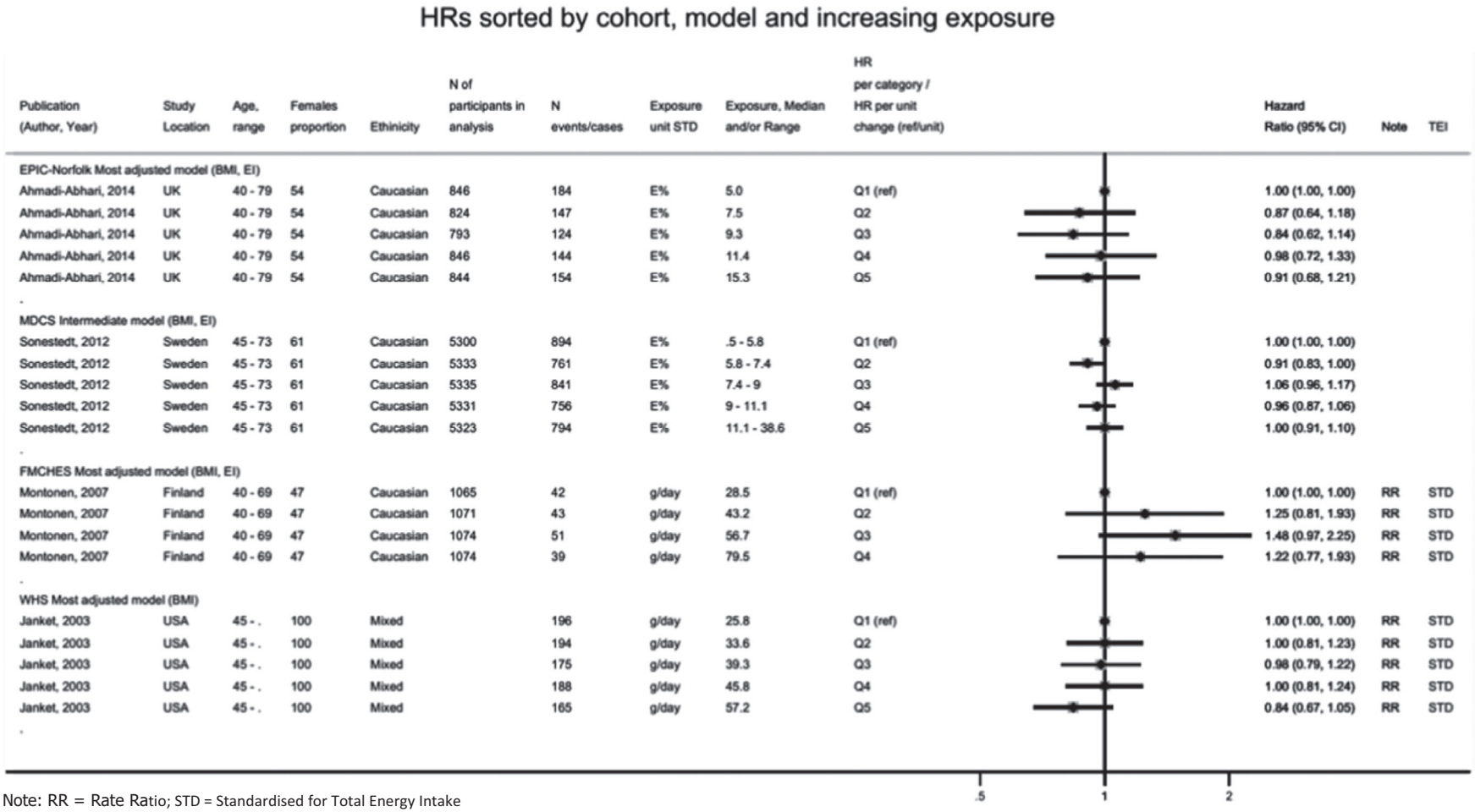
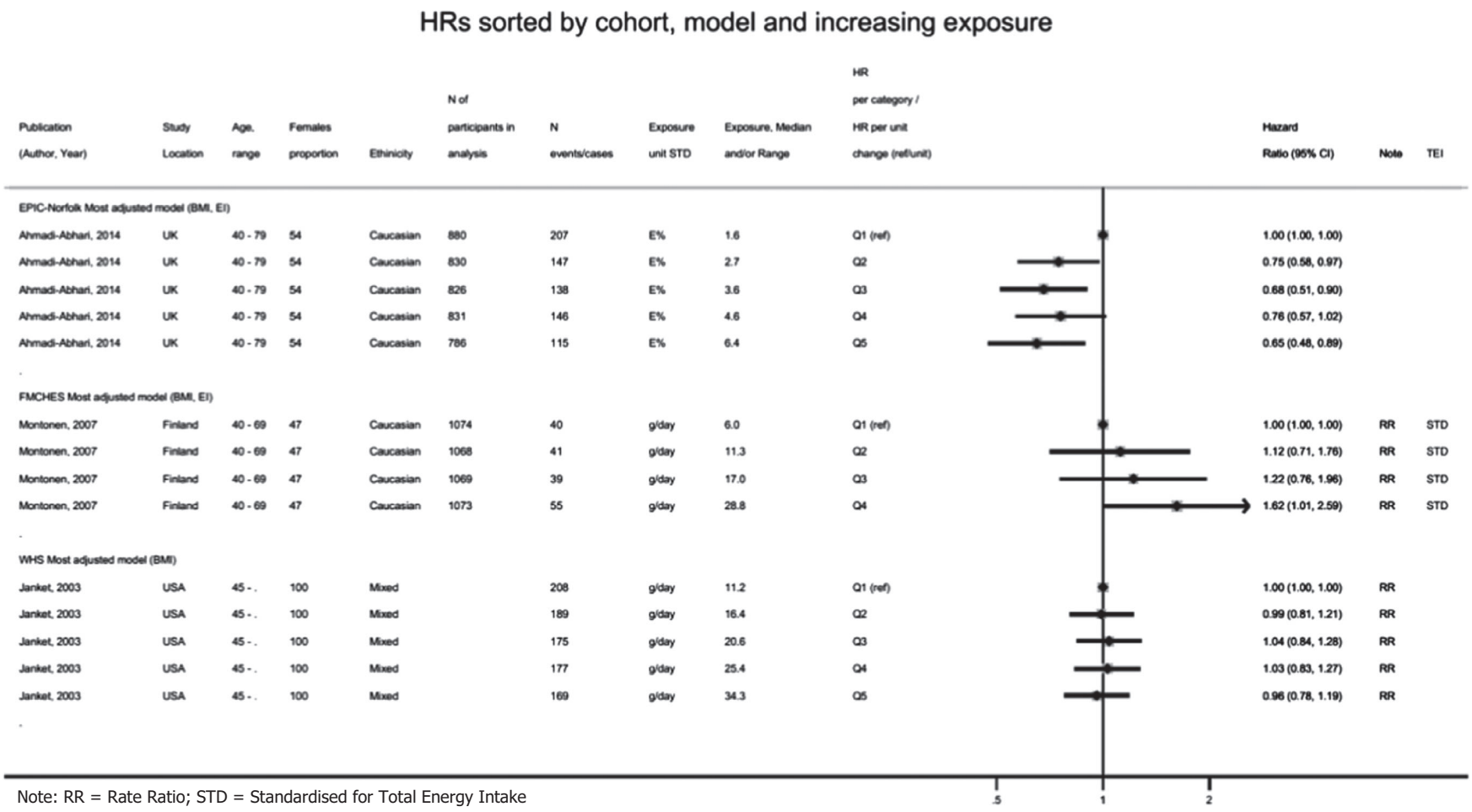
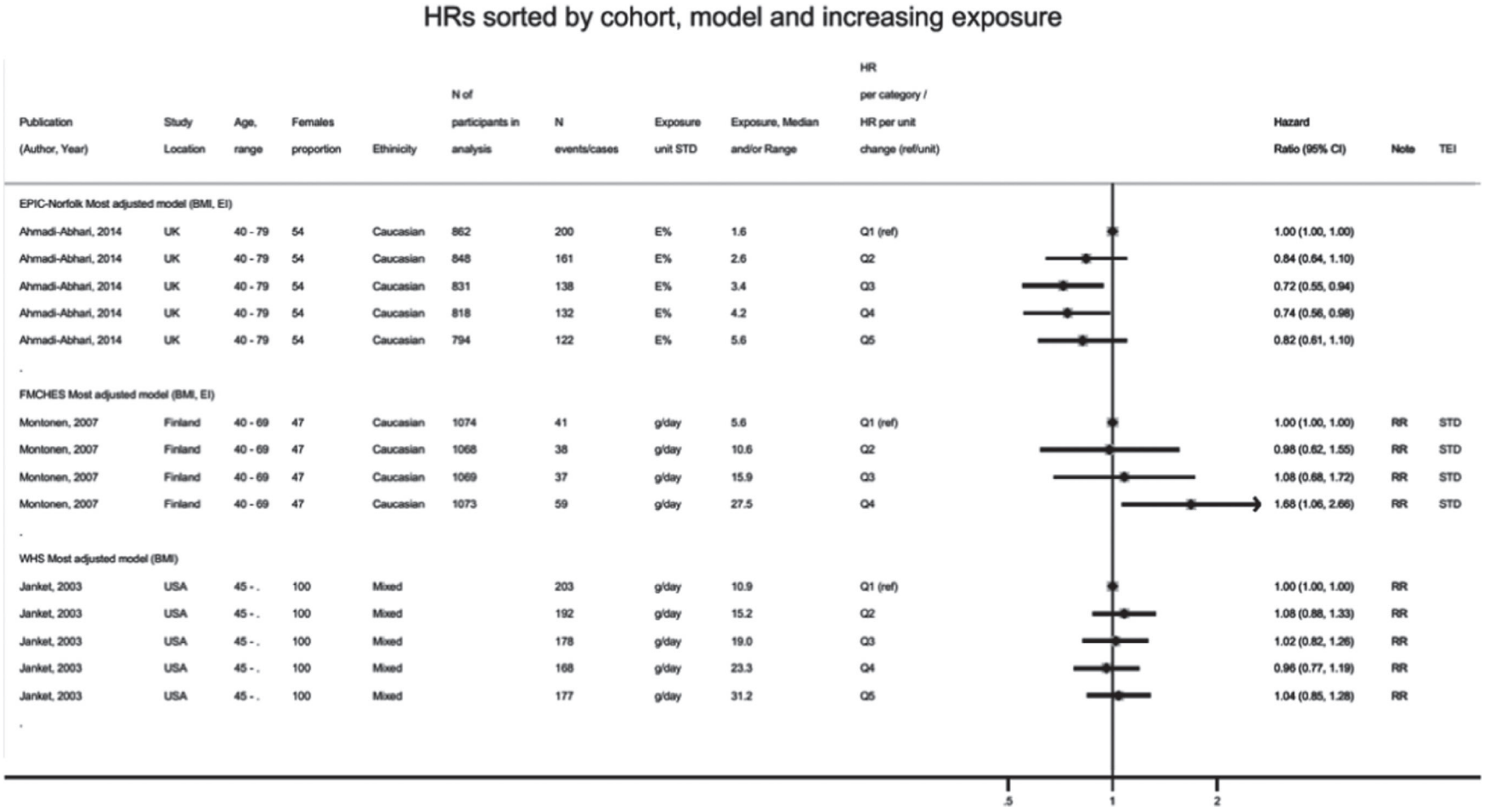


Figure K.7: Intake of sucrose and incidence of type 2 diabetes mellitus



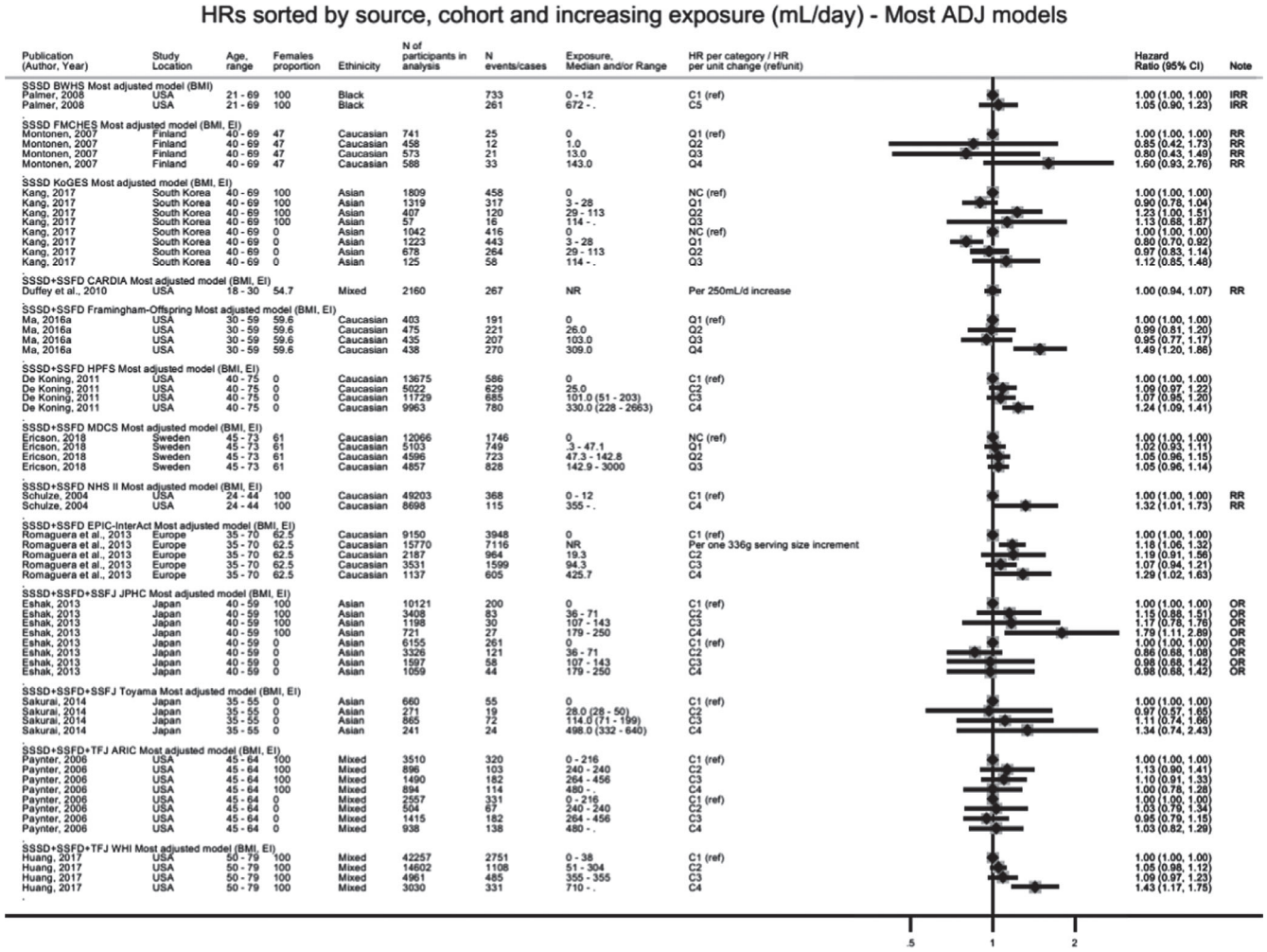
Note: RR = Rate Ratio; STD = Standardised for Total Energy Intake

Figure K.8: Free fructose and incidence of type 2 diabetes mellitus



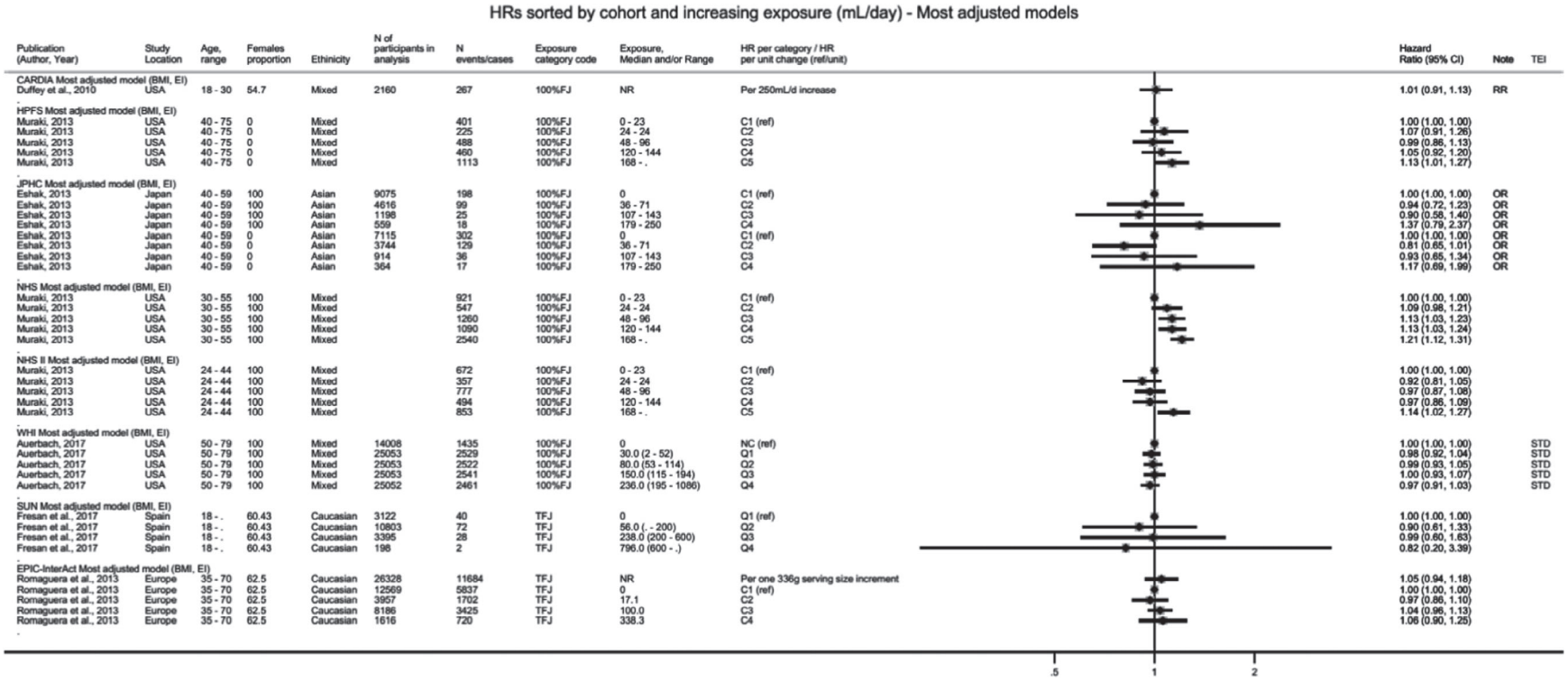
Note: RR = Rate Ratio; STD = Standardised for Total Energy Intake

Figure K.9: Free glucose intake and incidence of type 2 diabetes mellitus



Note: NC (ref) = non-consumers; RR = Rate Ratio; IRR = Incidence Rate Ratio; OR = Odds Ratio; ARIC cohort = results plotted are from a model that did not include BMI and EI as covariates, however, the authors stated adjustment for these covariates did not materially change the HRs (datawas not shown); in Framingham-Offspring cohort (Ma et al., 2016a) exposure = cumulative average intake (mean intake reported at examinations up to and including the examination of prediabetes diagnosis)

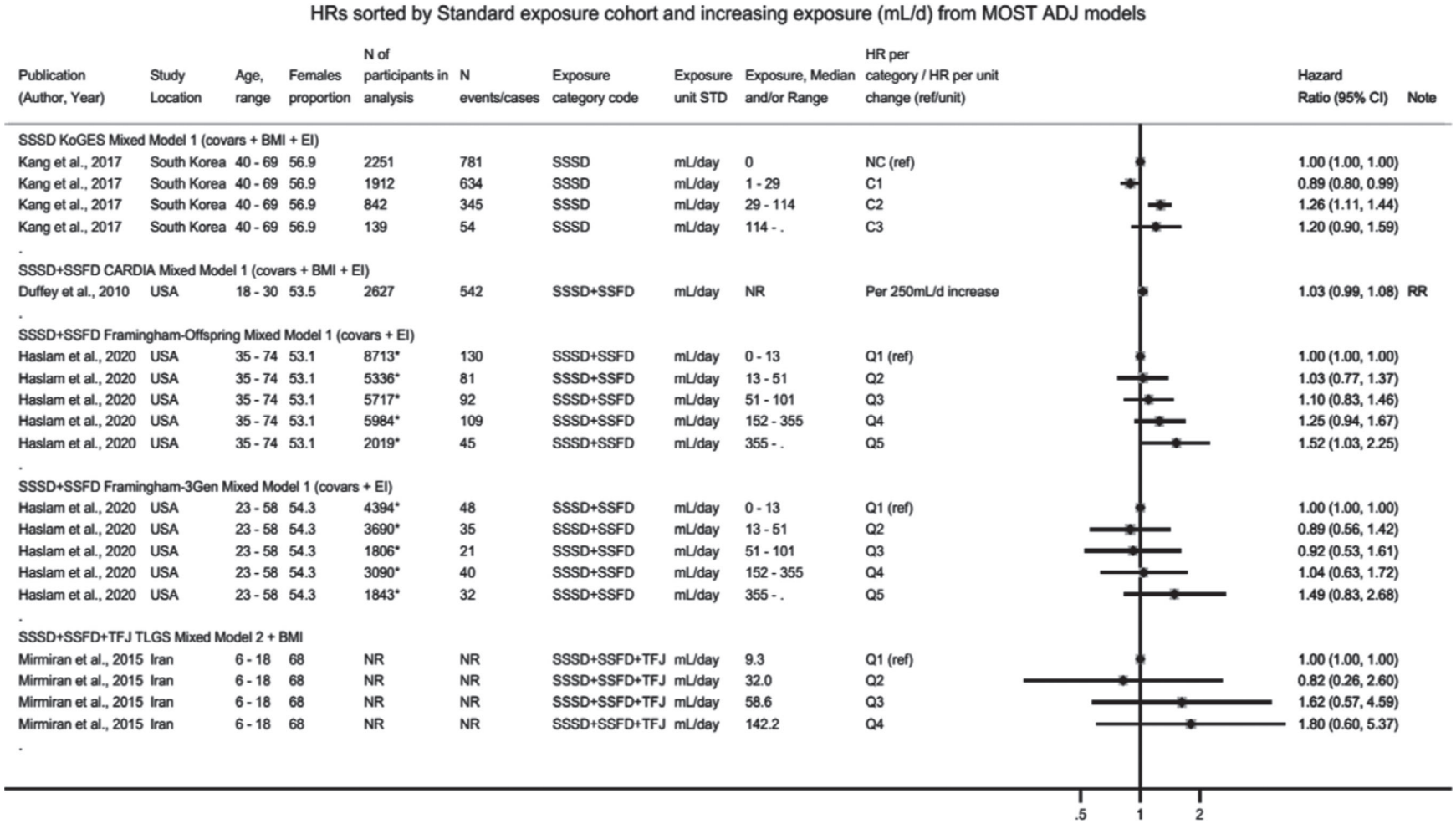
Figure K.10: SSBs and incidence of type 2 diabetes mellitus



Publication (Author, Year)	Study Location	Age, range	Females proportion	Ethinicity	N of participants in analysis	N events/cases	Exposure category code	Exposure, Median and/or Range	HR per category / HR per unit change (ref/unit)	Hazard Ratio (95% CI)	Note	TEI
CARDIA Most adjusted model (BMI, EI)												
Duffey et al., 2010	USA	18 - 30	54.7	Mixed	2160	267	100%FJ	NR	Per 250mL/d increase	1.01 (0.91, 1.13)	RR	
HPFS Most adjusted model (BMI, EI)												
Muraki, 2013	USA	40 - 75	0	Mixed		401	100%FJ	0 - 23	C1 (ref)	1.00 (1.00, 1.00)		
Muraki, 2013	USA	40 - 75	0	Mixed		225	100%FJ	24 - 24	C2	1.07 (0.91, 1.26)		
Muraki, 2013	USA	40 - 75	0	Mixed		488	100%FJ	48 - 96	C3	0.99 (0.86, 1.13)		
Muraki, 2013	USA	40 - 75	0	Mixed		460	100%FJ	120 - 144	C4	1.05 (0.92, 1.20)		
Muraki, 2013	USA	40 - 75	0	Mixed		1113	100%FJ	168 - .	C5	1.13 (1.01, 1.27)		
JPHC Most adjusted model (BMI, EI)												
Eshak, 2013	Japan	40 - 59	100	Asian	9075	198	100%FJ	0	C1 (ref)	1.00 (1.00, 1.00)	OR	
Eshak, 2013	Japan	40 - 59	100	Asian	4616	99	100%FJ	36 - 71	C2	0.94 (0.72, 1.23)	OR	
Eshak, 25	Japan	40 - 59	100	Asian	1198	25	100%FJ	107 - 143	C3	0.90 (0.58, 1.40)	OR	
Eshak, 2013	Japan	40 - 59	100	Asian	559	18	100%FJ	179 - 250	C4	1.37 (0.79, 2.37)	OR	
Eshak, 2013	Japan	40 - 59	0	Asian	7115	302	100%FJ	0	C1 (ref)	1.00 (1.00, 1.00)	OR	
Eshak, 2013	Japan	40 - 59	0	Asian	3744	129	100%FJ	36 - 71	C2	0.81 (0.65, 1.01)	OR	
Eshak, 2013	Japan	40 - 59	0	Asian	914	36	100%FJ	107 - 143	C3	0.93 (0.65, 1.34)	OR	
Eshak, 2013	Japan	40 - 59	0	Asian	364	17	100%FJ	179 - 250	C4	1.17 (0.69, 1.99)	OR	
NHS Most adjusted model (BMI, EI)												
Muraki, 2013	USA	30 - 55	100	Mixed		921	100%FJ	0 - 23	C1 (ref)	1.00 (1.00, 1.00)		
Muraki, 2013	USA	30 - 55	100	Mixed		547	100%FJ	24 - 24	C2	1.09 (0.98, 1.21)		
Muraki, 2013	USA	30 - 55	100	Mixed		1260	100%FJ	48 - 96	C3	1.13 (1.03, 1.23)		
Muraki, 2013	USA	30 - 55	100	Mixed		1090	100%FJ	120 - 144	C4	1.13 (1.03, 1.24)		
Muraki, 2013	USA	30 - 55	100	Mixed		2540	100%FJ	168 - .	C5	1.21 (1.12, 1.31)		
NHS II Most adjusted model (BMI, EI)												
Muraki, 2013	USA	24 - 44	100	Mixed		672	100%FJ	0 - 23	C1 (ref)	1.00 (1.00, 1.00)		
Muraki, 2013	USA	24 - 44	100	Mixed		357	100%FJ	24 - 24	C2	0.92 (0.81, 1.05)		
Muraki, 2013	USA	24 - 44	100	Mixed		777	100%FJ	48 - 96	C3	0.97 (0.87, 1.08)		
Muraki, 2013	USA	24 - 44	100	Mixed		494	100%FJ	120 - 144	C4	0.97 (0.86, 1.09)		
Muraki, 2013	USA	24 - 44	100	Mixed		853	100%FJ	168 - .	C5	1.14 (1.02, 1.27)		
WHI Most adjusted model (BMI, EI)												
Auerbach, 2017	USA	50 - 79	100	Mixed	14008	1435	100%FJ	0	NC (ref)	1.00 (1.00, 1.00)		STD
Auerbach, 2017	USA	50 - 79	100	Mixed	25053	2529	100%FJ	30.0 (2 - 52)	Q1	0.98 (0.92, 1.04)		STD
Auerbach, 2017	USA	50 - 79	100	Mixed	25053	2522	100%FJ	80.0 (53 - 114)	Q2	0.99 (0.93, 1.05)		STD
Auerbach, 2017	USA	50 - 79	100	Mixed	25053	2541	100%FJ	150.0 (115 - 194)	Q3	1.00 (0.93, 1.07)		STD
Auerbach, 2017	USA	50 - 79	100	Mixed	25052	2461	100%FJ	236.0 (195 - 1086)	Q4	0.97 (0.91, 1.03)		STD
SUN Most adjusted model (BMI, EI)												
Fresan et al., 2017	Spain	18 - .	60.43	Caucasian	3122	40	TFJ	0	Q1 (ref)	1.00 (1.00, 1.00)		
Fresan et al., 2017	Spain	18 - .	60.43	Caucasian	10803	72	TFJ	56.0 (. - 200)	Q2	0.90 (0.61, 1.33)		
Fresan et al., 2017	Spain	18 - .	60.43	Caucasian	3395	28	TFJ	238.0 (200 - 600)	Q3	0.99 (0.60, 1.63)		
Fresan et al., 2017	Spain	18 - .	60.43	Caucasian	198	2	TFJ	796.0 (600 - .)	Q4	0.82 (0.20, 3.39)		
EPIC-InterAct Most adjusted model (BMI, EI)												
Romaguera et al., 2013	Europe	35 - 70	62.5	Caucasian	26328	11684	TFJ	NR	Per one 336g serving size increment	1.05 (0.94, 1.18)		
Romaguera et al., 2013	Europe	35 - 70	62.5	Caucasian	12569	5837	TFJ	0	C1 (ref)	1.00 (1.00, 1.00)		
Romaguera et al., 2013	Europe	35 - 70	62.5	Caucasian	3957	1702	TFJ	17.1	C2	0.97 (0.86, 1.10)		
Romaguera et al., 2013	Europe	35 - 70	62.5	Caucasian	8186	3425	TFJ	100.0	C3	1.04 (0.96, 1.13)		
Romaguera et al., 2013	Europe	35 - 70	62.5	Caucasian	1616	720	TFJ	338.3	C4	1.06 (0.90, 1.25)		

Note: NC (ref) = non-consumers; RR = Rate Ratio; IRR = Incidence Rate Ratio; OR = Odds Ratio; STD = Standardised for Total Energy Intake

Figure K.11: Fruit juices and incidence of type 2 diabetes mellitus



Note: RR = relative risk; * = person-years; in Duffey et al. (2010) exposure = average across years 0 and 7; in Framingham-Offspring cohort (Haslam et al., 2020) exposure = cumulative average intake (the mean intake reported at examinations up to and including the examination of dyslipidaemia diagnosis)

Figure K.12: SSBs and incidence of high triglycerides

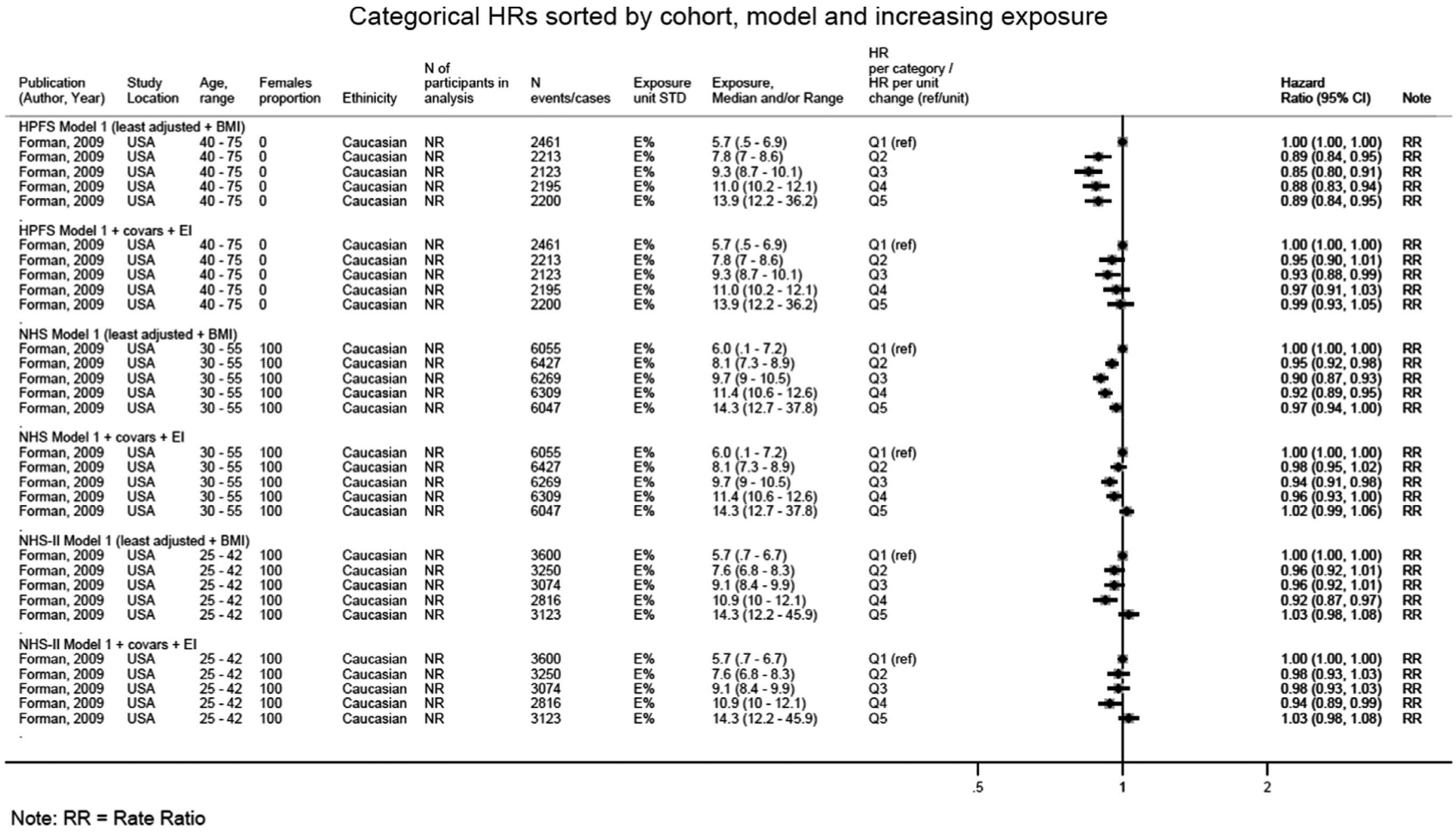
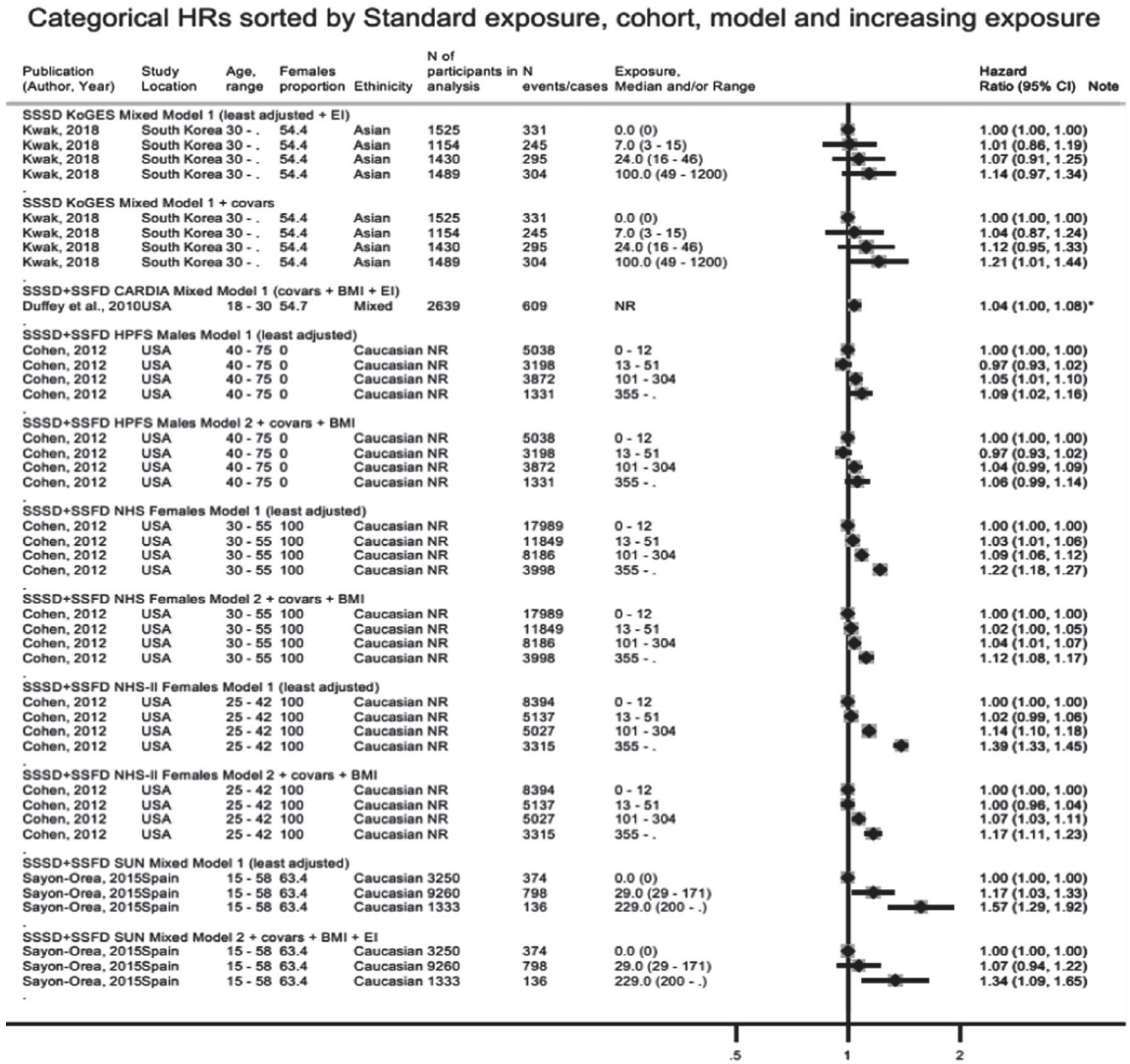


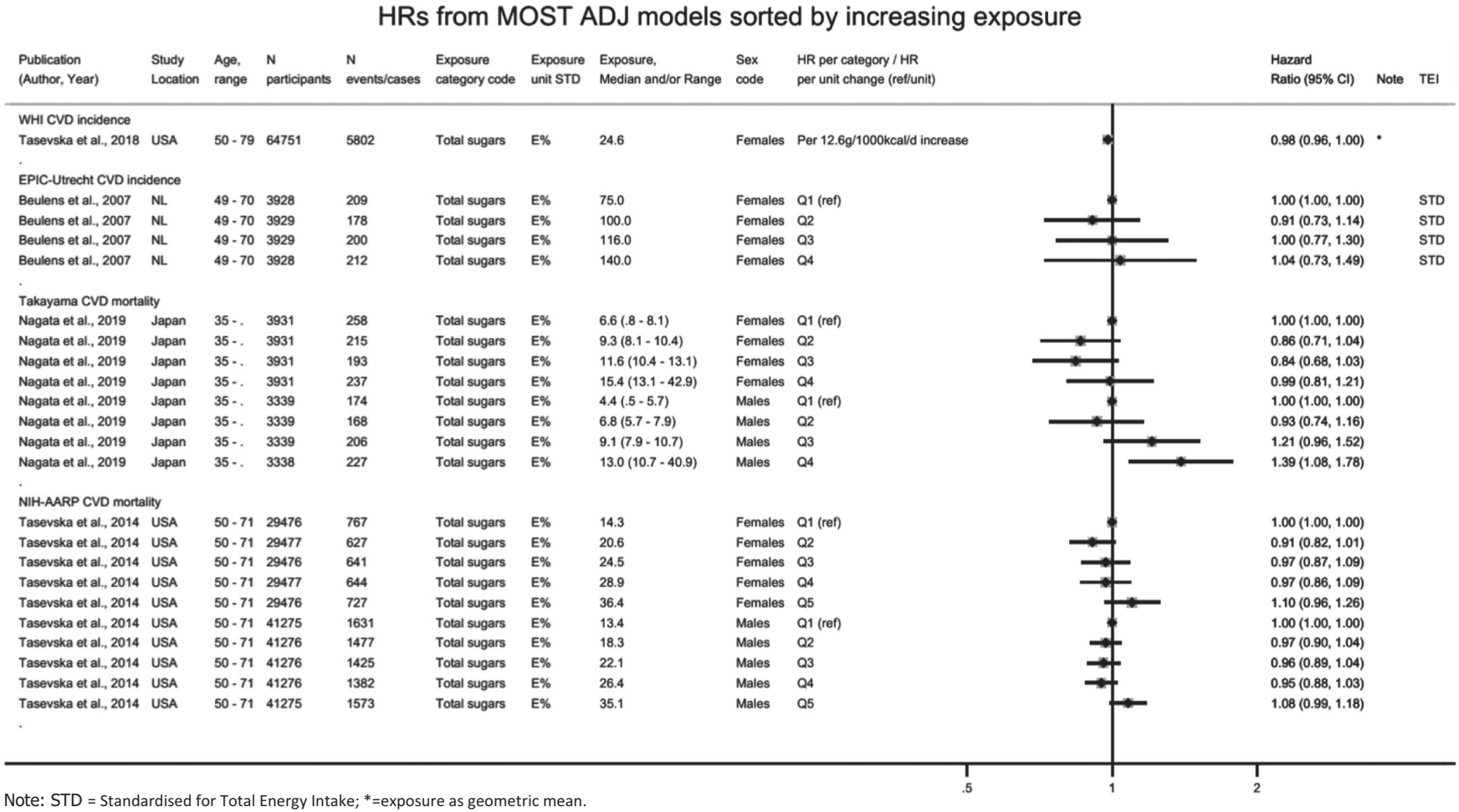
Figure K.13: Fructose and incidence of hypertension



Note: * = per 250 ml/d increase; Unit of exposure = ml/day; in Duffey et al. (2010) exposure = average across years 0 and 7.

Figure K.14: Intake of SSBs and incidence of hypertension

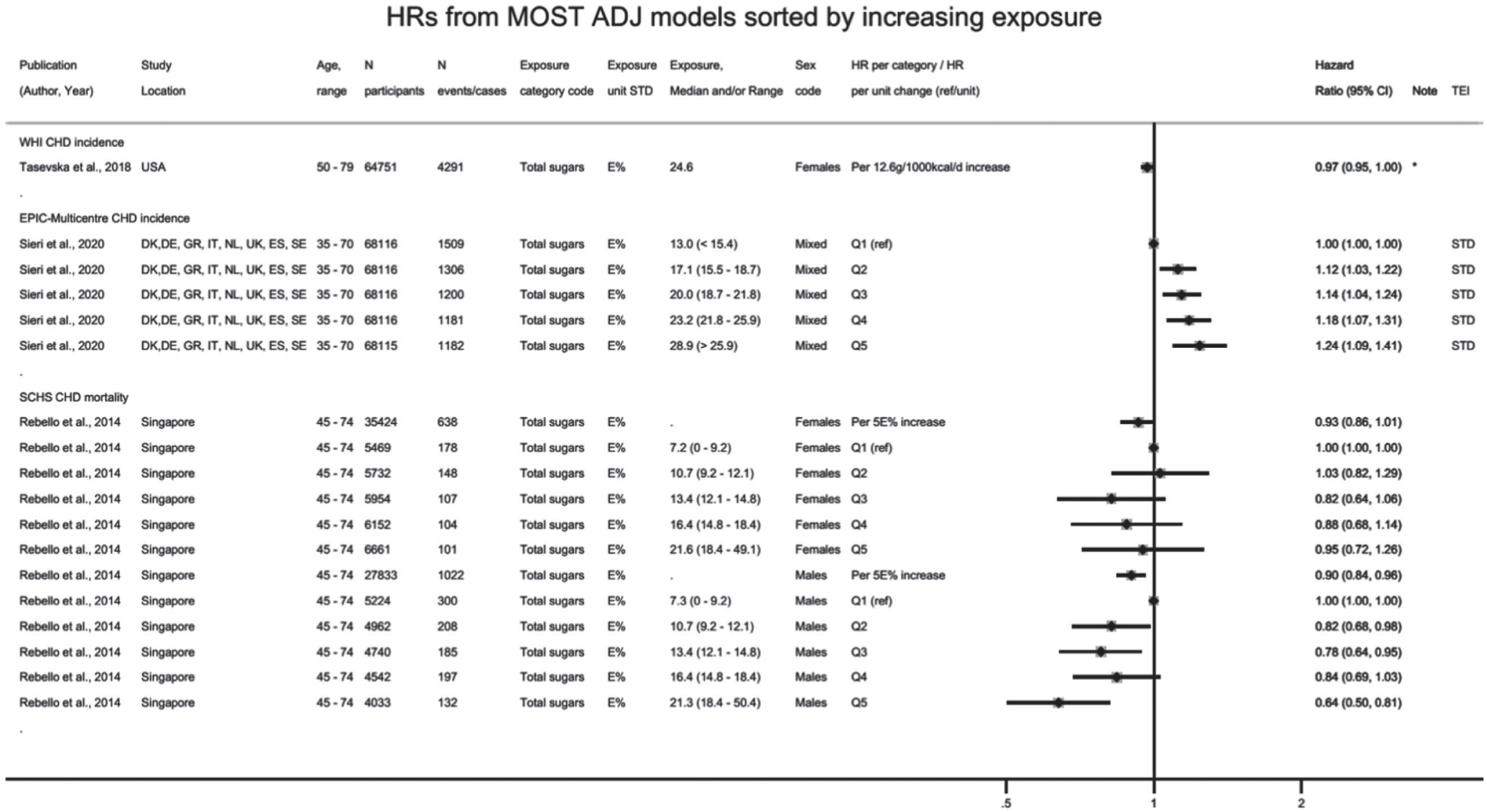
Figure K.15: Intake of total sugars and incidence and mortality of cardiovascular diseases



Publication (Author, Year)	Study Location	Age, range	N participants	N events/cases	Exposure category code	Exposure unit STD	Exposure, Median and/or Range	Sex code	HR per category / HR per unit change (ref/unit)	Hazard Ratio (95% CI)	Note	TEI
WHI CVD incidence												
Tasevska et al., 2018	USA	50 - 79	64751	5802	Total sugars	E%	24.6	Females	Per 12.6g/1000kcal/d increase	0.98 (0.96, 1.00)	*	
EPIC-Utrecht CVD incidence												
Beulens et al., 2007	NL	49 - 70	3928	209	Total sugars	E%	75.0	Females	Q1 (ref)	1.00 (1.00, 1.00)		STD
Beulens et al., 2007	NL	49 - 70	3929	178	Total sugars	E%	100.0	Females	Q2	0.91 (0.73, 1.14)		STD
Beulens et al., 2007	NL	49 - 70	3929	200	Total sugars	E%	116.0	Females	Q3	1.00 (0.77, 1.30)		STD
Beulens et al., 2007	NL	49 - 70	3928	212	Total sugars	E%	140.0	Females	Q4	1.04 (0.73, 1.49)		STD
Takayama CVD mortality												
Nagata et al., 2019	Japan	35 - .	3931	258	Total sugars	E%	6.6 (.8 - 8.1)	Females	Q1 (ref)	1.00 (1.00, 1.00)		
Nagata et al., 2019	Japan	35 - .	3931	215	Total sugars	E%	9.3 (8.1 - 10.4)	Females	Q2	0.86 (0.71, 1.04)		
Nagata et al., 2019	Japan	35 - .	3931	193	Total sugars	E%	11.6 (10.4 - 13.1)	Females	Q3	0.84 (0.68, 1.03)		
Nagata et al., 2019	Japan	35 - .	3931	237	Total sugars	E%	15.4 (13.1 - 42.9)	Females	Q4	0.99 (0.81, 1.21)		
Nagata et al., 2019	Japan	35 - .	3339	174	Total sugars	E%	4.4 (.5 - 5.7)	Males	Q1 (ref)	1.00 (1.00, 1.00)		
Nagata et al., 2019	Japan	35 - .	3339	168	Total sugars	E%	6.8 (5.7 - 7.9)	Males	Q2	0.93 (0.74, 1.16)		
Nagata et al., 2019	Japan	35 - .	3339	206	Total sugars	E%	9.1 (7.9 - 10.7)	Males	Q3	1.21 (0.96, 1.52)		
Nagata et al., 2019	Japan	35 - .	3338	227	Total sugars	E%	13.0 (10.7 - 40.9)	Males	Q4	1.39 (1.08, 1.78)		
NIH-AARP CVD mortality												
Tasevska et al., 2014	USA	50 - 71	29476	767	Total sugars	E%	14.3	Females	Q1 (ref)	1.00 (1.00, 1.00)		
Tasevska et al., 2014	USA	50 - 71	29477	627	Total sugars	E%	20.6	Females	Q2	0.91 (0.82, 1.01)		
Tasevska et al., 2014	USA	50 - 71	29476	641	Total sugars	E%	24.5	Females	Q3	0.97 (0.87, 1.09)		
Tasevska et al., 2014	USA	50 - 71	29477	644	Total sugars	E%	28.9	Females	Q4	0.97 (0.86, 1.09)		
Tasevska et al., 2014	USA	50 - 71	29476	727	Total sugars	E%	36.4	Females	Q5	1.10 (0.96, 1.26)		
Tasevska et al., 2014	USA	50 - 71	41275	1631	Total sugars	E%	13.4	Males	Q1 (ref)	1.00 (1.00, 1.00)		
Tasevska et al., 2014	USA	50 - 71	41276	1477	Total sugars	E%	18.3	Males	Q2	0.97 (0.90, 1.04)		
Tasevska et al., 2014	USA	50 - 71	41276	1425	Total sugars	E%	22.1	Males	Q3	0.96 (0.89, 1.04)		
Tasevska et al., 2014	USA	50 - 71	41276	1382	Total sugars	E%	26.4	Males	Q4	0.95 (0.88, 1.03)		
Tasevska et al., 2014	USA	50 - 71	41275	1573	Total sugars	E%	35.1	Males	Q5	1.08 (0.99, 1.18)		

Note: STD = Standardised for Total Energy Intake; *=exposure as geometric mean.

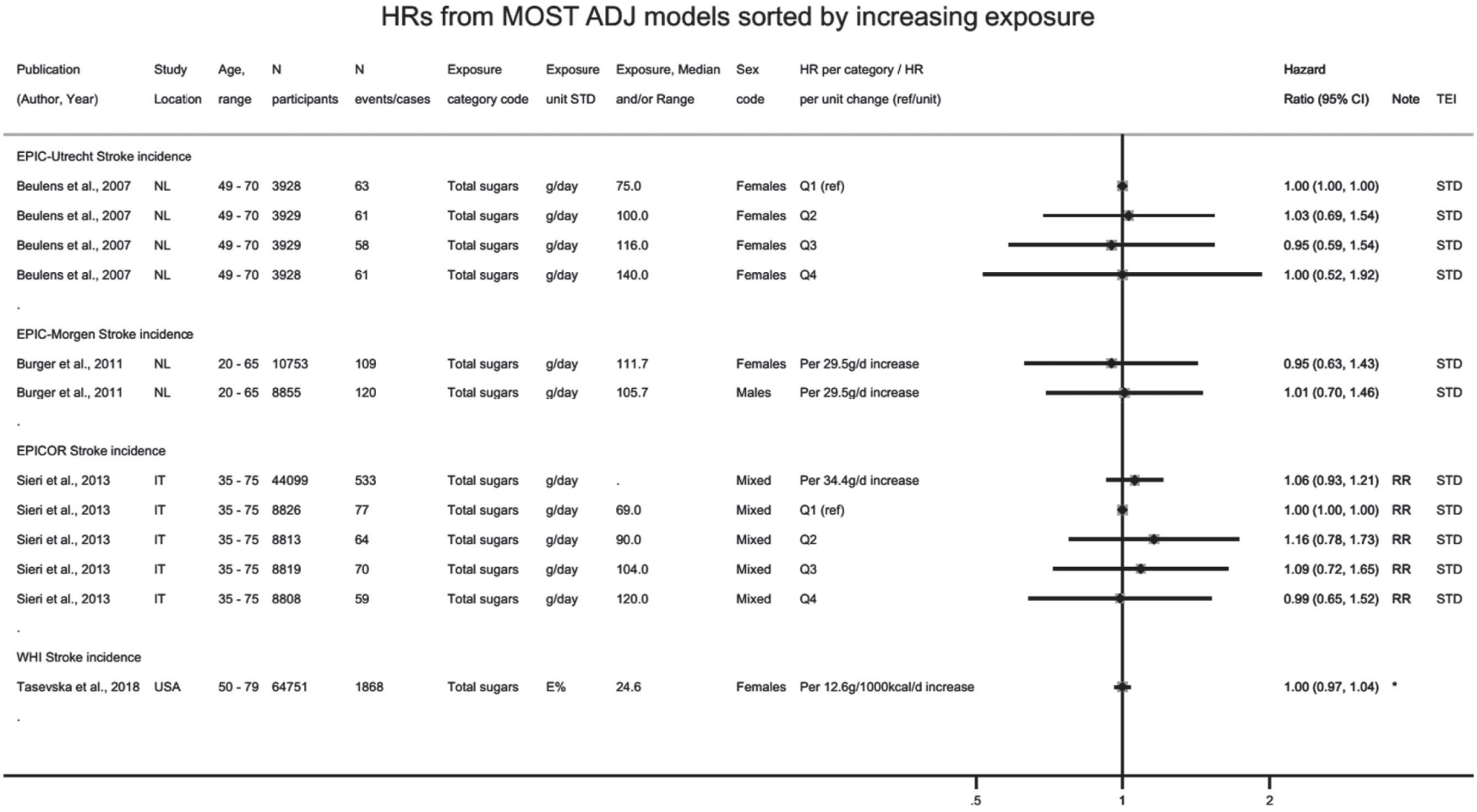
Figure K.15a: Intake of total sugars and cardiovascular disease (composite endpoints) incidence and mortality



Publication (Author, Year)	Study Location	Age, range	N participants	N events/cases	Exposure category code	Exposure unit STD	Exposure, Median and/or Range	Sex code	HR per category / HR per unit change (ref/unit)	Hazard Ratio (95% CI)	Note	TEI
WHI CHD incidence												
Tasevska et al., 2018	USA	50 - 79	64751	4291	Total sugars	E%	24.6	Females	Per 12.6g/1000kcal/d increase	0.97 (0.95, 1.00)	*	
.												
EPIC-Multicentre CHD incidence												
Sieri et al., 2020	DK,DE, GR, IT, NL, UK, ES, SE	35 - 70	68116	1509	Total sugars	E%	13.0 (< 15.4)	Mixed	Q1 (ref)	1.00 (1.00, 1.00)		STD
Sieri et al., 2020	DK,DE, GR, IT, NL, UK, ES, SE	35 - 70	68116	1306	Total sugars	E%	17.1 (15.5 - 18.7)	Mixed	Q2	1.12 (1.03, 1.22)		STD
Sieri et al., 2020	DK,DE, GR, IT, NL, UK, ES, SE	35 - 70	68116	1200	Total sugars	E%	20.0 (18.7 - 21.8)	Mixed	Q3	1.14 (1.04, 1.24)		STD
Sieri et al., 2020	DK,DE, GR, IT, NL, UK, ES, SE	35 - 70	68116	1181	Total sugars	E%	23.2 (21.8 - 25.9)	Mixed	Q4	1.18 (1.07, 1.31)		STD
Sieri et al., 2020	DK,DE, GR, IT, NL, UK, ES, SE	35 - 70	68115	1182	Total sugars	E%	28.9 (> 25.9)	Mixed	Q5	1.24 (1.09, 1.41)		STD
.												
SCHS CHD mortality												
Rebello et al., 2014	Singapore	45 - 74	35424	638	Total sugars	E%	.	Females	Per 5E% increase	0.93 (0.86, 1.01)		
Rebello et al., 2014	Singapore	45 - 74	5469	178	Total sugars	E%	7.2 (0 - 9.2)	Females	Q1 (ref)	1.00 (1.00, 1.00)		
Rebello et al., 2014	Singapore	45 - 74	5732	148	Total sugars	E%	10.7 (9.2 - 12.1)	Females	Q2	1.03 (0.82, 1.29)		
Rebello et al., 2014	Singapore	45 - 74	5954	107	Total sugars	E%	13.4 (12.1 - 14.8)	Females	Q3	0.82 (0.64, 1.06)		
Rebello et al., 2014	Singapore	45 - 74	6152	104	Total sugars	E%	16.4 (14.8 - 18.4)	Females	Q4	0.88 (0.68, 1.14)		
Rebello et al., 2014	Singapore	45 - 74	6661	101	Total sugars	E%	21.6 (18.4 - 49.1)	Females	Q5	0.95 (0.72, 1.26)		
Rebello et al., 2014	Singapore	45 - 74	27833	1022	Total sugars	E%	.	Males	Per 5E% increase	0.90 (0.84, 0.96)		
Rebello et al., 2014	Singapore	45 - 74	5224	300	Total sugars	E%	7.3 (0 - 9.2)	Males	Q1 (ref)	1.00 (1.00, 1.00)		
Rebello et al., 2014	Singapore	45 - 74	4962	208	Total sugars	E%	10.7 (9.2 - 12.1)	Males	Q2	0.82 (0.68, 0.98)		
Rebello et al., 2014	Singapore	45 - 74	4740	185	Total sugars	E%	13.4 (12.1 - 14.8)	Males	Q3	0.78 (0.64, 0.95)		
Rebello et al., 2014	Singapore	45 - 74	4542	197	Total sugars	E%	16.4 (14.8 - 18.4)	Males	Q4	0.84 (0.69, 1.03)		
Rebello et al., 2014	Singapore	45 - 74	4033	132	Total sugars	E%	21.3 (18.4 - 50.4)	Males	Q5	0.64 (0.50, 0.81)		
.												

Note: STD = Standardised for Total Energy Intake; *=exposure as geometric mean.

Figure K.15b: Intake of total sugars and coronary heart disease incidence and mortality



Note: STD = Standardised for Total Energy Intake; *=exposure as geometric mean.

Figure K.15c: Intake of total sugars and stroke incidence and mortality

Figure K.16: Intake of fructose and incidence and mortality of cardiovascular diseases

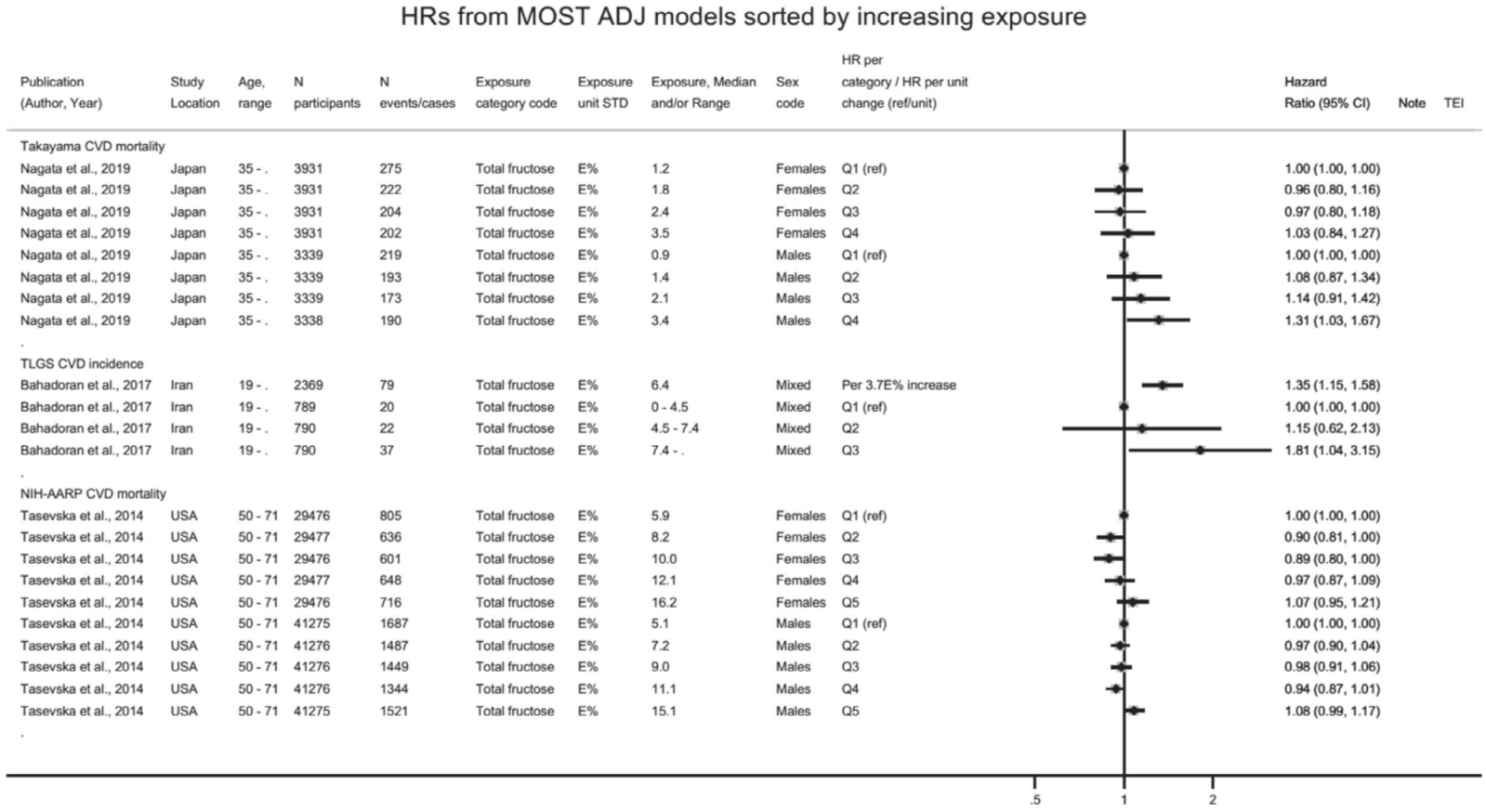


Figure K.16a: Intake of fructose and incidence and mortality of cardiovascular diseases (composite endpoint) – General plot

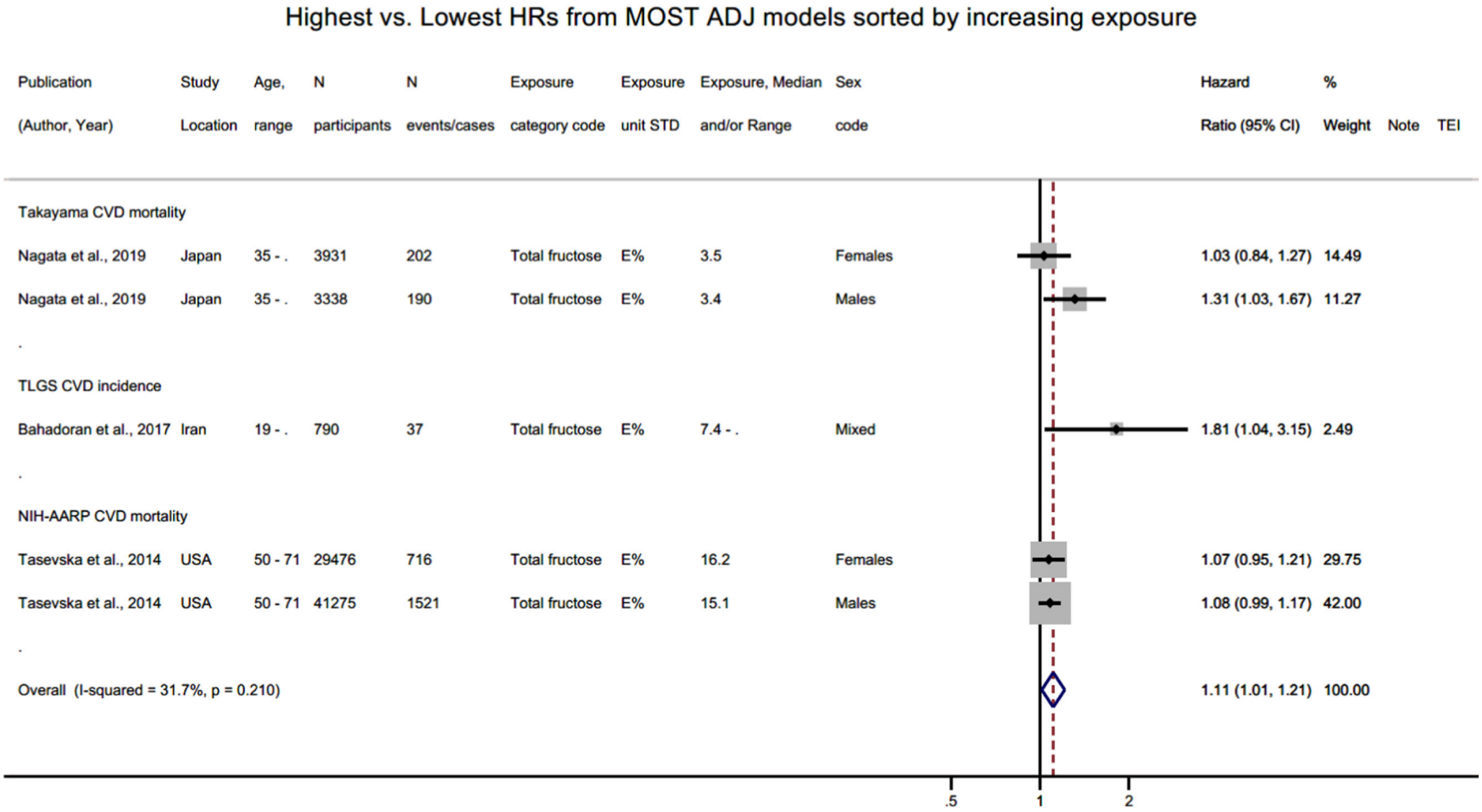
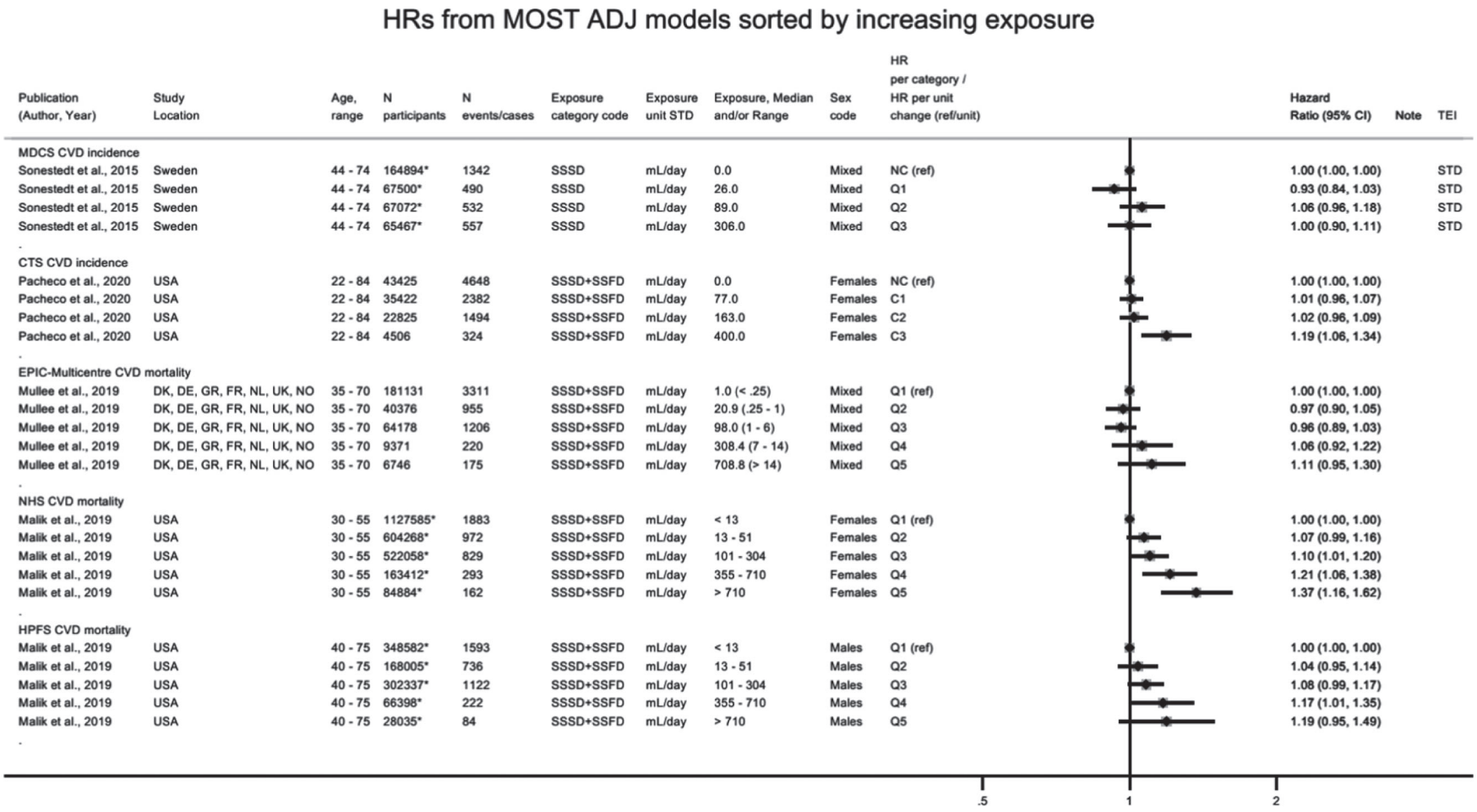


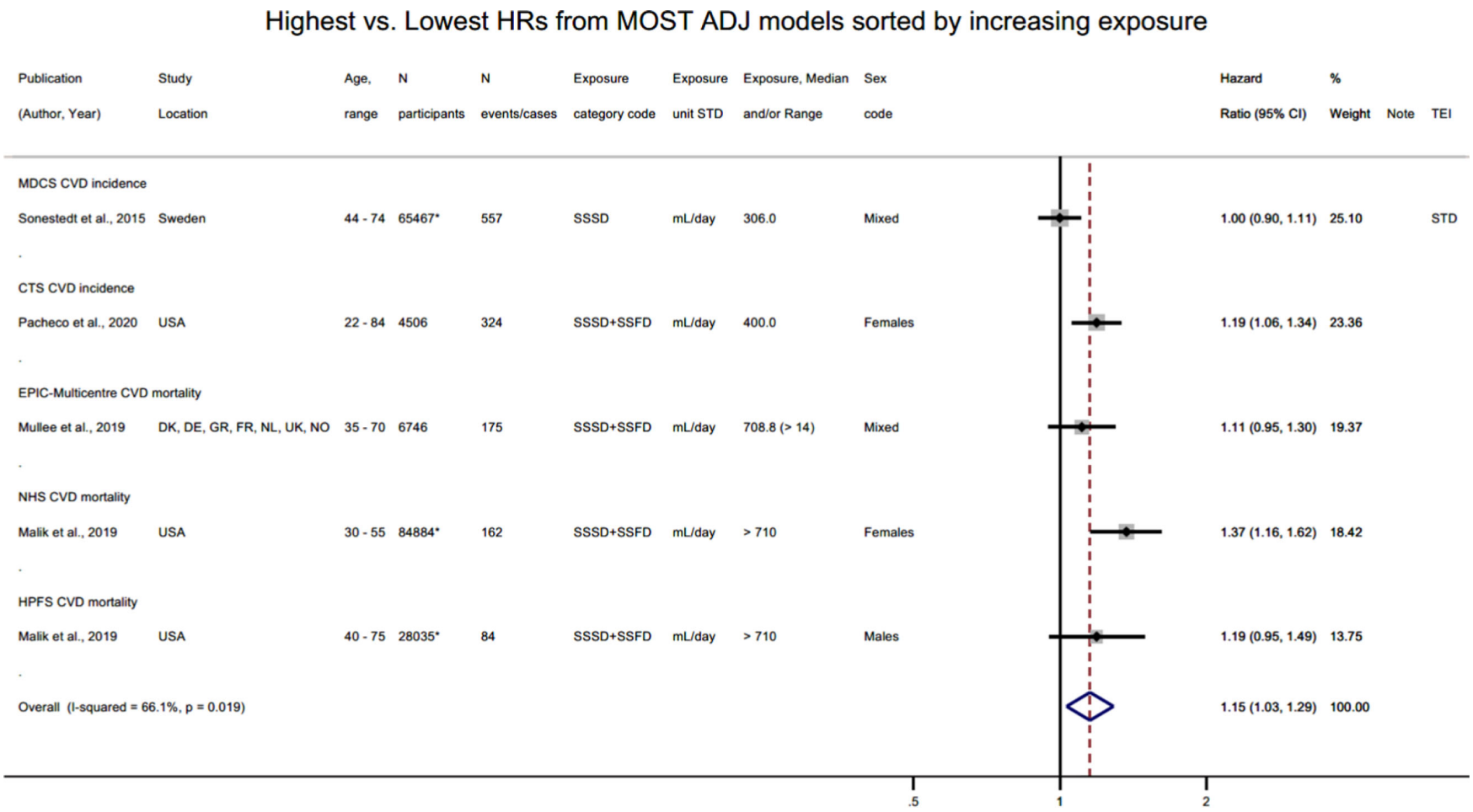
Figure K.16b: Intake of fructose and incidence and mortality of cardiovascular diseases (composite endpoint) – Pooled plot

Figure K.17: Intake of SSBs and incidence and mortality of cardiovascular diseases



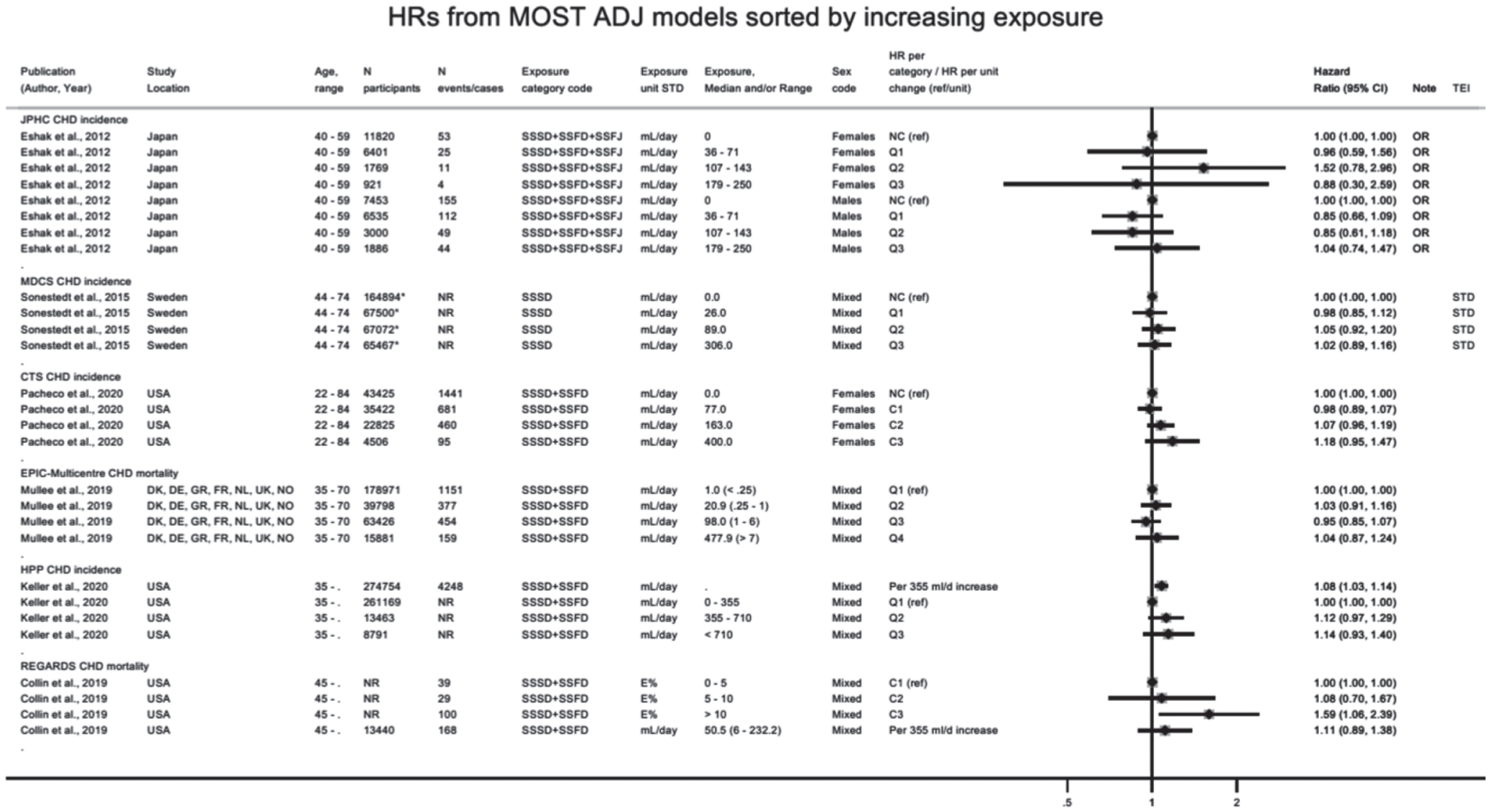
Note: STD = Standardised for Total Energy Intake; *=Person-years.

Figure K.17a1: Intake of SSBs and cardiovascular disease (composite endpoint) incidence and mortality – General plot



Note: STD = Standardised for Total Energy Intake; *=Person-years.

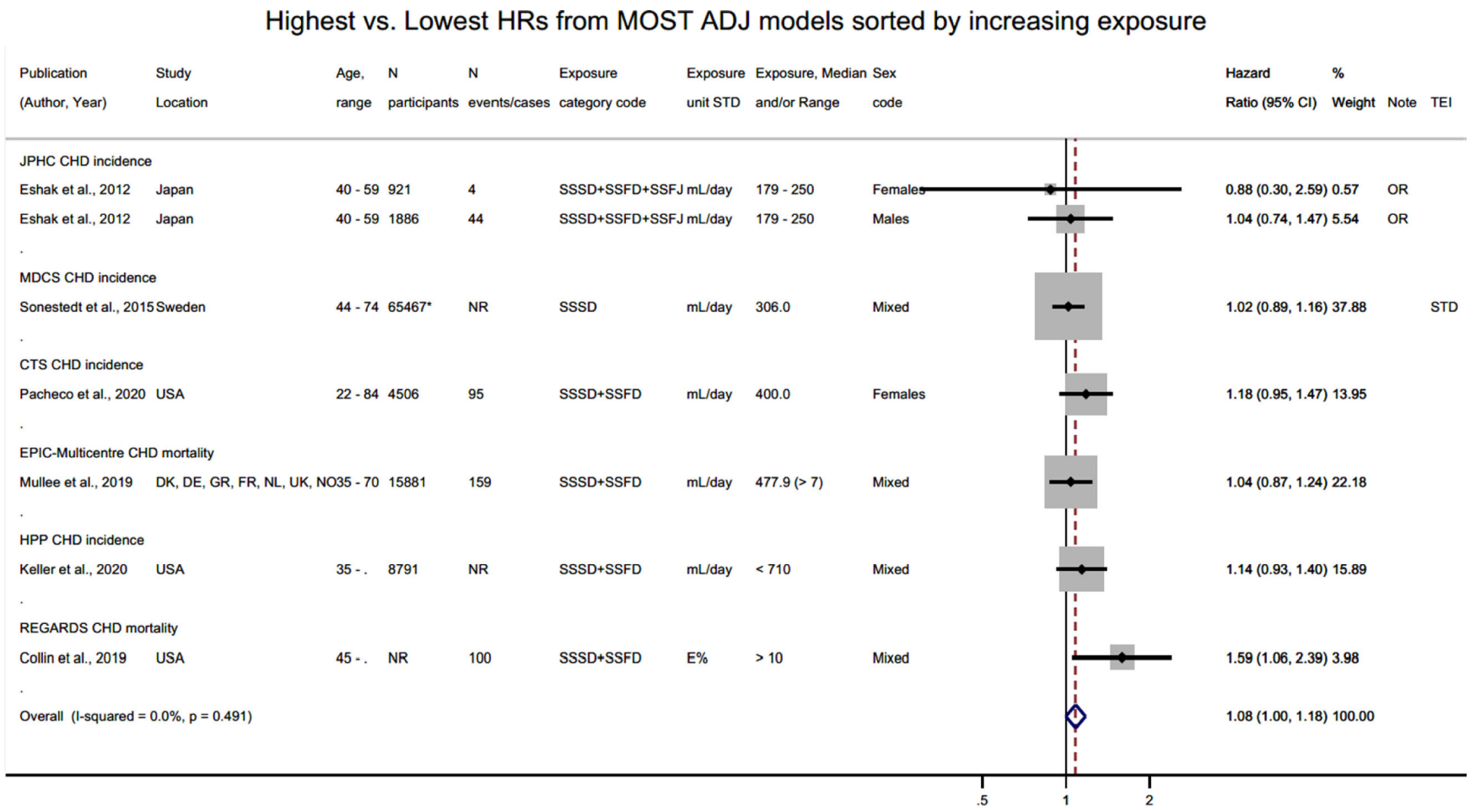
Figure K.17a2: Intake of SSBs and cardiovascular disease (composite endpoint) incidence and mortality – Pooled plot



Publication (Author, Year)	Study Location	Age, range	N participants	N events/cases	Exposure category code	Exposure unit STD	Exposure, Median and/or Range	Sex code	HR per category / HR per unit change (ref/unit)	Hazard Ratio (95% CI)	Note	TEI
JPHC CHD incidence												
Eshak et al., 2012	Japan	40 - 59	11820	53	SSSD+SSFD+SSFJ	mL/day	0	Females	NC (ref)	1.00 (1.00, 1.00)	OR	
Eshak et al., 2012	Japan	40 - 59	6401	25	SSSD+SSFD+SSFJ	mL/day	36 - 71	Females	Q1	0.96 (0.59, 1.56)	OR	
Eshak et al., 2012	Japan	40 - 59	1769	11	SSSD+SSFD+SSFJ	mL/day	107 - 143	Females	Q2	1.52 (0.78, 2.96)	OR	
Eshak et al., 2012	Japan	40 - 59	921	4	SSSD+SSFD+SSFJ	mL/day	179 - 250	Females	Q3	0.88 (0.30, 2.59)	OR	
Eshak et al., 2012	Japan	40 - 59	7453	155	SSSD+SSFD+SSFJ	mL/day	0	Males	NC (ref)	1.00 (1.00, 1.00)	OR	
Eshak et al., 2012	Japan	40 - 59	6535	112	SSSD+SSFD+SSFJ	mL/day	36 - 71	Males	Q1	0.85 (0.66, 1.09)	OR	
Eshak et al., 2012	Japan	40 - 59	3000	49	SSSD+SSFD+SSFJ	mL/day	107 - 143	Males	Q2	0.85 (0.61, 1.18)	OR	
Eshak et al., 2012	Japan	40 - 59	1886	44	SSSD+SSFD+SSFJ	mL/day	179 - 250	Males	Q3	1.04 (0.74, 1.47)	OR	
MDCS CHD incidence												
Sonestedt et al., 2015	Sweden	44 - 74	164894*	NR	SSSD	mL/day	0.0	Mixed	NC (ref)	1.00 (1.00, 1.00)		STD
Sonestedt et al., 2015	Sweden	44 - 74	67500*	NR	SSSD	mL/day	26.0	Mixed	Q1	0.98 (0.85, 1.12)		STD
Sonestedt et al., 2015	Sweden	44 - 74	67072*	NR	SSSD	mL/day	89.0	Mixed	Q2	1.05 (0.92, 1.20)		STD
Sonestedt et al., 2015	Sweden	44 - 74	65467*	NR	SSSD	mL/day	306.0	Mixed	Q3	1.02 (0.89, 1.16)		STD
CTS CHD incidence												
Pacheco et al., 2020	USA	22 - 84	43425	1441	SSSD+SSFD	mL/day	0.0	Females	NC (ref)	1.00 (1.00, 1.00)		
Pacheco et al., 2020	USA	22 - 84	35422	681	SSSD+SSFD	mL/day	77.0	Females	C1	0.98 (0.89, 1.07)		
Pacheco et al., 2020	USA	22 - 84	22825	460	SSSD+SSFD	mL/day	163.0	Females	C2	1.07 (0.96, 1.19)		
Pacheco et al., 2020	USA	22 - 84	4506	95	SSSD+SSFD	mL/day	400.0	Females	C3	1.18 (0.95, 1.47)		
EPIC-Multicentre CHD mortality												
Mullee et al., 2019	DK, DE, GR, FR, NL, UK, NO	35 - 70	178971	1151	SSSD+SSFD	mL/day	1.0 (< .25)	Mixed	Q1 (ref)	1.00 (1.00, 1.00)		
Mullee et al., 2019	DK, DE, GR, FR, NL, UK, NO	35 - 70	39798	377	SSSD+SSFD	mL/day	20.9 (.25 - 1)	Mixed	Q2	1.03 (0.91, 1.16)		
Mullee et al., 2019	DK, DE, GR, FR, NL, UK, NO	35 - 70	63426	454	SSSD+SSFD	mL/day	98.0 (1 - 6)	Mixed	Q3	0.95 (0.85, 1.07)		
Mullee et al., 2019	DK, DE, GR, FR, NL, UK, NO	35 - 70	15881	159	SSSD+SSFD	mL/day	477.9 (> 7)	Mixed	Q4	1.04 (0.87, 1.24)		
HPP CHD incidence												
Keller et al., 2020	USA	35 - .	274754	4248	SSSD+SSFD	mL/day	.	Mixed	Per 355 ml/d increase	1.08 (1.03, 1.14)		
Keller et al., 2020	USA	35 - .	261169	NR	SSSD+SSFD	mL/day	0 - 355	Mixed	Q1 (ref)	1.00 (1.00, 1.00)		
Keller et al., 2020	USA	35 - .	13463	NR	SSSD+SSFD	mL/day	355 - 710	Mixed	Q2	1.12 (0.97, 1.29)		
Keller et al., 2020	USA	35 - .	8791	NR	SSSD+SSFD	mL/day	< 710	Mixed	Q3	1.14 (0.93, 1.40)		
REGARDS CHD mortality												
Collin et al., 2019	USA	45 - .	NR	39	SSSD+SSFD	E%	0 - 5	Mixed	C1 (ref)	1.00 (1.00, 1.00)		
Collin et al., 2019	USA	45 - .	NR	29	SSSD+SSFD	E%	5 - 10	Mixed	C2	1.08 (0.70, 1.67)		
Collin et al., 2019	USA	45 - .	NR	100	SSSD+SSFD	E%	> 10	Mixed	C3	1.59 (1.06, 2.39)		
Collin et al., 2019	USA	45 - .	13440	168	SSSD+SSFD	mL/day	50.5 (6 - 232.2)	Mixed	Per 355 ml/d increase	1.11 (0.89, 1.38)		

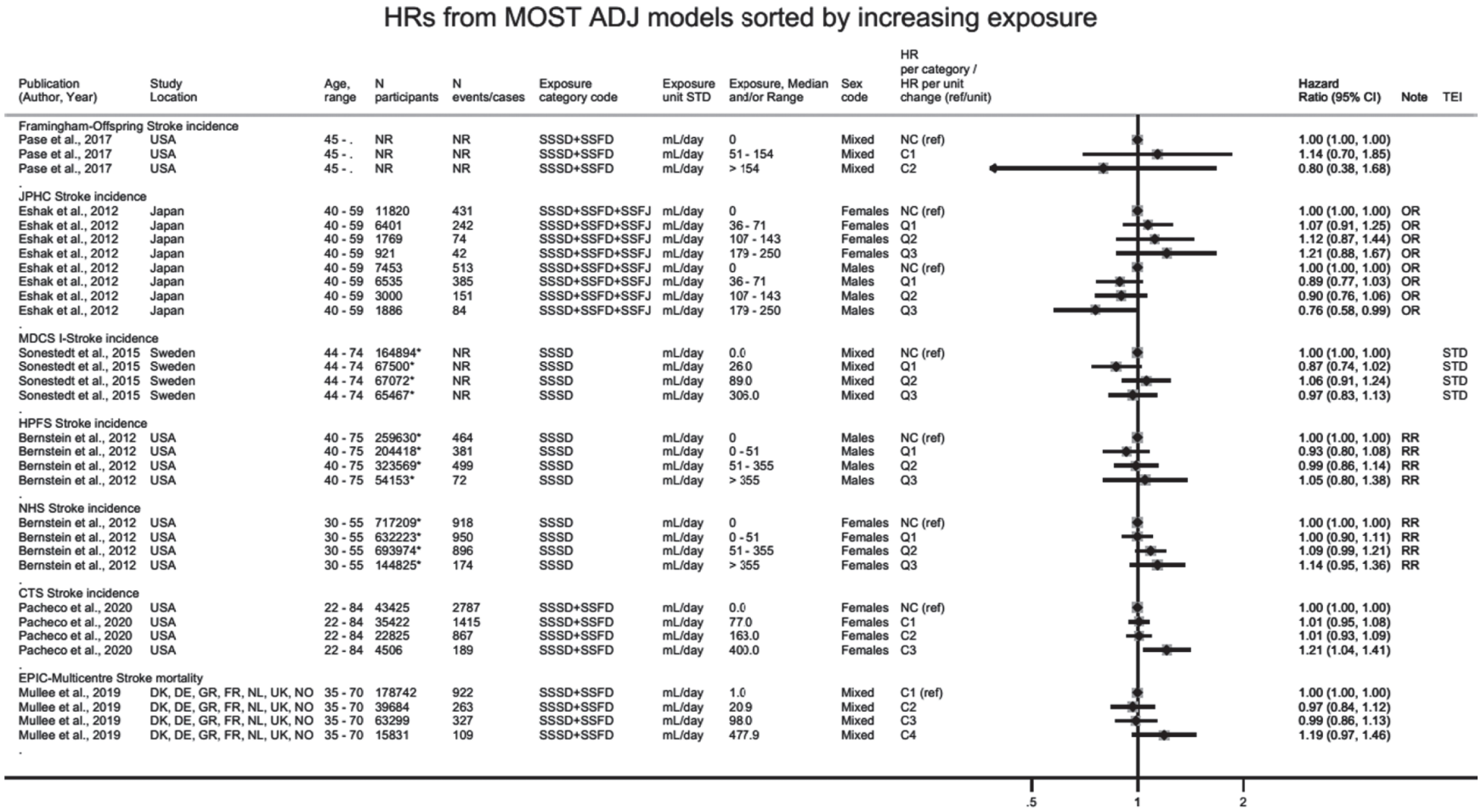
Note: OR = Odds Ratio; STD = Standardised for Total Energy Intake; *=Person-years.

Figure K.17b1: Intake of SSBs and coronary heart disease incidence and mortality – General plot



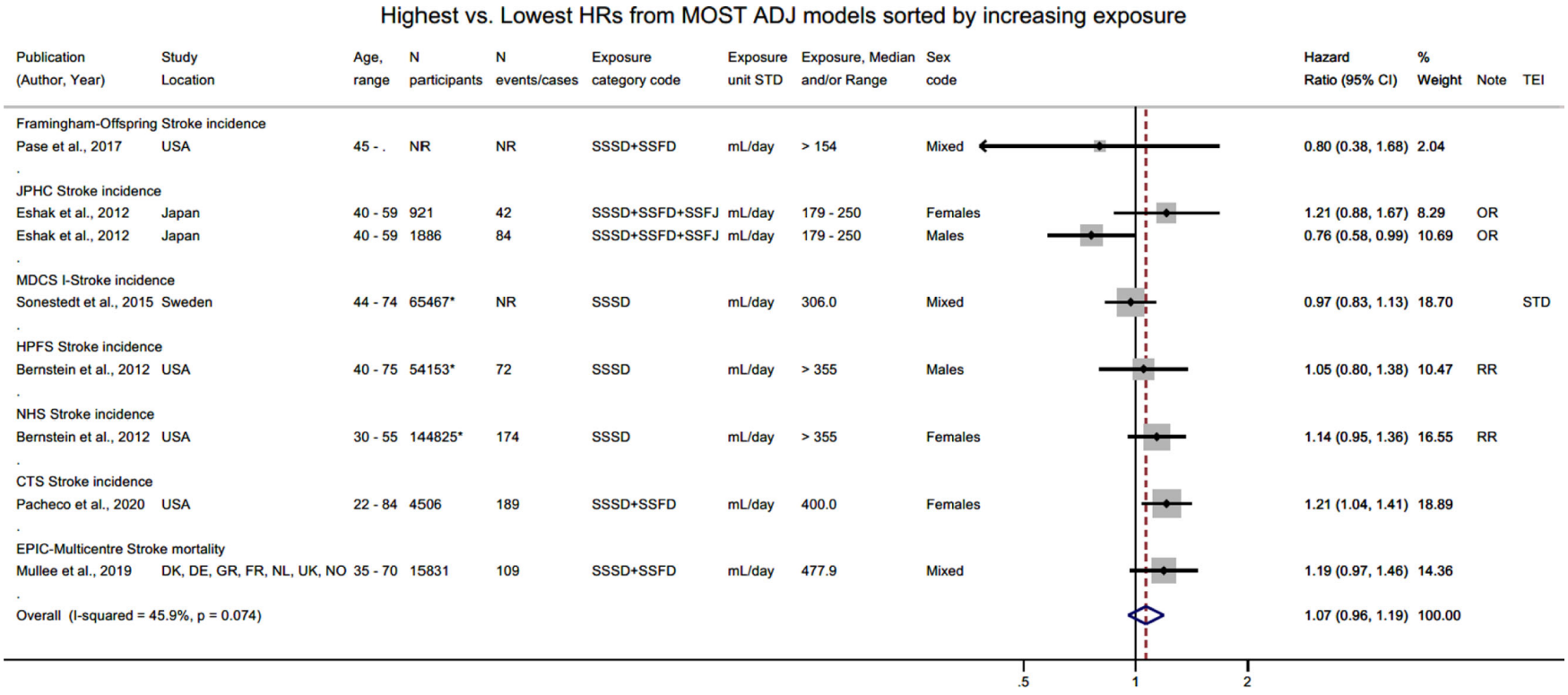
Note: OR = Odds Ratio; STD = Standardised for Total Energy Intake; *=Person-years.

Figure K.17b2: Intake of SSBs and coronary heart disease incidence and mortality – Pooled plot



Note: OR = Odds Ratio; RR= Rate ratio; STD = Standardised for Total Energy Intake; *=Person-years; in Framingham-Offspring cohort (Pase et al., 2017) exposure = cumulative intake.

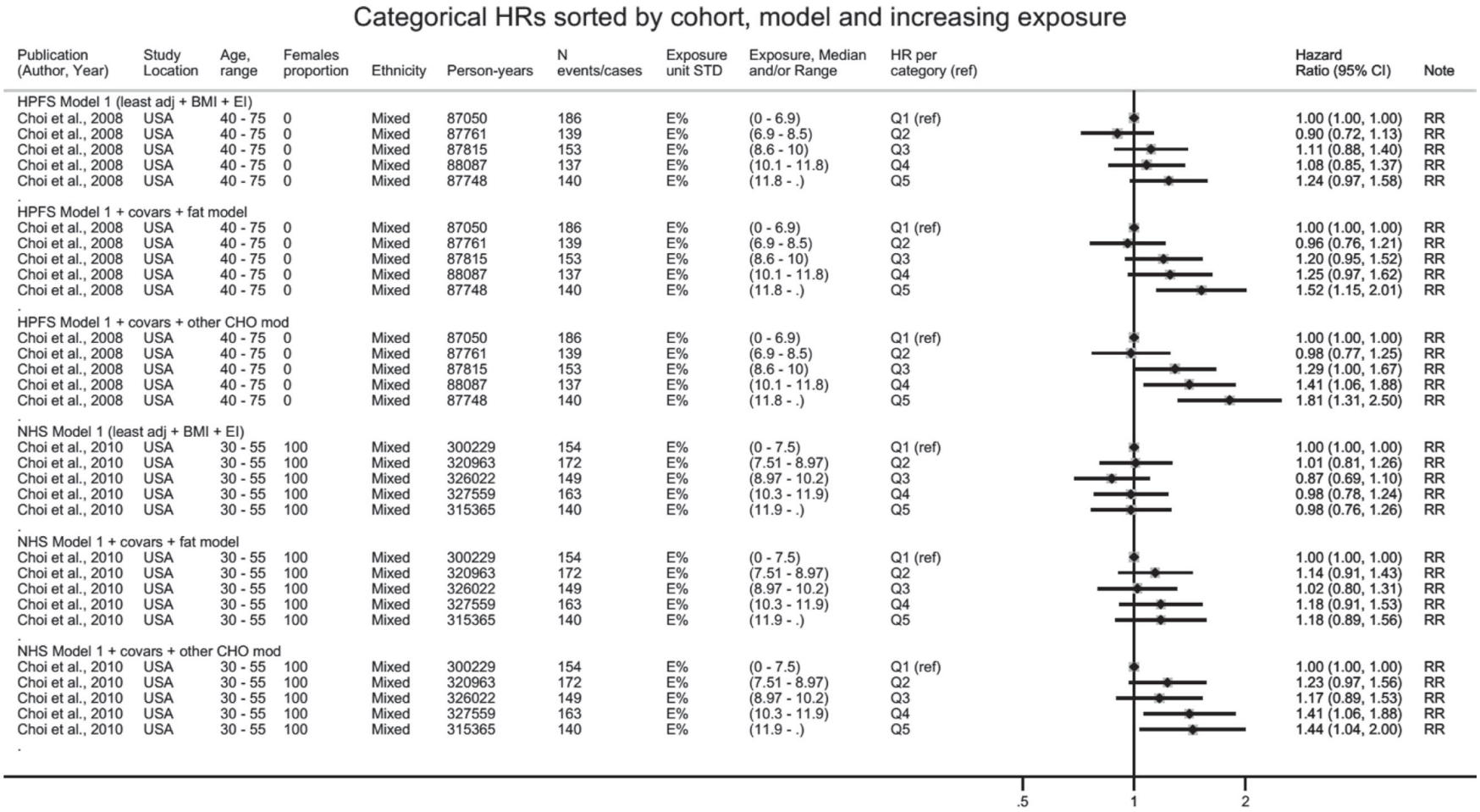
Figure K.17c1: Intake of SSBs and stroke incidence and mortality – General plot



Note: OR = Odds Ratio; RR= Rate ratio; STD = Standardised for Total Energy Intake.

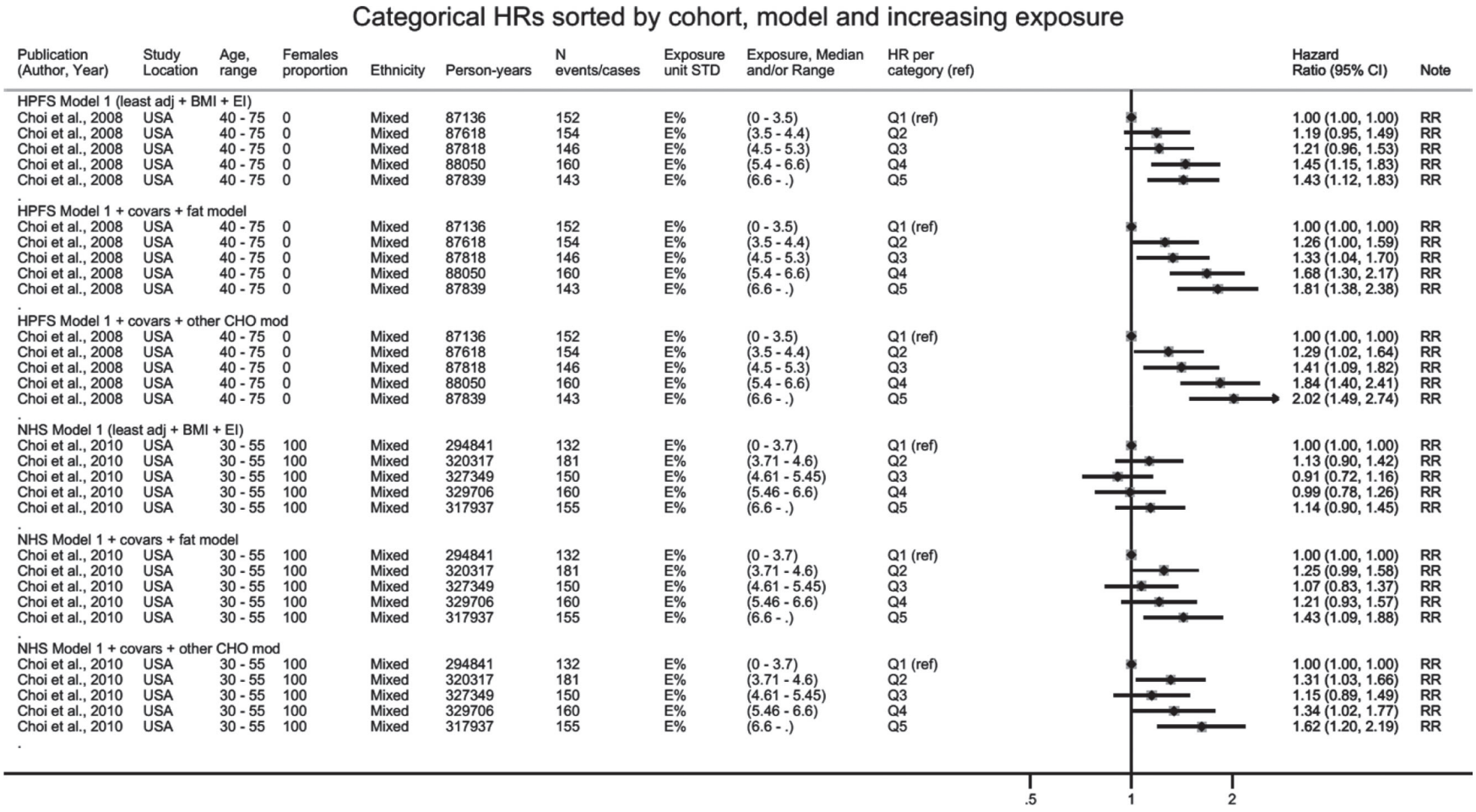
Figure K.17c2: Intake of SSBs and stroke incidence and mortality – Pooled plot

Figure K.18: Fructose and incidence of gout



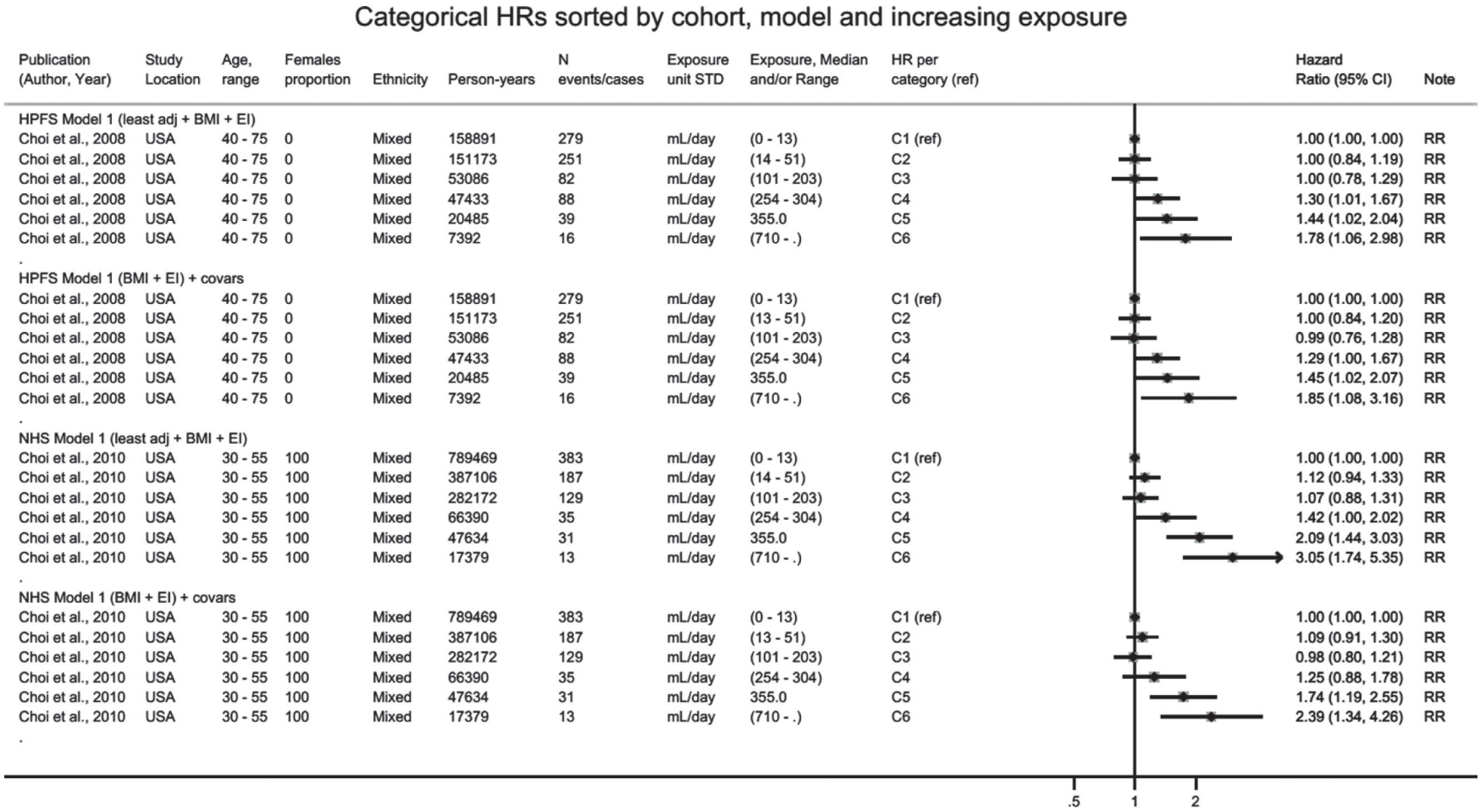
Note: RR= Rate ratio.

Figure K.18a: Total fructose and incidence of gout



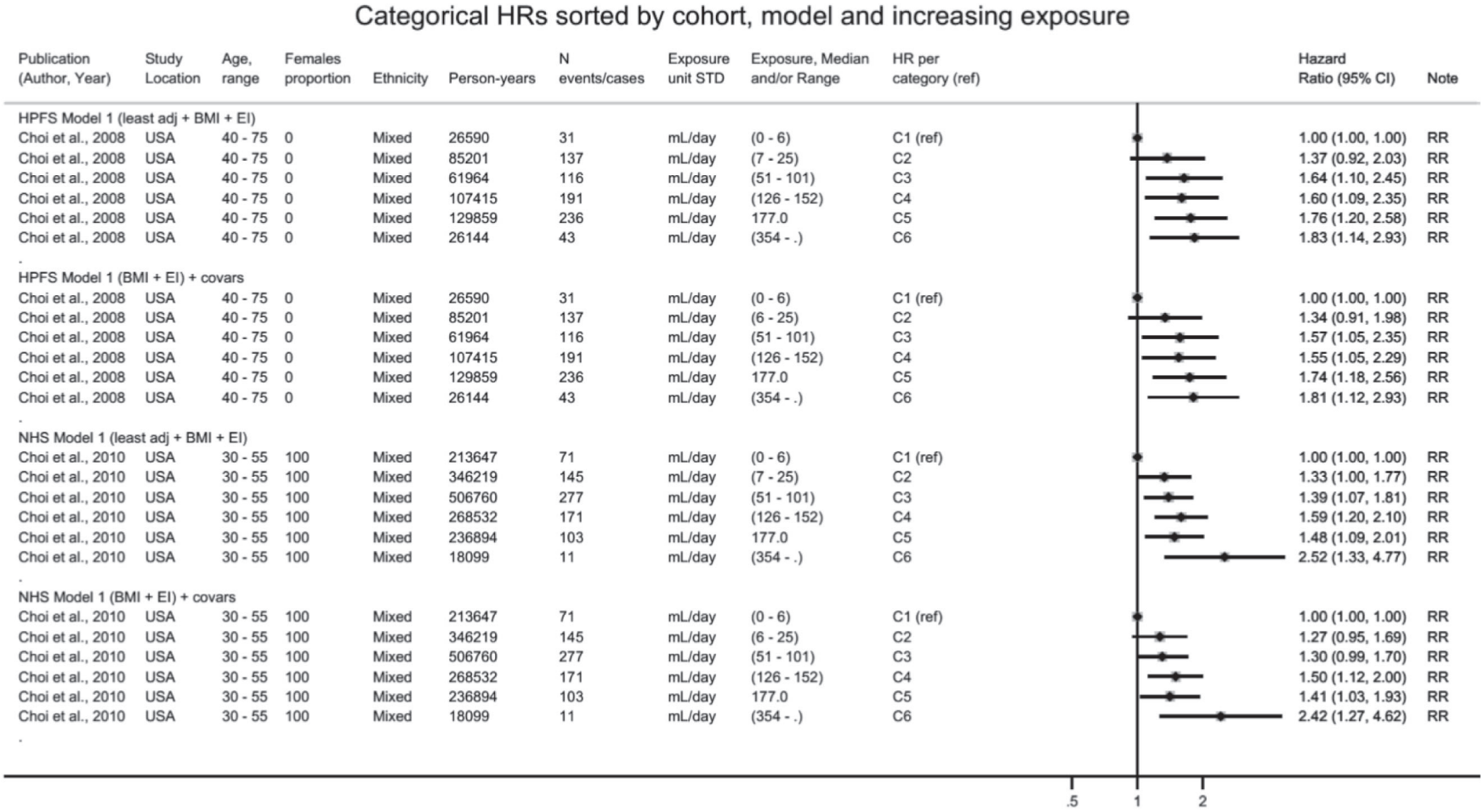
Note: RR= Rate ratio.

Figure K.18b: Free fructose and incidence of gout



Note: RR= Rate ratio

Figure K.19: SSBs and incidence of gout



Note: RR= Rate ratio

Figure K.20: Fruit juices and incidence of gout

Appendix L – Summary of risk of bias ratings for observational studies by endpoint

Table L.1a: Added and free sugars and continuous variables related to the risk of obesity and abdominal obesity

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
DONALD	BMIz	–/NR	+	++	–/NR	+	2
EPIC-Norfolk	BMI; WC	–/NR	+	++	–/NR	++	2
KoCAS	BMIz	– –	–/NR	+	–/NR	+	3
Mr and Ms OS	BW; BMI	–/NR	+	+	+	–/NR	2
NGHS	BMIz; WC	+	+	++	–/NR	+	1
NSHDS	BMI	–	+	+	–/NR	+	2
PHHP	BW	–/NR	+	+	–/NR	–/NR	2
QUALITY	BW; BMI; WC	+	+	+	–/NR	+	1

Table L.1b: Added and free sugars and measures of body fat and abdominal fat

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
DONALD	BF (%)	–/NR	+	–/NR	–/NR	+	3
KoCAS	BF (%)	– –	–/NR	– –	–/NR	+	3
Mr and Ms OS	BF (% and kg)	–/NR	+	++	+	–/NR	2
Mr and Ms OS	Central fat mass (kg)	–/NR	+	+	+	–/NR	2
QUALITY	BF (kg)	+	+	++	–/NR	+	1

Table L.2: SSBs and incidence of obesity

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
Amsterdam	–	–/NR	–/NR	–/NR	+	3
BWHS	+	+	+	+	+	1
DDHP	–	–	++	+	++	2
ELEMENT	–/NR	–/NR	++	–/NR	+	3
Generation-R	+	–/NR	++	–/NR	++	2
PHI	+	–/NR	+	–/NR	++	2

Table L.3: SSBs and incidence of abdominal obesity

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
CARDIA	+	+	++	–/NR	+	1
ELEMENT	–/NR	–/NR	++	–/NR	+	3
Girona	+	+	+	–/NR	+	1
KoGES	+	–/NR	++	–/NR	+	2
TLGS	–/NR	–/NR	–/NR	–/NR	–/NR	3

Table L.4a: SSBs and continuous variables related to the risk of obesity and abdominal obesity

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
AGAHLS	BMI	–/NR	–/NR	++	–/NR	–/NR	3
ALSPAC	BW; BMI; WC	++	+	+	+	++	1
CoSCIS	BMI	–/NR	+	+	–/NR	++	2
DCH	BW; WC; WC_{BMI}	–/NR	–/NR	–/NR	+	++	3
DONALD	BMI	–/NR	+	++	+	+	1
EPIC-Diogenes	WC_{BMI}	–/NR	–/NR	–/NR	–/NR	++	3
Framingham-3Gen	BW	+	–/NR	+	+	++	1
GUTS	BMI	–/NR	+	–/NR	+	–/NR	3
GUTSII	BMI	–/NR	+	–/NR	–/NR	++	3
HPFS	BW	+	+	+	+	++	1
HSS-DK	BW; BMIz	+	+	++	+	++	1
Inter99	BW; WC; WC_{BMI}	–/NR	–/NR	+	–/NR	++	3
MIT-GDS	BMI	–/NR	–/NR	+	+	++	2
MONICA	BW	–/NR	–/NR	+	–/NR	++	3
MOVE	BMI	–	–/NR	+	+	+	2
MTC	BW; WC	+	+	–/NR	–/NR	+	2
NGHS	BMI	–/NR	+	+	+	–/NR	2
NHS	BW	+	+	+	+	++	1
NHS II	BW	+	+	+	+	++	1
SUN	BW	+	+	–/NR	+	+	1
WAPCS	BMI	+	+	+	–/NR	+	1
WAPCS	WC	+	+	–/NR	–/NR	+	2
WHI	BW	+	+	+	–/NR	++	1

WC_{BMI} = WC regressed on BMI.

Table L.4b: SSBs and measures of body fat and abdominal fat

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
AGAHLS	BF (%)	–/NR	–/NR	++	–/NR	+	3
AGAHLS	Trunk fat (%)	–/NR	–/NR	+	–/NR	–/NR	3
ALSPAC(1)	BF (kg)	++	+	++	+	++	1
ALSPAC(2)	BF (kg)	+	+	++	–/NR	+	1
CoSCI	BF (log SFT)	–/NR	+	+	–/NR	++	2
DONALD	BF (%)	–/NR	+	–/NR	+	+	2
MIT-GDS	BF (%)	–/NR	–/NR	–	+	++	3
MOVE	BF (%)	–	–/NR	–	+	+	3

(1): Bigornia et al. (2015).
(2): Johnson et al. (2007).

Table L.5: FJs and continuous variables related to the risk of obesity

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
EPIC-DiOGenes*	WC_{BMI}	–/NR	–/NR	–/NR	–/NR	++	3
DONALD	BMI	–/NR	+	++	+	+	1
GUTS	BMIz	–/NR	+	–/NR	+	+	2
HPFS	BW	+	+	+	+	++	1
MOVE	BMI	–	–/NR	+	+	+	2
NGHS	BMI	–/NR	+	+	+	–/NR	2
NHS	BW	+	+	+	+	++	1
NHS II	BW	+	+	+	+	++	1
Project Viva	BMIz	–/NR	–/NR	++	–/NR	+	3
WHI	BW	+	+	+	–/NR	++	1

WC_{BMI} = WC regressed on BMI.

Table L.6 : Total sugars and incidence of T2DM

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
EPIC-InterAct	–/NR	+	+	–/NR	++	2
FMCHES	+	+	++	++	++	1
WHI	++	++	–/NR	NR	++	2
WHS	+	+	–/NR	+	+	1

Table L.7 : Sucrose and incidence of T2DM

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
EPIC-Norfolk	+	+	–/NR	+	++	1
FMCHES	+	+	++	++	++	1
MDCS	–	+	+	++	–/NR	2
WHS	+	+	–/NR	+	+	1

Table L.8: SSBs and incidence of T2DM

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
ARIC	+	–/NR	+	+	++	1
BWHS	+	+	–/NR	+	+	1
CARDIA	–/NR	+	++	–/NR	+	2
EPIC-InterAct	–/NR	–/NR	+	+	++	2
FMCHES	+	–/NR	++	++	–/NR	2
Framingham-Offspring	–/NR	+	+	+	++	1
HPFS	+	+	–/NR	+	++	1
JPHC	+	+	–/NR	–/NR	+	2
KoGES	–/NR	–/NR	++	–/NR	+	3
MDCS	–	–/NR	+	++	–/NR	3
NHS II	+	+	–/NR	NR	++	2
TLGS	+	–/NR	+	–/NR	–/NR	2
Toyama	+	–/NR	++	++	+	1
WHI	+	–/NR	–/NR	NR	+	3

Table L.9: FJs and incidence of T2DM

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
BWHS	+	+	–/NR	+	+	1
CARDIA	–/NR	+	++	–/NR	+	2
EPIC-InterAct	–/NR	–/NR	+	+	++	2
HPFS	+	+	–/NR	++	+	1
JPHC	+	––	–/NR	–/NR	+	3
NHS	+	+	–/NR	NR	+	2
NHS II	+	+	–/NR	NR	+	2
SUN	+	+	–/NR	–/NR	+	2
WHI	+	+	–/NR	+	+	1

Table L.10: SSBs and incidence of dyslipidaemia

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
CARDIA	–/NR	+	++	–/NR	+	2
Framingham-3Gen‡	+	–/NR	+	–/NR	++	2
Framingham-Offspring‡	+	+	+	+	++	1
KoGES	–/NR	–/NR	++	–/NR	+	3
TLGS	+	–/NR	++	–/NR	–/NR	2

‡: Study identified through an update of the literature search.

Table L.11 : SSBs and incidence of hypertension

Cohort	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
CARDIA	+	+	++	–/NR	+	1
HPFS	+	+	+	+	+	1
KoGES	++	–/NR	++	–/NR	+	2
NHS	+	+	+	+	+	1
NHS II	+	+	+	+	+	1
SUN	+	+	–/NR	+	++	1
TLGS	–/NR	–/NR	+	–/NR	–/NR	3

Table L.12 : Total sugars and incidence and/or mortality of cardiovascular diseases

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
EPIC-Multicentre‡	CHD	+	+	+	+	++	1
EPIC-Morgen	Stroke	+	+	+	+	++	1
EPICOR	Stroke	+	+	+	++	+	1
EPIC-Utrecht	CVD; Stroke	++	+	+	+	+	1
NIH-AARP	CVD	+	+	–/NR	++	+	1
SCHS	CHD	+	+	–/NR	++	++	1
Takayama‡	CVD	+	–/NR	–/NR	+	+	2
WHI	CVD; CHD; Stroke; Heart failure; CABG; PCI	++	+	–/NR	NR	++	2

‡: Study identified through an update of the literature search.

Table L.13: Fructose and incidence and/or mortality of cardiovascular diseases

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
NIH-AARP	CVD	+	+	–/NR	++	+	1
TLGS	CVD	–/NR	–/NR	–/NR	NR	–/NR	3
Takayama‡	CVD	+	–/NR	–/NR	+	+	2

‡: Study identified through an update of the literature search.

Table L.14 : SSBs and incidence and/or mortality of cardiovascular diseases

Cohort	Outcome	Confounding	Exposure	Outcome	Attrition	Other sources of bias	Tier
CTS‡	CVD; CHD; Stroke	+	–/NR	–/NR	++	++	2
CTS‡	Revascularisation	+	–/NR	+	++	++	1
EPIC-Multicentre‡	CVD; CHD; Stroke	–/NR	–/NR	–/NR	++	++	3
HPFS	Stroke	+	+	–/NR	+	++	1
HPFS‡	CVD	+	++	+	–/NR	++	1
HPP‡	CHD	+	–/NR	–/NR	++	++	2
JPHC	CHD; Stroke	+	+	–/NR	++	++	1
MDCS	CVD; CHD; Stroke	+	–/NR	+	++	++	1
NHS	Stroke	+	+	–/NR	+	++	1
NHS‡	CVD	+	++	+	–/NR	++	1
REGARDS‡	CHD	–/NR	–/NR	+	–/NR	+	3
Framingham-Offspring	Stroke	+	++	++	–/NR	+	1

‡: Study identified through an update of the literature search.

Appendix M – Observational studies on dental caries

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
Exposure: total sugars								
1	**Finnish cohort** Bernabé et al. (2016) Finland Up to 11 years Public funding	**N** = 6,335 **Population sampled:** General population **Excluded**: being edentate, lack of caries outcome in at least 2 of the three surveys (2000, 2004 and 2011), missing data on covariates. **n** = 1,702 **Sex:** 56% females **Ethnicity**: Caucasian **Age:** 30–89 years	**DMFT index increment** **DMFT index = sum of decayed, missing and filled teeth** Identical clinical oral examinations were conducted at baseline and follow-ups by dentists. The overall kappa value for inter- and intra-examiner reliability at the baseline survey was 0.87 and 0.95 at tooth level, respectively.	**SFFQ of 128 food items and mixed dishes – previous year** SFFQ only administered at baseline. Standard portion size assigned to each FFQ item and specified with natural units The **overall frequency of sugars** intake (times/day) was estimated by adding the weighted responses for 15 sugary food items The amount of sugars intake (g/day) was estimated by multiplying the food consumption frequency by fixed portion sizes. The ingredients of mixed foods were broken down into their components as well as the contents of different nutrients via	**Amount (g/day)** (mean ± SD; range) 110.9 ± 47.8; 13.7–442.3 **Frequency (times/day)** (mean ± SD; range) 3.2 ± 2.4; 0–15.6	Mean **DMFT** units (95%CI) increase from baseline **2004:** 0.47 (0.37, 0.58) **2011:** 0.74 (0.64, 0.84)	**Model 1:** crude **Model 2**: sex, age and education **Model 3:** model 2 + dental behaviours (toothbrushing frequency, dental attendance pattern and use of fluoride toothpaste) **Model 4**: model 3 + mutual adjustment for amount of sugar intake and frequency of intake, respectively	**DMFT units increment (95%CI)** **Amount, for each 10 g/day of TS intake** **Model 1** 0.06 (0.00, 0.12); **P = 0.055** **Model 2** 0.10 (0.04, 0.15); **P: < 0.001** **Model 3** 0.10 (0.04, 0.15); **P: < 0.001** **Model 4** 0.09 (0.02, 0.15); **P = 0.014** **Frequency, for each time/day** **Model 1** 0.10 (−0.0, 0.22); **P = 0.101** **Model 2** 0.14 (0.03, 0.24); **P = 0.011** **Model 3** 0.15 (0.04, 0.25); **P = 0.007** **Model 4** 0.03 (−0.10, 0.17); **P = 0.628**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
				the Finnish Food Composition Database.				**A level of intake of total sugars associated with a zero increment in the DMFT index could not be identified****
3	**VA-DLS** Kaye et al. (2015)* USA 11 ± 5 years (mean) Public funding	**N** = 687 **Population sampled**: U.S Veterans from greater Boston area **Excluded**: less than 2 teeth at first examination, no follow-up examination, no teeth with an exposed root surface, missing dietary data (baseline in 1987, end of follow-up. Examinations every 2 to 4 years) **n** = 533 **Sex:** men **Age:** 47–90 years	**Adjusted root caries increment** A single calibrated periodontist examiner performed clinical assessments. An exposed root surface was considered at risk for caries if recession was 2 mm or greater. Full-mouth intraoral radiographs were taken at	Repeated administration of an expanded self-administered 131-item **SFFQ** at each visit. Validation against two 7-day diet records administered 6 months apart.[65,66] The SFFQ was administered twice to 127 men at one-year interval. Average dietary variables were computed from all SFFQs after the first root surface was exposed until edentulism or the end of the study for	**E% (range)** **Q1**: 3.8–15.0 **Q2:** 15.1–17.9 **Q3:** 18.0–20.4 **Q4**: 20.5–36.7 **n** **Q1:** 130 **Q2:** 133 **Q3**: 134 **Q4**: 136	**Teeth with new root caries events (mean ± SD (range)):** 2.6 ± 2.9 (0–23) **Teeth with reversals:** 1.1 ± 1.5 (0–10)	**Model**: years at risk of root caries and baseline values of age, smoking status, number of teeth at risk for root caries, existing root caries/ restorations, subgingival calculus on one or more surfaces, dental prophylaxis in past year and removable denture	**Adjusted Root Caries Increment, mean (95%CI)** **Q1**: 2.60 (2.05, 3.31) **Q2:** 2.64 (2.07, 3.36) **Q3:** 2.56 (2.01, 3.27) **Q4**: 2.51 (1.98, 3.18) **P per trend NS**

[65] Rimm EB, Giovannucci EL, Stampfer MJ et al. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–1126.
[66] Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993;93:790–796.

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
			each examination. Incident root caries events were defined as decay or restorations on teeth that were previously sound and recurrent events as restorations plus decay on previously restored teeth. Root caries events recorded between each pair of examinations were adjusted for reversals.	analyses of root caries increment.				
2	**UK cohort** Rugg-Gunn et al. (1984) Rugg-Gunn et al. (1987) United Kingdom 2 year Public funding	**N** = 466 **Population sampled:** Children in their final 2 years of middle school from the area of south Northumberland **Excluded:** left the area or were absent for part of the study,	**Caries increment (continuous variable) of the following indices:** **DMFT** **DFS:** all surfaces **DFS (FS)**: pit and fissure	**5 times 3-day food diaries** (3 consecutive days) in the 2 years of the study (total of 15 days of dietary intake). All days of the week covered. Children were instructed to record all foods and beverages consumed, the	**Amount (g/day)** (mean±SD) 118 ± 29.4 ~ 21 E% **Frequency (times/day)** 6.8 ± 1.8	**Caries increment (C3) over 2 years:** (mean, 95% range) **DMFT:** 2.20 (0–7) **DFS:** 3.63 (0–12)	Model 1: crude Model 2: age, sex, gingival index, frequency of sugars intake, starch intake	**DMFS units increment (95%CI) for each 30 g/day of intake** **Model 2:** 0.36 (−0.07, 0.80) **Correlation coefficient (P value)**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
		children asked to leave the study, unreliable dietary diaries. **n** = 405 **Sex:** 52.35% females Ethnicity: Caucasian **Age:** 11.6 ± 0.3 year	**DFS (SS):** free smooth **DFS (AP):** approximal Dental examination at baseline, 1 and 2 years by the same examiner plus radiographs. Visual caries-examining system used to record one pre-cavitation grade (C1) and one cavitation grade (C3). The radiographic grading X1 (enamel only) corresponded to C1 and X2 (at enamel-dentine junction) corresponded to C3. A bilateral recording system was used in	amounts and the time of the day in which these were consumed. Interview the day of completion to check quantities and uncertainties. Food models and graduated cups used for quantification of the amount. Reliability of the measurement of total dietary sugars found to be 0.78[67]		**DFS (FS):** 2.10 (−1, 7) **DFS (SS):** 0.24 (0, 2) **DFS (AP):** 1.34 (0, 6) **Percentage of total carious surfaces** **DFS (FS):** 57 **DFS (SS):** 7 **DFS (AP):** 36		**Model 1:** **DMFT:** 0.077 **(NS)** **DFS:** 0. 105 **(P < 0.05)** **DFS (FS):** 0.143 **(P < 0.01)** **DFS (SS):** −0.01 **(NS)** **DFS (AP):** 0.042 **(NS)** **Model 2:** **DMFT: NR** **DFS:** 0. 082 **(NS)** **DFS (FS):** 0.142 **(P < 0.01)** **DFS (SS):** 0.023 **(NS)** **DFS (AP):** −0.010 **(NS)**

[67] Hackett A. F., Rugg-Gunn A. J. and Appleton D. R. (I 983) The use of a dietary diary and interview to estimate the food intake of children. Hum. Nutr. Appl. Nutr. 37A, 293–300.

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
			which 71% of teeth were assessed. The reliability of the measurement of dental caries was not assessed; 'previously found to be 0.85 for similar data'[68]					
1	**Michigan cohort** Burt et al. (1988) Burt and Szpunar (1994) Szpunar et al. (1995) USA 3 years Non-fluoridated area Funding source NR	N = 747 **Population sampled:** General population from three towns with non-fluoridated water supply **Excluded:** completed less than 3 dietary interviews, were not present for baseline and/or final dental examinations **Follow-up rate:** 66.8% **n** = 499	**Caries increment (dichotomous; none/some) of the following indices:** **DMFS:** all surfaces **DMFS (AP):** approximal **DMFS (FS)**: pit and fissure Teeth were dried before examination, transillumination used and caries	**3 times 2 24-h diet recalls** (as dietary interviews) administered for the previous day. Included weekdays and weekends and covered seasonal variations during the study period. Models provided to assess quantities Intake data from all the interviews for the same child over the 3-year follow-up was averaged.	**Amount (E%)** (mean ± SD) 26.7 ± 5.0 **Mean** Q1: 23.5 Q4: 29.5 **n** Q1: 125 Q4: 125 **Amount (g/day)** (mean ± SD) 142.90 ± 43.42 **Mean** Q1: 108.9 Q4: 175.0	**Number of subjects with 0 caries increment/> 0 caries increment** **DMFS:** 119/310 **DMFS (AP):** 336/93 **DMFS (FS):**130/299 **Number of subjects with > 0 caries increment (%)** **DMFS:** Q1: 76 (61.3)	**Model 1:** age and baseline DMFS **Mode 2:** sex, age, history of previous residence in a fluoridated community, use of fluoride tablets, frequency of topical fluorides, toothbrushing frequency, antibiotic use, parental	**Model 1** **RR (95%CI) Q4 vs. Q1 (E%)** **DMFS:** 1.22 (1.04, 1.46) **DMFS (AP)**: 1.80 (1.06, 3.10) **DMFS (FS)**: 1.19 (0.99, 1.43) **Model 2** **Correlation coefficient (P value)** **Amount (E%)** **DMFS:** 0.062 **(P < 0.01)** **DMFS (AP):** 0.055 **(P < 0.03)** **DMFS (FS):** 0.044 **(P < 0.05)**

[68] Rugg-Gunn AJ, 1972b. Reliability and Partial Recording in Caries Incremental Studies, pp. 84–93. PhD. thesis, Manchester University, Manchester.

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
		Sex: 47.9% females **Age:** 10–15 year	diagnosed only when a break in surface enamel was evident. Examiners saw the same children at both examinations (baseline and end of the study), and radiographs were not exposed for ethical reasons. Because these examiners had standardised their diagnoses and had worked together on many studies, their data were pooled, and their inter-examiner replicate examinations were conducted.		**Frequency (times/day)** (mean ± SD) **4.3** ± 0.6	Q4: 94 (75.2) **DMFS (AP):** Q1: 17 (13.7) Q4: 31 (24.8) **DMFS (FS):** Q1: 74 (59.2) Q4: 89 (71.2) **Caries increment (continuous) over 3 years** (mean ± SD) **DMFS:** 4.30 ± 3.47 **DMFS (AP):** 2.44 ± 2.33 **DMFS (FS):** 3.64 ± 2.71	education, family income	**Amount (g/day)** **DMFS:** 0.007 **(P < 0.02)** **DMFS (AP):** 0.003 **(P = 0.26)** **DMFS (FS):** 0.004 **(P = 0.15)** **Frequency (times/day)** **DMFS:** 0.108 **(P = 0.53)** **DMFS (AP)**: 0.093 **(P = 0.63)** **DMFS (FS)**: −0.042 **(P = 0.80)**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
2	**IFS*** Chankanka et al. (2011) USA 4 years Public funding	N = 608 **Population sampled**: General population **Excluded:** less than 2 food diaries between 5 and 8 years of age, missing covariates **n** = 198 **Sex**: 55% females **Ethnicity**: 94% Caucasian, 6% Other **Age:** 5-9 year	**Caries increment (continuous variable) over 4 years** (surfaces with transition from missing or sound to non-cavitated caries, cavitated caries or fillings). Clinical examinations for dental caries were conducted at 5 (primary dentition) and 9 (mixed dentition) years of age by the same trained and calibrated examiners. Examiners did not differentiate cavitated enamel (D2/d2) and dentine lesions (D3-4/d3-4), thus those lesions were	**3-day food diaries** (2 weekdays, 1 weekend day) were obtained every 1.5–6 months during the study period. Intakes were averaged for each child to reflect sugar intakes from 5 to 8 years of age.	**Amount (g/day)** (mean ± SD; range) 114.5 ± 27.3; 53.2, 216.0 **n** = 192 in analyses	**Caries increment (continuous) over 4 years** (mean ± SD) 1.63 ± 2.35	**Model:** Age at medical exam for mixed dentition (follow-up), time interval between exams for primary (baseline) and mixed dentition, sex, surfaces with non-cavitated or cavitated caries or filling at age 5 years, brushing frequency, water fluoride concentration	**Any surfaces with new non-cavitated or cavitated caries or filling (age 5–9)** **Per each 10 g/day increase, OR (95%CI)** 0.93 (0.83, 1.04) **Surfaces with new non-cavitated or cavitated caries or filling (counts, age 5–9)** **Per each 10 g/day increase, OR (95%CI)** 0.97 (0.91, 1.04)

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
			categorised together as D2-3/d2-3.					
Exposure: total sucrose								
2	**STRIP-1** Ruottinen et al. (2004) Finland 9 years Funding source NR Fluoride concentration in drinking water = 0.3 ppm	**N** = 1,066 **Population sampled:** Children attending well-baby clinics of the city of Turku, where the fluoride concentration in drinking water is 0.3 ppm **Excluded:** refusal to participate in the dental caries examination at 10 year, type 1 diabetes or other diseases that may affect sucrose intake (unspecified) **Selected:** children in the 5th highest and lowest percentile of sucrose intake **n** = 66 G1: 33 G2: 33 **Sex:** 31% females **Ethnicity**: Caucasian	**$d_3$mft, $d_3$mft+ D_3MFT and D_3MFT scores** Dental visit at 10 years of age by the same expert, blinded to the exposure. Caries recorded at the level of cavitation and expressed as $d_3$mft+/D_3MFT scores according to WHO (1997). Recordings from visual inspection were completed with radiographic findings (two intra-oral radiographs taken and evaluated by two independent experts in a	**3-day food records** (at 13 months) and 4-day food records (thereafter every 6 months until 7 years of age, every 2 years thereafter in the intervention group and every year in the control group until 10 years of age. Records included one weekend day and were reviewed by nutritionist at next visit. Sucrose intake frequency was assessed at 10 years (***cross-sectional analysis only, data not extracted***)	**E%** Age 13 mo G1: 2.92 ± 1.73 G2: 7 ± 2.9 Age 10 year G1: 7.29 ± 3.39 G2: 11.92 ± 2.76 **g/day** Age 13 mo G1: 7.1 ± 4.7 G2: 16.6 ± 7.4 Age 10 year G1: 32.5 ± 18.4 G2: 52.6 ± 13.1	-	**None** Authors state that the association between sugar intake and caries was tight in all tooth-brushing frequency groups (sub-group analysis), but failed to reach significance because of the small number of children in each group	**$d_3$mft** G1: 1.1 ± 1.2 G2: 2.7 ± 3.3 **P = 0.177** **$d_3$mft+D_3MFT** G1: 0.5 ± 1.1 G2: 1.9 ± 2.5 **P = 0.032** **D_3MFT** G1: 1.4 ± 2.0 G2: 3.9 ± 3.9 **P = 0.01**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
		Age: 13 months	random order and blinded to the exposure)					
2	**STRIP-2*** Karjalainen et al. (2001) Karjalainen et al. (2015) Finland 13 years Funding source NR Fluoride concentration in drinking water = 0.3 ppm	**N** = 1,066 **Population sampled:** Children attending well-baby clinics of the city of Turku, where the fluoride concentration in drinking water is 0.3 ppm Every fifth child was invited (n = 178) to the dental health study at 3 years of age and attended **n** = 142 Follow-up rate at 16 year: 55.6% **Sex:** 45.8% females **Ethnicity**: Caucasian **Age:** 3 years	**$d_3$mft/D_3MFT scores** Dental visits at 3, 6, 9, 12 and 16 years of age by the same expert, blinded to the exposure. Caries recorded at the level of cavitation and expressed as $d_3$mft+/D_3MFT scores according to WHO (1997). At 16 years, recordings from visual inspection were completed with radiographic findings (two intra-oral radiographs taken and evaluated by two independent experts in a random order	**4-day food records** at 3, 6, 9, 12 and 16 years of age. Records included one weekend day and were reviewed by nutritionist at next visit.	**g/day (median, range)** **3 years** **Q1 (ref)**: 15.9 (7.4, 20.9) **Q2:** 23.1 (21.0, 25.4) **Q3:** 29.6 (25.6, 34.4) **Q4**: 44.0 (34.5, 65.9) **n** = 128 in analyses **12 years** **Q1 (ref)**: 19.4 (7.1, 25.7) **Q2:** 29.4 (26.4, 33.9) **Q3:** 38.36 (34.3, 42.5.4) **Q4**: 56.0 (43.7, 78.8) **n** = 81 in analyses	**$d_3$mft increment (3–6 years)** (mean ± SD) 0.82 ± 1.89 **D_3MFT increment (12–16 years)** (mean ± SD) 2.14 ± 2.47 **Proportion of counts > 0 (mean ± SD)** Any new $d_3$mft (3–6 years) 0.23 ± 0.42 Any new D_3MFT (12–16 years) 0.68 ± 0.47	**Model:** sex, STRIP study group, caries-free age and daily toothbrushing	**$d_3$mft increment between 3 and at 6 years (yes/no)** **Per each 10 g/day increase** 1.64 (1.13, 2.37) **OR (95%CI)** **Q1 (ref)**: 1 **Q2:** 1.03 (0.26, 4.01) **Q3:** 0.91 (0.63, 3.54) **Q4**: 4.32 (1.31, 14.25) **$d_3$mft increment between 3 and at 6 years (counts)** **Per each 10 g/day increase** 1.21 (0.91, 1.61) **OR (95%CI)** **Q1 (ref)**: 1 **Q2:** 0.59 (0.17, 2.05) **Q3:** 0.66 (0.23, 1.91) **Q4**: 1.54 (0.61, 3.89) **D_3MFT increment between 12 and at 16 years (yes/no)**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
			and blinded to the exposure)					**Per each 10 g/day increase** 0.95 (0.68, 1.34) **OR (95%CI)** **Q1 (ref)**: 1 **Q2:** 1.16 (0.30, 4.50) **Q3:** 3.16 (0.63, 15.75) **Q4**: 0.70 (0.17, 2.84) **D_3MFT increment between 12 and at 16 years (counts)** **Per each 10 g/day increase** 0.99 (0.84, 1.18) **OR (95%CI)** **Q1 (ref)**: 1 **Q2:** 1.35 (0.66, 1.78) **Q3:** 1.29 (0.69, 2.42) **Q4**: 1.09 (0.53, 2.22)
Exposure: SSSD								
2	**VA-DLS** Kaye et al. (2015)* USA mean 11 ± 5 years, range 2.5–19.6 years Public funding?	**Same population and exclusion criteria as for total sugars**	**Same ascertainment of outcome as for total sugars**	**Same exposure assessment as for total sugars**	**Servings/wk (median, range)** **Q1**: 0, 0–0.09 **Q2:** 0.34, 0.11–0.84 **Q3:** 1.52, 0.85–2.35 **Q4**: 4.20, 2.36–24.8	**Same as for total sugars**	**Model**: years at risk of root caries and baseline values of age, smoking status, number of teeth at risk for root caries, existing root caries/ restorations,	**Adjusted Root Caries Increment, mean (95%CI)** **Q1**: 2.17 (1.68–2.79) **Q2:** 2.64 (2.06–3.37) **Q3:** 2.57 (2.01–3.29) **Q4**: 2.86 (2.28–3.60) **P per trend < 0.05**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
					Serving size = 12 oz (335 mL) **n** **Q1**: 118 **Q2**: 148 **Q3**: 133 **Q4**: 134		subgingival calculus on one or more surfaces, prophylaxis in past year and removable denture	
2	**IFS** (Chankanka et al., 2011) USA Public funding	**Same population and exclusion criteria as for total sugars**	**Same ascertainment of outcome as for total sugars**	**Same exposure assessment as for total sugars**	**Amount (mL/day)** (mean ± SD; range) 272 ± 175; 0, 1,079	**Same as for total sugars**	**Model:** Age at medical exam for mixed dentition (follow-up), time interval between exams for primary (baseline) and mixed dentition, sex, surfaces with non-cavitated or cavitated caries or filling at age 5 years, brushing frequency, water fluoride concentration	**Any surfaces with new non-cavitated or cavitated caries or filling (age 5–9)** **Per each 100 mL/day increase, OR (95%CI)** 1.01 (0.85, 1.21) **Surfaces with new non-cavitated or cavitated caries or filling (counts, age 5–9)** **Per each 100 mL/day increase, OR (95%CI)** 1.01 (0.88, 1.17)
Exposure: FJs								
2	**IFS** Chankanka et al. (2011)	**Same population and exclusion criteria as for total sugars**	**Same ascertainment of outcome as**	**Same exposure assessment as for total sugars**	**Amount (mL/day)** (mean ± SD; range)	**Same as for total sugars**	**Model:** Age at medical exam for mixed dentition (follow-	**Any surfaces with new non-cavitated or cavitated caries or filling (age 5–9)**

RoB Tier	Cohort References Country Follow-up Funding	Population (recruited) Exclusion criteria Study population (n, sex and age at baseline)	Outcome Ascertainment of outcome	Exposure assessment, time coverage and validation	Exposure groups n/person-years	Outcome measure	Model covariates	Results
	USA Public funding		**for total sugars**		**87** ± 79; 0, 525		up), time interval between exams for primary (baseline) and mixed dentition, sex, surfaces with non-cavitated or cavitated caries or filling at age 5 years, brushing frequency, water fluoride concentration	**Per each 100 mL/day increase, OR (95%CI)** 0.83 (0.55, 1.26) **Surfaces with new non-cavitated or cavitated caries or filling (counts, age 5–9)** **Per each 100 mL/day increase, OR (95%CI)** 0.96 (0.75, 1.24)

D3MFT, decayed into dentine, missing and filled permanent teeth; d3mft, decayed into dentine, missing and filled primary teeth; DFS: decayed, filled surfaces; DFS (AP), approximal surfaces; DFS (FS), pit and fissure surfaces; DFS (SS), free smooth surfaces; DMFS: decayed, missing and filled surfaces; DMFT: decayed, missing and filled permanent teeth; dmft: decayed, missing and filled primary teeth; FFQ, food frequency questionnaire; FJ, fruit juice; SFFQ, semiquantitative food frequency questionnaire; SSSD, sugar-sweetened soft drinks.
*: Individual data provided by the authors.
**: Information provided by the authors.

List of Annexes

These Annexes can be found in the online version of this output, under the section 'Supporting information', at: https://doi.org/10.2903/j.efsa.2022.7074

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Annex G – Additional information requested at full-text screening and data extraction and decisions taken for the assessment

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Annex N – Statistical analysis of observational studies on dental caries

Annex O – Technical report: outcome of the public consultation on the draft Scientific opinion on the Tolerable Upper Intake Level for dietary sugars