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REVIEW ARTICLE

Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review

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Abstract

The effects of both the amount and quality of dietary fat have been studied intensively during the past decades. Previously, low-fat diets were recommended without much attention to the quality of fat, whereas there is general emphasis on the quality of fat in current guidelines. The objective of this systematic review (SR) was to assess the evidence of an effect of the amount and type of dietary fat on body weight (BW), risk factors, and risk of non-communicable diseases, that is, type 2 diabetes (T2DM), cardiovascular diseases (CVD), and cancer in healthy subjects or subjects at risk for these diseases. This work was performed in the process of updating the fourth edition of the Nordic Nutrition Recommendations from 2004. The literature search was performed in October 2010 covering articles published since January 2000. A complementary search was done in February 2012 covering literature until December 2011. Two authors independently selected articles for inclusion from a total of about 16,000 abstracts according to predefined criteria. Randomized controlled trials (RCT) and prospective cohort studies (PCS) were included as well as nested case–control studies. A few retrospective case–control studies were also included when limited or no data were available from other study types. Altogether 607 articles were quality graded and the observed effects in these papers were summarized. *Convincing* evidence was found that partial replacement of saturated fat (SFA) with polyunsaturated fat (PUFA) or monounsaturated fat (MUFA) lowers fasting serum/plasma total and LDL cholesterol concentrations. The evidence was *probable* for a decreasing effect of fish oil on concentration of serum/plasma total triglycerides as compared with MUFA. Beneficial effect of MUFA both on insulin sensitivity and fasting plasma/serum insulin concentration was considered as *probable* in comparisons of MUFA and carbohydrates versus SFA, whereas no effect was found on fasting glucose concentration in these comparisons. There was *probable* evidence for a moderate direct association between total fat intake and BW. Furthermore, there was *convincing* evidence that partial replacement of SFA with PUFA decreases the risk of CVD, especially in men. This finding was supported by an association with biomarkers of PUFA intake; the evidence of a beneficial effect of dietary total PUFA, n-6 PUFA, and linoleic acid (LA) on CVD mortality was *limited suggestive*. Evidence for a direct association between total fat intake and risk of T2DM was *inconclusive*, whereas there was *limited-suggestive* evidence from biomarker studies that LA is inversely associated with the risk of T2DM. However, there was *limited-suggestive* evidence in biomarker studies that odd-chain SFA found in milk fat and fish may be inversely related to T2DM, but these associations have not been supported by controlled studies. The evidence for an association between dietary n-3 PUFA and T2DM was *inconclusive*. Evidence for effects of fat on major types of cancer was *inconclusive* regarding both the amount and quality of dietary fat, except for prostate cancer where there was *limited-suggestive* evidence for an inverse association with intake of ALA and for ovarian cancer for which there was *limited-suggestive* evidence for a positive association with intake of SFA. This SR reviewed a large number of studies focusing on several different health outcomes. The time period covered by the search may not have allowed obtaining the full picture of the evidence in all areas covered by this SR. However, several SRs and meta-analyses that covered studies published before year 2000 were evaluated,

which adds confidence to the results. Many of the investigated questions remain unresolved, mainly because of few studies on certain outcomes, conflicting results from studies, and lack of high quality–controlled studies. There is thus an evident need of highly controlled RCT and PCS with sufficient number of subjects and long enough duration, specifically regarding the effects of the amount and quality of dietary fat on insulin sensitivity, T2DM, low-grade inflammation, and blood pressure. New metabolic and other potential risk markers and utilization of new methodology in the area of lipid metabolism may provide new insight.

Keywords: *body weight*; *cancer*; *cardiovascular disease*; *fat*; *fatty acid*; *diet*; *vegetable oil*; *stroke*; *type 2 diabetes*

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The role of dietary fat in health has been under intensive research and debate during the past decades. In some countries, for example, in Finland, there has been a dramatic decline in coronary heart disease (CHD) mortality along with decreased intake of fat, in particular saturated fat (SFA) (1). Low-fat diets have previously been recommended by some official bodies without much attention to the quality of fat, whereas current guidelines generally put more emphasis on the quality of fat (2–4). The quality of fat is generally specified by the relative content of SFA, monounsaturated (MUFA), and polyunsaturated fatty acids (PUFA) including the proportion or amount of essential fatty acids, that is, linoleic acid (LA) and α-linolenic acid (ALA), as well as the proportion or amount of long-chain n-3 fatty acids (n-3 LCPUFA), that is, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

In many observational studies, the total amount of dietary fat has been shown to have only a minor, and in most studies even no effect on the risk of lifestyle diseases, for example, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and cancer or the level of the risk factors of these diseases, or markers of the cardiometabolic syndrome, including abdominal adiposity, blood pressure (BP), serum lipid profile, and measures of insulin sensitivity (2). On the contrary, the quality of fat has been shown to have a significant effect on serum lipid profile and BP as well as endothelial function and low-grade inflammation and has furthermore, been shown to affect the risk of CVD either in itself or as an important component of a health promoting diet (2, 5–9).

The objective of this systematic review (SR) was to assess the effect and grade of the evidence of the amount and type of dietary fat as well as biomarkers of the quality of dietary fat on risk factors, body weight (BW), and risk of non-communicable diseases, that is, T2DM, CVD (including CHD and stroke), and cancer. This work was performed in the process of updating the fourth edition of the Nordic Nutrition Recommendations (NNR) from 2004 (10).

Methods

Research questions

The research questions were:

1. What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other energy-giving nutrients, on
   a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations, BP, and markers of low-grade inflammation?
   b. clinical outcomes including BW, T2DM, CVD, cancer, and all-cause mortality?
2. What is the association between the biomarkers of the quality of dietary fat and the above-mentioned outcomes (namely a and b).

Birth outcomes, growth and development, and maintenance of body functions were included in the systematic literature search as well, but these topics were transferred to the expert groups of pregnancy and lactation, and children and the elderly and are not included in this review. Studies assessing the effect of minor dietary fat components such as trans-fatty acids (TFA), conjugated linoleic acid (CLA), or dietary cholesterol were not included in this SR and neither were studies assessing the effect of dietary fat intake on postprandial lipemia.

Inclusion criteria

The a *priori* defined inclusion criteria were as follows:

1. Publication year: January 2000–October 2010 (first search), until February 2012 in the complementary search. A few papers were identified through reference lists. Relevant SRs published after searches were also evaluated.
2. Publication type: Only original articles, for research questions 1b and 2b also SRs.

3. Study design: Randomized controlled trials (RCT), prospective cohort studies (PCS), and nested case–control studies (NCC). Retrospective case–control studies (RCC) were included only if data were not available from other study types or there were only very few studies available. Cross-sectional studies and animal studies were excluded.
4. Subjects: Aged 18–70. Healthy, that is, disease-free subjects at baseline, but subjects with dyslipidemia, glucose intolerance, or overweight (mean body mass index (BMI) of the study population not exceeding 30 kg/m^2) were included. Studies without Caucasians or Caucasians as clear minority were excluded.
5. Number of participants for RCTs: ≥ 10 in cross-over studies, and per group in studies with parallel design.
6. Intervention/exposure: The amount and/or quality of dietary fat.
7. Dietary assessment methods: food record, food frequency questionnaire (FFQ), dietary recall, or valid biomarkers.
8. Nutrient database used: Updated and relevant to the country where the study was performed.
9. Length of the study: Minimum of 4 weeks in RCTs except in studies on BW and body composition where a minimum of 6 months was required. PCS had to have a follow-up of >4 years whereas studies on cancer had to have a follow-up of >5 years in.
10. Dropout rate in RCTs: $<30\%$ in 6 months, $<40\%$ in 12 months, $<50\%$ in 24 months.

Search methods and terms

The search strategy is presented in Appendix 1. The literature search was performed by an independent librarian. The first search was run in October 2010 by the PubMed platform supplied by the United States National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed). An additional search for papers on inflammatory markers as well as papers of relevance for research questions 1a and 1b was committed in January–February 2012. Finally, a complementary search was performed in order to include the most recent articles (published before December 31, 2012) to see whether there is a need to reformulate the conclusions made based on the first search and the additional search. SweMed/SweMed+ databases, supplied by the Karolinska Institute in Sweden (http://micr.kib.ki.se/), were also included in the complementary search. Few additional papers found in the complementary search were included in the quality grading because a small number of studies on the specific issue.

Selection of articles

The list of abstracts for each research question was evaluated independently by two experts. In case at least one of the experts found the abstract eligible, the article was ordered in full text. If additional potential relevant papers were identified after going through the literature lists, abstracts, and full-text papers, these were ordered in full text and reviewed by two independent experts. The experts jointly decided which articles to include. Only the papers, which both experts found ineligible after the full-text review, were excluded before the quality assessment, and all these are listed in Appendix 2 with reasons for exclusion.

Quality assessment and grading of evidence

The included full-text papers were quality assessed independently by two experts using individual quality assessment tools (QAT) for RCT, PCS, or RCC (see SLR Guidelines on the homepage of the fifth Nordic Nutrition Recommendation (NNR5, www.nnr5.org). SRs were included in the research questions 2a and 2b and they were quality assessed by a specific QAT. The QATs included a number of questions regarding several aspects of the study including study design, population characteristics, exposure measure, and outcome measures (NNR5 SLR Guide, www.nnr5.org).

The quality was assessed for all included studies in categories from A to C: A (a high-quality study with very low risk of bias), B (good-quality study, some bias, but not enough to invalidate the results), and C (low-quality study, significant bias and weaknesses which may invalidate the results). The quality assessment was cross-checked with the two assessors and potential disagreement was discussed within the group. Papers graded as A or B were included in the evidence tables (Appendices 3–6), where the results were arranged according to the intervention/exposure and the outcome. The results of the quality assessment of the individual studies were summarized to evaluate the quality and strength of the overall evidence in relation to the posed research questions (Tables 1–4). The evidence for each exposure–outcome association was categorized according to the directions given by the NNR5 committee guidelines into four categories: *convincing (high)*, *probable (moderate)*, *limited-suggestive (low)*, and *limited-no conclusion (insufficient)*.

Results

In total, 8,398 abstracts from the first search, 6,111 from the additional search, and 1,409 from the complementary search were screened for eligibility (Fig. 1), of which 733 were on birth outcomes, growth and development, and maintenance of body functions. Full-text papers of potential relevance for the research questions in this review were ordered for 704 of the abstracts. In addition, 89 papers from other sources were included. Altogether 151 papers were found ineligible after thorough examination, and 35 were for birth outcomes, growth, development and maintenance of body functions, and not

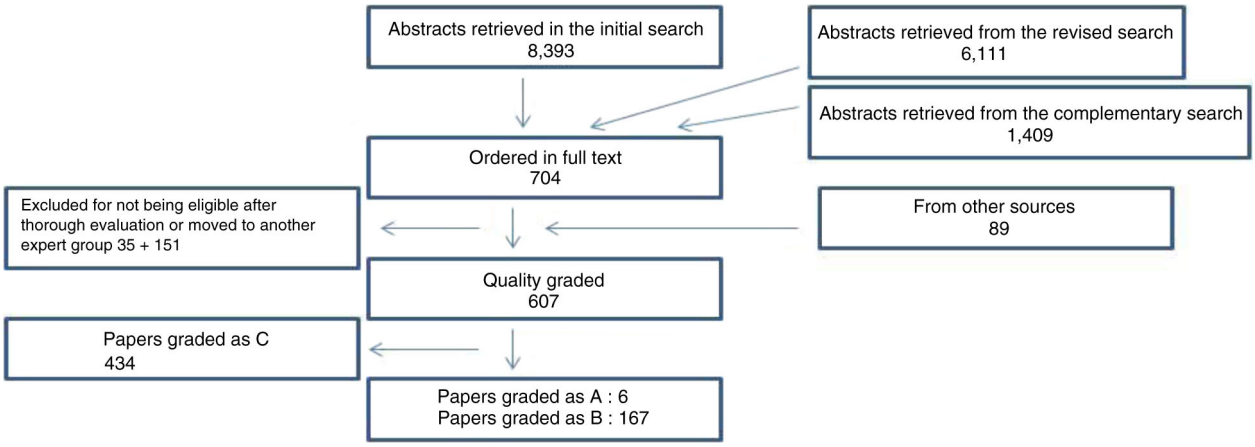

Fig. 1. Flow chart.

included in this review. In total, 607 articles were included in the quality grading.

The reasons for exclusion of papers before the quality assessment were: 1) the aim of the study was out of the scope of the research questions; 2) the studied exposure was a food pattern or a whole food, e.g. almods or fish. 3) the study design was not in accordance with the inclusion criteria, for example, uncontrolled intervention or non-randomized study; 4) there were too few subjects or the subjects were non-healthy or obese or only from a non-Caucasian population; 5) the duration of the study was too short; or 6) there were no data on nutrient composition.

The results of all 607 quality-assessed studies are presented in evidence tables in Appendices 3–6. The combined results, that is, a summary of the graded evidence are presented in Appendices 7–10. In general, there were very few studies which were quality graded as A and the most of the papers were graded as B or C (Fig. 1). The most frequent reasons for not meeting grade A were lack of valid biomarkers for measuring compliance to the dietary exposure, for example, fatty acid composition of serum/plasma lipids, lack of power calculations, problems in the quality of randomization and blinding, lack of a clear compliance reporting, and lack of reporting of the food composition database. A limiting factor for many of the PCS was that only one baseline dietary assessment was available and that the response rate was low or not stated. Multiple testing was also quite common in the PCS.

Almost all of the included studies for research question 1a were RCTs – only one was a PCS. Studies graded as C were not tabulated because of abundance in B-graded studies. Most studies in research question 1b were PCS (except for the studies on BW which were mainly RCT). In addition to studies graded as A or B, studies graded as C were tabulated for certain of the outcomes in research question 1b because of the low number of studies (e.g. certain types of cancer). For research questions 2a and 2b, only PCS were included, including NCC and other prospective case-cohort studies, but RCC studies were not included. All of the studies included for research question 2a and 2b were graded as B.

Plasma or serum lipid profile

This SR includes altogether 45 studies on the intake of dietary fat – both total amount and quality – and serum or plasma lipid profile (Appendix 3, Table 1a), and the overall evidence from these studies is summarized in Appendix 7, Table 1a. The specific evidence regarding effects of amounts and types of fat on apolipoprotein concentrations, apoB and apoA-I, are not given in detail because these data in general follow the data of LDL and HDL cholesterol concentrations (LDL-C and HDL-C), respectively. Furthermore, these variables are not generally used in clinical work to assess the risk of CVD.

MUFA and/or PUFA versus SFA. There were nine studies with randomized comparisons of unsaturated fat (MUFA and/or PUFA) versus SFA (11–19). One of these studies was a comparison of margarine versus butter (12), the others were comparisons between fatty acid classes. The proportion of SFA in these studies was roughly 13–19% of energy (E%) in the SFA diet and MUFA 14–21 E% in the unsaturated fat–enriched diet. There were two studies in which SFA and PUFA were compared. The proportion of SFA was about 20 E% or 52% of the total fat in the SFA diet and the proportion of PFA was about 9 E% or 41% of total fat in the PUFA diet (14, 17). All of these nine studies found that fasting plasma/serum cholesterol concentration was lower after a diet rich in MUFA and/or PUFA compared with a diet rich in SFA. The evidence was, therefore, considered as *convincing*. The evidence was also considered as *convincing* regarding the effect of MUFA and/or PUFA versus SFA on plasma/serum LDL-C concentration, because eight out of nine studies found that diets rich in unsaturated fatty acids resulted in lower concentrations as compared with diets

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rich in SFA. In one study, the difference between the diet periods was not significant (15). The overall evidence for the effect of MUFA and/or PUFA versus SFA on HDL-C was categorized as *limited-no conclusion*, as diets rich in MUFA and/or PUFA as compared with a diet rich in SFA were found to result in lower plasma/serum HDL-C concentration in three studies, higher concentration in one study, and no difference between the diets in five studies. Fasting plasma/serum triglyceride (TAG) concentration was examined in eight of the nine studies. A diet rich in MUFA and/or PUFA was found to result in lower concentration in two studies, whereas six studies showed no difference between the diets – thus association is *unlikely*.

MUFA and/or PUFA versus CHO. Seven of the included studies compared diets enriched in MUFA (five studies) or both MUFA and PUFA (two studies) with diets rich in carbohydrates (CHO) with respect to effects on concentrations of plasma/serum total cholesterol, LDL-C and HDL-C, and total TAG (MUFA: (20–24); both MUFA and PUFA: (25, 26)) and one study that only assessed the effect of MUFA on TAG concentrations (27). The mean proportion of dietary CHO in these studies ranged from 50 to 58 E% and that of MUFA from 20 to 25 E%. One of the studies used an overall energy-restricted diet (6,000 kJ), which supplied with 35 or 12 E% of fat of which 20 versus 4 E% was provided by MUFA (21). In five of the studies, plasma/serum total cholesterol concentration did not differ between the diets, whereas in one study it was found to be lower in a diet rich in unsaturated fat (25) and in one study in a diet rich in CHO (21). The concentration of plasma/serum LDL-C did not differ between the diets in any of the seven studies, whereas HDL-C was lower in a CHO diet in three studies (21, 23, 25). The four other studies showed no difference between the diets. Plasma/serum total TAG concentration was lower in a diet rich in MUFA and/or PUFA in three studies (20, 23, 25), whereas no difference between the diets was observed in the other five studies. The evidence was considered as *unlikely* regarding LDL-C concentration and *limited-no conclusion* for concentrations of serum/plasma total cholesterol, HDL-C and TAG.

Fish oil/n-3 LCPUFA versus MUFA. The effect of fish oil supplementation, that is, n-3 LCPUFA, on serum lipid profile was compared with MUFA (olive oil) in seven studies (28–34). One of these studies (28) did not report effects on plasma/serum total cholesterol concentration. Three of these studies specifically compared the effect of DHA with MUFA (29, 30, 34). The amount of n-3 LCPUFA given in the studies ranged from 0.7 to 6 g/day. In the KANWU study (31), diets enriched either in SFA or MUFA were supplemented with fish oil 3.6 g/day or placebo (olive oil).

Intake of n-3 LCPUFA was found to result in higher plasma/serum total cholesterol concentration in two studies with 2.1 g/day DHA + DPA (32) or 0.7 g/day DHA (34). No difference was observed in four studies; two studies with 3 or 4 g/day of both EPA or DHA (29, 30), one with 3.6 g/day fish oil (31), and one with a dose–response of EPA + DHA from 0.45 to 1.8 g/day (33).

The effect of n-3 LCPUFA on plasma/serum LDL-C concentration was reported in seven studies. In two studies it was found to be higher after the intake of fish oil of 3.6 g/day or 6 g/day (28, 31). Three studies examined the effect of DHA versus MUFA (29, 32, 34) and found higher LDL-C concentration after DHA; in two studies with an intake of DHA of either 4 or 0.7 g/day, respectively (29, 34), and one study with an intake of 1.5 g/day DHA + 0.6 g/day of DPA (32). In the study with either 3 g/day of EPA or DHA there was no difference between the groups – neither between the n-3 LCPUFA nor as compared with MUFA (30). In a study by Sanders et al. (33), combined doses of 0.45 g, 0.9 g, or 1.8 g per day of EPA and DHA with an EPA-to-DHA ratio of 1.51 did not find any difference compared with MUFA.

In five studies, fish oil resulted in lower TAG concentration than MUFA (28–31, 33), whereas no differences were seen in two studies that compared either DHA and DPA (32) or DHA (34) with MUFA. DHA resulted in a higher HDL-C concentration in one study (32), whereas two studies that compared DHA, EPA, and olive oil found no difference (29, 30). In the study by Theobald et al. (34), HDL-C concentration increased in subjects who received DHA during the first period of the study. In one study, fish oil resulted in higher plasma HDL-C concentration compared with MUFA (olive oil) (28), whereas no difference was found in two other studies (31, 33).

The evidence was considered as *limited-suggestive* regarding the effect of DHA versus MUFA on LDL-C concentration and *limited-no conclusion* for the effect of DHA on concentrations of TAG. The evidence regarding fish oil versus MUFA was considered as *limited-no conclusion* for the effect on concentrations of plasma/serum total cholesterol, LDL-C, and HDL-C, and as *probable* for the effect on plasma/serum TAG.

Fish oil/n-3 LCPUFA versus other PUFA. No difference on plasma/serum total cholesterol concentration was found in any of the seven studies that compared fish oil with different types of other PUFA, that is, EPA and DHA with gamma-linolenic acid (an n-6 PUFA) (35), EPA or DHA with ALA (36), fish oil with ALA (37), or PUFA rich vegetable oils (corn, soybean, evening primrose, or black currant seed oils) (38–41). LDL-C concentration was higher after a fish oil period in three studies (37, 39, 41), whereas no difference was observed in four studies (35, 36, 38, 40). In one study, fish oil of 4 g/day was found

to result in higher HDL-C concentration (39), whereas in the other six studies no effect on HDL-C concentration was found (35–38, 40, 41). Plasma TAG concentration was found to be lower in four studies (37–40), but not in the studies of Egert et al. (36), Laidlaw and Holub (35), and Tahvonen et al. (41). The effect of fish oil relative to other source of PUFA on concentrations of TAG, LDL-C, and HDL-C was considered as *limited-no conclusion.* The evidence for an effect on plasma/serum total cholesterol concentration was considered as *unlikely.*

Diet studies. When a diet according to nutrition recommendations was compared with a control diet (42, 43), a recommended diet resulted in lower plasma/serum LDL-C concentration. Total cholesterol concentration was lower in the study by Brekke et al. (42) at 2 years. There was no difference in HDL-C concentration. In a study including physical activity (43), TAG concentration was lower on a recommended diet (25 E% fat, 7 E% SFA), whereas in the study by Brekke et al. (42), no difference in TAG concentration was found between the groups.

LDL and VLDL particle size

There were seven studies in which the effect of the amount or quality of fat on LDL and VLDL particle size was studied (Appendix 3, Table 1b). The total intake of fat was not found to have an effect on LDL particle size (44). When comparing the effect of the intakes of SFA and MUFA, one study showed a favorable, that is, increased, effect of MUFA on LDL particle size (16), whereas no difference was found in one study (31). Intake of n-3 LCPUFA was also found to increase LDL particle size. This was shown in a study which compared n-3 LCPUFA from fish oil (1.6 E% n-3 PUFA) with ALA (1.2 E% n-3 PUFA) (37) or when fish oil (3 g/day) together with LA was compared with ALA or LA, of which LA was used as a control (45). ALA (1.1 E%) was found to have a favorable, that is, decreasing effect on VLDL particle size when compared with LA, that is, a low-ALA diet (0.4 E%) (46). DHA was found to result in the largest LDL particle size as compared with EPA and MUFA (olive oil) (4 g/day each) (29). The effect of LA, ALA, and n-3 LCPUFA on LDL particle size was considered as *limited-no conclusion*. The effect of the amount of fat and the effect of MUFA as compared either with SFA or EPA/DHA was considered as *limited-no conclusion* (Appendix 7, Table 1b).

Summary. There is *convincing* evidence that partial replacement of SFA with PUFA or MUFA lowers fasting total and LDL-C concentrations, and data suggest that there is no effect on TAG concentration. The evidence for HDL-C was found to be *limited-no conclusion*. The evidence of an effect of the replacement of CHO with PUFA or MUFA on plasma/serum concentrations of total cholesterol, TAG, and HDL-C was found to be *limited-no conclusion*, whereas an effect of replacing CHO with PUFA or MUFA on LDL-C concentration was considered *unlikely.* The evidence for the different effect of DHA than MUFA on LDL-C concentration was considered as *limited-suggestive* whereas the effect on concentrations of TAG was considered as *limited-no conclusion.* On the contrary, the evidence regarding fish oil/n-3 LCPUFA versus MUFA was considered as *probable* for the effect on plasma/serum TAG concentration. An effect of fish oil/n-3 LCPUFA versus MUFA on plasma/serum total cholesterol concentrations was judged as *limited-no conclusion*.

Insulin sensitivity and plasma/serum insulin and glucose concentrations

There are 11 studies included in this SR regarding the amount and quality of dietary fat on insulin sensitivity and 20 on fasting serum/plasma insulin concentrations (Appendix 3).

Insulin sensitivity

The effect of MUFA versus SFA on insulin sensitivity measured either by insulin sensitivity index SI or homeostasis model insulin resistance (HOMA-IR) was examined in four studies (11, 15, 18, 19) and the effect of PUFA versus SFA in one study (17). Insulin sensitivity was better on MUFA (MUFA 13 E% vs. 21 E%) in one study (19) and on PUFA (about 8 vs. 22 E%) in one other study (17). In three studies there was no difference.

When MUFA and CHO were compared with SFA (24, 47–49), MUFA resulted in better HOMA-IR or SI in all studies, and in one study CHO also resulted in better SI than SFA. The intake of MUFA in the MUFA diet ranged from 20 to 24 E%, and the intake of SFA in the SFA diet ranged from 15 to 23 E%. Because of small number of subjects, altogether 229 in four studies, the strength of evidence was graded as *probable* regarding the effect of MUFA versus SFA in studies in which both MUFA and CHO were compared with SFA.

When diets supplemented with fish oil or a plant source of n-3 fatty acids (ALA) were compared, no difference in SI was found (37). When added either to the diet high in MUFA or SFA, fish oil providing 2.1 g/day EPA and 1.5 g/day DHA did not have an effect on SI, first phase insulin secretion, disposition index or K_G (50).

Plasma/serum insulin concentrations

Fasting plasma/serum insulin concentration was lower on a MUFA-rich diet in two studies (47, 48), and on MUFA- and CHO-rich diets in two studies (27, 49) as compared with a SFA-rich diet. When an isocaloric replacement of MUFA (11, 15, 19) or PUFA (17) was compared with SFA, three studies showed no difference, whereas one study showed a favorable effect for MUFA (19).

In studies comparing MUFA with CHO (21, 22, 24), fish oil, with no fish oil, or ALA (37, 41, 50, 51), a recommended diet with a generally consumed diet (42) or a low-fat diet with a low-fat PUFA-enriched diet with or

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without energy restriction (52) no differences between the intervention periods was found. A low-fat diet (26 E%) resulted in lower insulin concentration in one study after both 1 and 5 years as compared with a general diet (53). A very low-fat diet (20 E%) did not differ from a generally recommended diet (37 E%) in terms of fasting plasma/serum insulin concentration (54).

In summary, in comparisons of MUFA versus CHO versus SFA, the beneficial effect of MUFA both on insulin sensitivity and fasting insulin concentration was considered as *probable*. In comparisons of MUFA or PUFA versus SFA, the evidence was considered as *limited-no conclusion* (Appendix 7).

Plasma/serum glucose concentration

There are 20 studies included in this SR on the amount and quality of dietary fat on fasting serum/plasma glucose concentrations (Appendix 3, Table 1c).

The effect of MUFA (14 to 21 E%) on fasting plasma/serum glucose concentration was compared with SFA (15 to 31 E%) in three studies (11, 15, 19) and with SFA (15 to 23 E%) and CHO (57 to 58 E%) in four studies with MUFA ranging from 20 to 22 E% (27, 47–49). In one study, PUFA was compared with SFA (17). When unsaturated fat (MUFA or PUFA) was compared with SFA, no difference was found in any of the four studies. When CHO were included in the comparison, MUFA resulted in better fasting glucose concentration in one study (48), whereas in other three studies no difference between the periods was found.

When MUFA was compared with CHO (21, 22, 24), a MUFA-rich diet (23 E% MUFA, 40 E% CHO) resulted in better fasting plasma/serum glucose concentration than a diet with a higher CHO intake (52 E% CHO, 11 E% MUFA) in one study (22), whereas in two other studies no difference was found. Of these studies, one was conducted with a low calorie diet (6,000 kJ) (21). When diets with added fish oil were compared with diets with no fish oil or ALA or stearidonic acid, (C18:4 n-3) (37, 41, 50, 51) no difference in glucose concentration was found in three studies, whereas in one study in healthy young females a fish oil supplement of 2.8 g/day resulted in lower glucose concentration compared with 3 g/day of black currant seed oil, a source of stearidonic acid (41).

A recommended diet resulted in better glucose concentration in one study including also physical activity (43), whereas in another study a recommended diet without physical activity intervention no effect was found (42). Neither was there any effect of a fat-reduced diet (30 E%) or fat-reduced, PUFA-enriched diet with or without energy restriction (52). A low-fat diet (26 E%) resulted in better glucose concentration in one study after a 5-year intervention, whereas no difference was seen after 1 year as compared with a general diet (53). A very low-fat diet (20 E%) did not differ from a generally recommended diet (37 E%) in terms of glucose concentration (54).

In summary, an effect of replacement of SFA with MUFA or PUFA on fasting plasma/serum glucose concentration was considered as *unlikely*. The evidence of the effect of other type of modification of the quality of fat or replacement of fat with CHO on fasting glucose concentrations was considered *limited-no conclusion* (Appendix 7, Table 1c).

Blood pressure

Altogether 14 RCTs were included in this SR regarding the quality and amount of dietary fat on BP (Appendix 3, Table 1d). Three RCTs compared the intake of MUFA with SFA in a total of 647 subjects. One PCS with 28,100 subjects also included this comparison. A diet enriched in MUFA (20–21 E%) and reduced SFA resulted in lower BP in two of the RCTs (55, 56). In the study by Rasmussen et al. (56) in which ambulatory BP was measured, the response to a MUFA-enriched diet (21 E%) was pronounced when the amount of total fat was <37 E% compared with a total fat intake 37 E% or above. In the RCT by Bos et al. (11) and in the PCS by Wang et al. (57), the quality of dietary fat did not affect BP. When unsaturated fat was compared with CHO, an unsaturated fat enriched diet resulted in lower BP in one study (25), whereas the other study showed no difference between MUFA and CHO (21). A recommended diet including also physical activity did not affect BP as compared with an average diet (43), whereas a very low-fat diet (20 E%) resulted in a lower BP than a generally recommended diet (37 E%) (54). Overall, the evidence for an association between total fat, proportions of SFA, MUFA or total unsaturated fat and BP was *limited-no conclusion* (Appendix 7, Table 1d).

The effect of fish oil supplements (2.1–4 g/day) on BP has been examined in three RCT studies in comparison with dietary sources of ALA and/or LA (38, 45, 58). Two of the studies did not find any difference between the diets, whereas one study found that a higher intake of EPA + DHA (3.6 g/day) resulted in lower BP as compared with a lower intake of EPA + DHA (1.2 g/day), low ALA (2.2 g/day), or high ALA (6.6 g/day) (58). Fish oil 12 g/day resulted in lower mean arterial BP than SFA in an energy-restricted settings (59). Furthermore, no difference between the groups was found in the study by Sanders et al. (32), which compared the intake of DHA and DPA (1.5 + 0.6 g/day) with MUFA from olive oil. The evidence for an effect of the quality or the amount of dietary fat was considered as *limited-no conclusion* (Appendix 7, Table 1d).

Coagulation factors, platelet aggregation, inflammatory markers, endothelial function, and intima media thickness

In five studies the effect of the quality of dietary fat on coagulation factors and platelet aggregation was examined

(Appendix 3, Table 1e). Two studies where n-6 PUFA (LA) and n-3 PUFA (ALA and/or fish oil) were compared showed no differences (45, 51). MUFA was beneficial on platelet aggregation in one study as compared with SFA (16). Fish oil (6 g/day) resulted in a lower platelet thromboxane B_2 concentration (28) and DHA + DPA (1.5 + 0.6 g/day) resulted in an increase in FVIIc as compared with olive oil (32). The evidence was too scarce to draw any conclusions (Appendix 7, Table 1e).

Altogether 12 studies examined the effect of the amount and/or quality of dietary fat on inflammatory markers (Appendix 3, Table 1e). A summary is presented regarding interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor α (TNF-α) (Appendix 7, Table 1e), because a variety of other inflammatory markers were included in very few studies.

Regarding CRP, the effect of dietary fat was examined in eight of the included studies. An intervention study with both a fat-reduced and fat-modified diet resulted in a significantly lower concentration than in subjects consuming their usual diet with a higher content of total fat, SFA, and cholesterol (60). One study found that replacement of 8 E% SFA with MUFA resulted in a lower CRP concentration with a borderline significance (61), whereas in another study no difference between the SFA period and the MUFA period was found (23). A diet rich in ALA (6.5 E%) and total PUFA (17 E%) resulted in a lower high sensitive CRP concentration compared with an average American diet with 0.8 E% ALA and 8.7 E% PUFA (62). In a comparison of ALA and LA, ALA resulted in lower CRP concentration in one study (63), but not in the other (64). Three studies compared the intake of fish oil with MUFA (32, 33, 65). One of these showed a higher concentration of high sensitivity CRP after the intake of fish oils as compared with high oleic acid sunflower oil (65). The other two studies found no difference between the diet groups.

IL-6 was measured in one study comparing MUFA, SFA, and CHO (61). MUFA resulted in the lowest concentration. Comparisons of ALA and LA (63, 64) or ALA and fish oil (58) showed no differences. In one study, TNF-α was examined and no difference between the ALA and LA diet groups was found (64).

In summary, because of conflicting results and scarce data, no conclusions could be drawn regarding the effect of the amount or quality of dietary fat on inflammatory markers.

Six studies investigated the effect of the quality of fat on intima media thickness and endothelial function (Appendix 3, Table 1f), and all of them studied the effects of n-3 PUFA, either of animal or plant origin. The study by Zhao et al. (62) compared ALA and LA with an average American diet. No effect was found in comparisons with LA, olive oil, or SFA (28, 33, 59, 63). Intercellular adhesion molecule 1 (ICAM-I) and E-selectin were lower on ALA and LA periods as compared with an average American diet. ALA period resulted in lower vascular cell adhesion molecule 1 (VCAM) and E-selectin than LA (62). Systemic arterial compliance increased both on a dose of 3 g/day of EPA or DHA as compared with MUFA/olive oil (30). No conclusions could be drawn (Appendix 7, Table 1e).

BW and body composition

The relationship between BW and reduced fat intake was examined in four RCTs with a duration of 6–12 months (48, 53, 54, 66), one of which also included a long-term (5 years) follow-up (53) (Appendix 4, Table 2a). A high-quality SR and meta-analysis of RCTs on fat intake and CVD (67) also included BW as tertiary outcome. Another high-quality SR and meta-analysis of RCTs, which specifically looked at the effect of fat intake and BW, was included after the bibliographic search because of high relevance (68). The studies were generally conducted in healthy subjects with different BW status (BMI 22–36 kg/m^2). Most of the RCTs had one to six BW-related outcomes.

One of the RCTs found no significant effect on outcome measures of adiposity (BW, fat mass, or waist circumference) (66), and one found an effect on four out of six outcome measures (48). In two RCTs, a low-fat diet (20 or 26 E%) resulted in greater weight loss than a control diet (34–37 E% fat) (53, 54). However, in one of these studies (53), the difference was found at 1 year only, with no significant difference at 5 years. The meta-analysis by Hooper et al. (67) concluded that there was a small significant effect of fat reduction on BW of around 1 kg. The subsequent meta-analysis of Hooper et al. (68) included 33 RCTs and 10 PCS. Baseline fat intakes were 28–43 E% and duration varied from 6 months to more than 8 years. This meta-analysis found that intervention with diets with reduced fat intake was associated with lower weight gain of 1.4–1.6 kg. In nine studies that reported BMI, lower fat intake was associated with a significantly lower BMI of −0.51 kg/m^2. The meta-analysis by Hooper et al. (67) included only two studies on fat modification, which showed no effect on BW. One of the included studies compared low-fat diets (22–24 E%) with diets with higher fat content (30–40 E%), either high in MUFA or SFA, after an initial weight reduction with no significant differences in BW regain (48). However, regain in body fat was lower on the low-fat and high MUFA diets.

In summary, there was *probable* evidence for a moderate direct association between total fat intake and BW (Appendix 8, Table 2a).

Type 2 diabetes mellitus

The association between the risk of a T2DM and total fat intake was examined in three PCS (69–71) (Appendix 4, Table 2b). Three PCS looked at the relationship with PUFA (or LA) intake (69–71), three at the intake of n-3

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LCPUFA (70, 72, 73), and one at the intake of ALA (73). These and other cohort studies were included in a SR with 16 studies from 18 separate cohorts with a total of 540,184 individuals and 25,670 cases of incident T2DM (74). The paper by Salmerón et al. (69) was not included, although articles reporting results from longer follow-up from the same cohort were included. The number of subjects in the included PCS ranged from 3,000–4,000 to 91,000, with a follow-up of 4–16 years. In addition, one RCT examined the effect of a fat reduction from 34 to 26 E% on the risk of developing T2DM in 100 subjects with impaired glucose tolerance (53).

Overall, total fat intake did not have an effect on T2DM incidence (53, 69–71). An increase in PUFA intake as n-6 PUFA mainly (from 3 to around 6 E% in exchange of CHO or SFA) may, however, be associated with a T2DM risk reduction of around 20% (69–71, 75).

Some PCS found that increased intakes of n-3 LCPUFA of marine origin, that is, EPA and DHA, were associated with a 20–40% increased risk of T2DM (70, 72, 73). In a SR and meta-analysis of 13 PCS conducted in Europe, the United States, and Asia/Australia, no overall association with intake of n-3 LCPUFA, assessed as 0.3 g/day increment, was found (76). However, a significant positive association with T2DM risk was found in studies carried out in the United States (relative risk (RR) 1.17, 95% CI: 1.09–1.26) (76). There was large heterogeneity among studies, and those using self-administered FFQ were associated with higher, and significant, risk estimates compared to interviewer-administered FFQ. In an SR by Wu et al. (74), a meta-analysis showed no significant association between dietary EPA + DHA (16 PCS) and T2DM incidence (RR per 250 mg/day: 1.04 (95% CI: 0.97–1.10). No association for circulating levels of EPA + DHA (5 PCS), assessed per 3% of total fatty acids (RR 0.94, 95% CI: 0.75–1.17), was found. For dietary ALA (7 PCS), the RR per 0.5 g/day was 0.93 (95% CI: 0.83–1.04) and for circulating ALA levels (6 PCS) RR per 0.1% of total fatty acid was 0.90 (95% CI: 0.80–1.00, $p = 0.06$).

Tissue fatty acids and T2DM

Four PCS were identified with T2DM as outcome; two regular cohort studies and two NCC studies were evaluated (77–80) (Appendix 6, Table 4a). No PCS were found that assessed fatty acids in other tissues. Two of the evaluated studies assessed fatty acid composition in erythrocytes (RBC), and the other studies assessed fatty acid composition in serum or plasma lipid fractions, for example, phospholipids (PL) and cholesteryl esters (CE) or total serum lipids.

n-6 PUFA. LA was inversely related to diabetes risk in three of the four studies (78–80). In the NCC by Krachler et al. (77), an inverse relation was found between LA in RBC and T2DM, which did not remain significant in multivariate analyses adjusted for age and HbA1c. The latter may be because of over-adjustment as glucose levels might well be in the causal pathway of LA and a T2DM diagnosis. Taken together, the results imply that tissue LA is inversely associated with development of T2DM.

n-3 PUFA. Tissue levels of ALA showed inconsistent relations with the risk of T2DM as three out of four studies found no significant relationships in the multivariate analyses (77–79). However, one study did find an inverse association between ALA in plasma PL, but not in CE (80). Similarly, there was no significant association between blood n-3 LCPUFA levels and the risk of T2DM in any of the studies. Results from the SR and meta-analyses by Wu et al. (74) also did not show any significant association between circulating levels of EPA + DHA or ALA with T2DM.

SFA – Total and major SFA (14:0, 16:0, and 18:0). In the ARIC-PCS total SFA and 16:0 in both PL and CE were found to be directly associated with T2DM, whereas 18:0 was only significant in PL (80), in line with a similar association between 18:0 in PL and total SFA with the risk of T2DM in another PCS (79). In RBC, one study showed borderline significant association between 18:0 and risk of T2DM (78), whereas no significant associations were found in another study measuring major SFA in RBC, although 14:0, 16:0, and 18:0 were directly related in a model adjusting for alcohol only, but not after adjusting for HbA1c and BMI (77). The results indicate a direct association between 18:0 and total SFA with incidence of T2DM, but this relationship should be interpreted with caution because major SFA including 18:0 are weak biomarkers of dietary SFA intake (81, 82).

Minor SFA (15:0 and 17:0). These SFA are not only present in milk fat but also in fish and seafood in amounts of 0.31 to 2.0% (83, 84). In the three studies that included data on 15:0 or 17:0, there was an inverse association with T2DM incidence for both in one study (77), and with15:0 in another (79). In the study by Kröger et al. (78), there was a trend for an inverse association which did not reach significance in the multivariate model. Because these studies were NCC studies without any data from any original PCS, the data are *limited-suggestive* to suggest an inverse relation between these fatty acids and diabetes incidence. The odds ratios were quite strong, and the data are consistent which strengthens the data for this finding.

In summary, there was *probable* evidence for an inverse association for total PUFA or LA intake and T2DM. This was further supported by *suggestive* evidence for an inverse association between the major dietary n-6 PUFA, that is, LA, and T2DM risk from biomarker studies. There were limited data to draw any conclusions regarding the association between intake of SFA and the risk of T2DM. There was, however, *limited-suggestive* evidence for an increased risk of major SFA (18:0) on T2DM risk.

In contrast, there was *limited-suggestive* evidence for an inverse association with the minor odd-chain SFA 15:0 and 17:0. The evidence for an association between dietary total fat, ALA, and n-3 PUFA and T2DM was *inconclusive* (Appendix 8, Table 2b) and there was no evidence of associations between neither plasma nor RBC ALA or n-3 LCPUFA and T2DM risk (Appendix 10, Table 4b).

Cardiovascular diseases

Altogether 29 studies are included in the SR in which the amount and quality of dietary fat on CVD risk was studied (Appendix 4, Table 2c).

Total fat. The association between the intake of total fat and mortality from CVD outcomes was examined in four PCS (85–88). Mean total fat intakes varied from 35 E% to about 45 E%. The Women's Health Initiative (WHI) RCT in 48,835 postmenopausal women (89) reports on CVD outcomes from an intervention aimed at reducing total fat intake to 20 E%, while maintaining habitual fat intake in the comparison group (38 E%); however, this goal was not reached (28–30 E%). One SR of RCTs also covered total fat intake (67). The results from the RCTs and the SR showed no difference with respect to the risk of any of the CVD outcomes. In the PCS no significant effect of the intake of total fat on CVD outcomes was found. In summary, a direct association between total fat intake and CVD outcomes is *unlikely.*

SFA. The association between SFA intake and CVD outcomes was examined in seven PCS (57, 85, 87, 90–92). Most of the studies did not find any direct association between the intake of SFA and risk of various CVD outcomes. One prospective study in a multi-ethnic population including 5,000 subjects, found that CVD risk was dependent on food source of SFA (91). After 10 years of follow-up, there was an overall inverse association with CVD risk with SFA intake, assessed per 5 g/day (hazard ratio (HR): 0.86, 95% CI: 0.75, 0.97) or 5 E% (HR: 0.71, 95% CI: 0.56, 0.89). Corresponding HRs for dairy SFA were (per 5 E%) 0.62 (95% CI: 0.47, 0.82) and for meat SFA (per g/day) 1.26 (95% CI: 1.02, 1.54). However, SFA intake range was relatively narrow, about 6 E% in the first and 12 E% in the fifth quintile, with a mean SFA intake around 10 E%. A secondary analysis of the data from the WHI RCT, showed that specifically lower intake of SFA was associated with decreased risk of CHD in women (89).

More recent studies have looked not only at the effect of reduced SFA intake as such, but rather the effect of specific substitutions with other macronutrients. In these analyses, a reduction of SFA compensated by an increase in the intake of CHO tended to be associated with increased risk of CVD outcomes (87, 92, 93). This association seems to be dependent on type of CHO, with increased risk with foods rich in simple CHOs, whereas consumption of sources of more complex CHO did not affect the risk (92). Similarly, a pooled analysis of data from 11 PCS with around 350,000 men and women observed a 20% decreased risk of CHD in both men and women when 5 E% PUFA was substituted for equal amounts of SFA (93). A SR concluded that there is moderate evidence that substitution of unsaturated fatty acids (MUFA or PUFA) for SFA can reduce CVD events by 14% (67). The reduction in CVD events was seen in studies of fat modification with duration of at least 2 years in which the risk reduction was 22%. Significant risk reductions were seen in men, but not in women. A meta-analysis of eight RCTs, including 13,614 participants, compared effect of interventions with increased intake of PUFA as a replacement for SFA on CHD. PUFA intake in the intervention groups was 15 E%, compared with 5 E% in the control groups. Results showed an overall significant risk reduction of 19%, corresponding to 10% reduced CHD risk for each 5 E% increase of PUFA intake. Studies of longer duration showed greater benefits (94).

MUFA. The effect of dietary intake of MUFA was studied in four PCS (57, 85–87), in a pooled analysis by Jakobsen et al. (93) and in a secondary analysis in an RCT (89). None of these found any significant association between MUFA intake and risk of CVD.

PUFA. Four PCS have examined the associations with the intake of PUFA and CVD risk and none of them found any significant direct association (57, 85–87).

n-3 LCPUFA. Fourteen PCS examined the associations between CVD outcomes and n-3 LCPUFA (95–108). Three of the studies used heart failure as the outcome and none of these found any clear association (99, 101, 106). In one study, no association with coronary calcification was found (102). However, six of the studies found a significant risk reduction for CVD, but in most cases only for specific outcomes (ischemic stroke, sudden cardiac death (SCD), fatal CHD, and CHD) (95, 96, 98, 100, 103–105). In two studies with similar outcomes, no association was found (107, 108). One of the studies found that the degree of risk reduction on sudden coronary mortality decreased with age in men and was not significant after the age of 65 years (100), which could explain the lack of an effect in the studies where most of the cases were above that age (99, 101, 102, 106). One of the recent Scandinavian studies did find an increase in an overall risk of CVD as well as in all its sub-disease classes (CHD, stroke, and hypertension) at very low n-3 LCPUFA intake ($\leq$0.06 g/day) compared with intakes $>$0.73 g/day in women aged 16–47 with a follow-up of up to 12 years (105). The typical effect size was a risk reduction of 30–60% at intakes $>$0.2 g/day. The associations were linked to total fish intake. An SR and meta-analysis of nine PCS concluded that intakes of dietary EPA + DHA up to 0.20 g/day (mean intake) were associated with a

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significant decreased risk of CVD mortality (OR 0.64, 95% CI: 0.45–0.89 per 0.20 g) (109). Mean or median intakes in cohorts ranged from 0.04 to about 0.90 g/day. Furthermore, one PCS found a lower risk of atrial fibrillation (AF) at higher plasma levels of n-3 LCPUFA, which was most pronounced for DHA (HR: 0.51–0.64 (0.32–0.92) (110).

ALA. Three of the six studies on CVD and dietary intake of ALA found no association with CHD outcomes (99, 104, 111), but one high-quality study found a significant risk reduction of CHD with increasing ALA intakes at low ($<$100 mg/day) n-3 LCPUFA intake. At higher intakes of n-3 LCPUFA no association was found (112). Two studies in which all subjects were $<$65 years at baseline found a risk reduction for SCD and stroke (RR around 0.5–0.6 at intakes $>$1 g/day) (113, 114). In one of the PCS that did not find any association, the subjects were around 70 years at baseline (111). No risk reduction by n-3 LCPUFA was found in this same PCS (100). Two of the studies have investigated potential interactions between n-3 PUFA (ALA and n-3 LCPUFA) and n-6 PUFA (LA) and neither of them found any evidence for such an effect (104, 112).

Biomarkers of the quality of dietary fat and CVD

The biomarkers in the included studies in this SR are fatty acid composition of plasma, plasma lipids (PL or CE), and RBC.

Cardiovascular mortality

Altogether six studies are included in the SR in which fatty acid biomarkers of the quality of dietary fat on CVD risk was studied (Appendix 6, Table 4b).

Two PCS showed inverse association with total PUFA or LA in serum or CE, and CVD mortality and total mortality (88, 115). Results from a NCC study among elderly British men showed that a higher SFA proportion in serum-PL was positively associated with CHD mortality, whereas higher PUFA was inversely associated with CHD mortality (116). Thus, these three studies were consistent in reporting an inverse association with especially n-6 PUFA (i.e. LA) and CVD mortality in men.

Higher proportions of 16:0, 16:1, and 18:1 in serum CE (1-SD increments) were associated with an increased risk for stroke/transient ischemic attack (TIA) and brain infarction (BI)/TIA in a PCS of men followed for 29 years (117). Higher proportions of LA were protective against stroke/TIA and BI/TIA. No significant relation between serum fatty acids and subsequent intracerebral hemorrhage was observed (Appendix 6, Table 4b).

Regarding AF only one study was found. Higher plasma levels of n-3 LCPUFA and especially DHA was associated with lower risk of AF (HR: 0.51–0.64 (0.32–0.92) in multivariate analyses. ALA was not associated with AF risk (110) (Appendix 6, Table 4b).

Regarding metabolic syndrome and inflammation, only one PCS assessing association between tissue fatty acids and inflammatory markers was included (118). Proportion of LA in serum CE was associated with lower plasma concentration of CRP, whereas oleic acid was associated with higher CRP concentration. Because of inclusion of one study only, no conclusion can be drawn (Appendix 6, Table 4c).

Summary – CVD

There was found to be *convincing* evidence that partial replacement of SFA with PUFA decreases the risk of CVD, especially in men. Furthermore, there was some evidence that the association between the type of fat and risk of CVD is modified by the food sources. The evidence for an association with total fat intake was considered to be *unlikely*, at observed mean intakes ranging from about 30 to 45 E%. The evidence for an inverse association with ALA and n-3 LCPUFA was found to be *suggestive* (Appendix 8, Table 2c).

Cancer

Altogether 60 studies are included in the SR in which the amount and quality of dietary fat on the risk of cancer was studied (Appendix 5).

Total cancer

The WHI RCT reports on several cancer outcomes including total invasive cancer incidence in 48,835 postmenopausal women (119–121). The intervention aimed at reducing total fat intake to 20 E%, while maintaining habitual fat intake in the comparison group (38 E%), but the actual fat reduction was somewhat lower (28–30 E%). The intervention also included other dietary advice such as increased intake of fruit and vegetables and wholegrain cereals. There was no significant difference in total cancer incidence between the groups during the 8 years of follow-up. One other PCS investigated the association between total cancer incidence and intake of fish and n-3 LCPUFA (97). No significant associations for n-3 LCPUFA were found during the 18 years of follow-up, but the average intake of EPA and DHA in this study was low compared to that in the Nordic countries.

Breast cancer

Total fat. Two RCTs investigated effects of reducing total fat intake from 30 E% to about 20 E% or 38 E% to about 28 E%, respectively, on breast cancer risk in postmenopausal women (119, 122). No significant differences were found (Appendix 5, Table 3a).

Five PCS on postmenopausal breast cancer, reported in six articles (123–128), and two on premenopausal breast cancer (129, 130) were also identified, which included more than 670,000 subjects. For postmenopausal breast cancer overall no significant associations were found. In the study by Sonestedt et al. (123), a positive

association was seen among women with BMI <27 kg/m^2. For premenopausal breast cancer a positive association was found in one study (129). In the studies that reported on ranges of total fat intake as E% in extreme categories (quartiles or quintiles) these were 24–29 E% to $\geq$34–45 E%. Results from three RCCs showed either no, an inverse, or a positive associations (131–133).

SFA. Six PCS reported on SFA intake, with non-significant associations in five (124–127, 129, 130). One study found a positive association among menopausal women who did not use hormone replacement therapy (125). Results from the three RCCs showed no associations in two and an inverse association among normal-overweight women (BMI <30 kg/m^2) (131–133).

MUFA. Six PCS reported on MUFA intake, with non-significant associations in five (124–127, 129, 130). One study found an inverse association among women age 50 years or more (126). Results from three RCCs showed no associations in two, while an inverse association was found among normal-overweight women (131–133).

PUFA. The same six PCS reported on associations between breast cancer and total PUFA intake, with non-significant associations in five of the studies (124–127, 129, 130), and only one study that found an inverse association among women above 50 years of age (126). Results from three RCCs also showed no associations (131–133). In one of these studies only LA intake was assessed (132).

Three PCS reported specifically on association between intake of n-6 PUFA and the incidence of breast cancer (123–125), two of these with non-significant associations, and a positive association in one. One study showed an inverse association in women in the highest intake (fifth quintile) of n-6 PUFA intake (134).

The specific association for n-3 PUFA was investigated in several studies and the results from eight papers, which included data from six different PCS, was analyzed in an SR (135). The SR concluded that there is insufficient evidence for an association between intake of n-3 PUFA and breast cancer. Two subsequent PCS also reported non-significant associations between breast cancer and total intake of n-3 PUFA (124, 134). However, one of these studies found an inverse association with n-3 PUFA among women in the fifth quintile of n-6 PUFA intake (134). Results from two RCCs (132, 133) also did not show any association between prevalent breast cancers and intake of n-3 PUFA. Two PCS have reported associations with ALA intake (124, 134), but none of them found an overall significant associations. However, Thiebaut et al. (134) did find either inverse or positive associations with ALA depending on food source.

The association between breast cancer and fatty acid composition in tissues was examined also in four PCS. These studies showed no consistent evidence for associations between proportion of any fatty acid in tissues and the incidence breast cancer (136–140) (Appendix 6, Table 4d).

In summary, the evidence for an association between fat intake and breast cancer was *inconclusive* (Appendices 9 and 10, Table 4c).

Other female specific cancers – ovarian cancer and endometrial cancer

Ovarian cancer (Appendix 5, Table 3a). The WHI RCT also investigated effects of a fat-restricted diet on ovarian cancer (119). The results indicated a reduced incidence in the intervention group compared to the comparison group among women without prior bilateral oophorectomy at baseline. The HR over the whole 8-year follow-up period was not significant. A pooled analysis of 12 PCS did not find any significant association with total fat, MUFA, or PUFA (141). For SFA, a weak, significantly positive, but non-linear, association was found comparing highest with lowest decile of intake. Results from subsequent CCs show no associations with total fat or subtypes (142, 143).

Endometrial cancer (Appendix 5, Table 3a). No significant differences in endometrial cancer incidence were seen during the follow-up period (8.1 year) in the WHI RCT (119). One meta-analysis was identified that included two PCS and nine case-control studies (CC) (144) and the results from this analysis did not show any significant association between endometrial cancer and intake of total fat or SFA in the PCS, but a positive association was seen in the CC. A more recent PCS reported no overall associations for total SFA, MUFA, PUFA, or n-3 PUFA (145), although a borderline inverse association was found comparing fat intake in highest versus lowest quartile.

In summary, the evidence for an association between fat intake and ovarian cancer and endometrial cancer was *inconclusive.* However, for ovarian cancer the evidence for a positive association with the intake of SFA was considered to be *suggestive* (Appendix 9).

Prostate cancer

A review and meta-analysis by Dennis et al. (146) covered four PCS, published between 1989 and 1999, and it also included 10 CCs published before 2000. The analysis by Dennis et al. (146) found no significant associations in studies where fat intakes were adjusted for energy, and the results of the meta-analysis also did not show any statistical associations between prostate cancer and any of the other fat exposures (SFA, MUFA, or PUFA). Three PCS on total fat, SFA, MUFA, and PUFA in relation to prostate cancer risk published after 2000 were identified (147–149), but none of these studies showed any significant associations. Another three CC studies published after 2000 were also identified (150–152) and of these three studies, one found a positive association for

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SFA, two found positive associations for MUFA, and one found an inverse association for PUFA (Appendix 5, Table 3b).

A review and meta-analysis by MacLean et al. (135) focusing on n-3 PUFA covered six PCS, published between 1989 and 2004. Results showed no statistical association. In a subsequent study by Wallström et al. (149), no significant association was found for total n-3 PUFA. A positive association was found for DHA, which according to the authors may have been a chance finding. A SR and meta-analysis of four PCS and one NCC published between 1999 and 2007 found no significant associations between intakes of ALA and prostate cancer when extreme intake categories were analyzed (153). In an analysis comparing fixed intakes ($\geq$1.5 vs. $<$1.5 g/day) a weak inverse association was found (pooled RR 0.95; 95% CI: 0.91–0.99). Two CC studies included total and individual n-3 PUFA with inverse or no significant associations (152, 154).

In summary, there was *suggestive* evidence for an inverse association between the intake of ALA with prostate cancer, but the association is likely to be non-linear. Evidence for total fat and other fat subtypes were *inconclusive* (Appendix 9).

Colorectal cancer

Total fat. In the WHI RCT, no significant difference in colorectal cancer incidence was seen during the follow-up period of about 8 years (121). Two PCS also investigated association with total fat intake (155, 156), and one of these did find a positive association with colon cancer (155). Three CCs were identified (157–159), all of which reported non-significant associations (Appendix 5, Table 3c).

SFA, MUFA, and PUFA. One PCS (156) and three CCs (157–159) investigated associations between colorectal cancer and intake of total SFA, MUFA, and PUFA. None of the studies reported any significant associations for any fatty acid category. One CC found an inverse association with total n-6 PUFA only among subjects with a fiber intake below the median (158).

n-3 PUFA. Eight PCS examined potential associations with total or individual n-3 PUFA (135, 160). Seven of these were included in an SR (135), which found no significant associations between intake of n-3 PUFA and colorectal cancer. One study found a positive association in women but not in men (160). One CC found no associations (161), whereas another found an inverse association with total n-3 PUFA among subjects with a fiber intake below the median (158).

In summary, the evidence for an association between the intakes of total fat or fat types was *limited–inconclusive* (Appendix 9).

Lung cancer

One article was identified that reported results from a pooled analysis of 8 PCS from Canada, Finland, Netherlands, and USA with follow-ups of 6–16 years (162). No significant associations were found between intake of total fat, SFA, MUFA, or PUFA and lung cancer (Appendix 5, Table 3e).

Other cancers

Pancreatic cancer (Appendix 5, Table 3e). Five PCS investigated associations with total fat intake (163–167), of which one found a positive and four no significant association. Total fat intake varied from 20 to 21 E% in the lowest quintile to 39–40 E% in the highest quintile. Four PCS (163–165, 167) and one CC (166) investigated associations with SFA intake, of which two found a positive and three no significant associations. SFA intake varied from 5–6 E% in the lowest quintile to 12–13 E% in the highest quintile. Three PCS and one case-cohort study investigated associations with total MUFA and PUFA intake with no significant associations (163, 165–167).

Esophageal cancer (Appendix 5, Table 3d). One PCS investigated intake of total fat, SFA, MUFA, PUFA, TFA, and total n-3 PUFA (168), with no overall significant associations with cancer incidence. Sub-group analyses revealed an inverse association for PUFA intake among subjects with normal BMI (18.5– $<$25 kg/m^2, HR for Q5 vs. Q1: 0.76; 95% CI: 0.63–0.92). One CC investigated intake of total fat, SFA, MUFA, PUFA, and several food groups in cases with esophagitis, Barrett's esophagus, and esophageal adenocarcinoma (169). For adenocarcinoma increased risks were seen for highest quintiles of total fat, SFA, and MUFA compared to lowest quintiles.

Gastric cancer (Appendix 5, Table 3d). One PCS investigated intake of total fat, SFA, MUFA, PUFA, TFA, and total n-3 PUFA (168). There were no overall significant associations with cancer incidence. One CC investigated intake of total fat, SFA, MUFA, PUFA, oleic acid, LA, ALA, vegetable and animal fat, and other macronutrients (170). A strong significant inverse association was found for PUFA of n-6 PUFA mainly (OR: 0.66, 95% CI: 0.44–0.97) and LA (OR: 0.67, 95% CI: 0.45–1.00) when comparing highest and lowest tertile.

Renal cell cancer (Appendix 5, Table 3e). Two articles reported results from 14 PCS (171, 172). The article by Lee et al. (172) comprises results from a pooled analysis of 13 PCS from Australia, Canada, Finland, Netherlands, Sweden, and the United States with follow-ups between 7 and 20 years. No significant associations were found between intake of total fat, SFA, MUFA, or PUFA and renal cell cancer. Similarly, no significant associations were found for intake of total fat, SFA, MUFA, or PUFA in the EPIC-study with a mean follow-up of 8.8 years reported by Allen et al. (171).

Bladder cancer (Appendix 5, Table 3e). Two CCs investigated risk of bladder cancer with intake of total fat, SFA, MUFA, or PUFA (173, 174). No significant associations were found for total fat, SFA, and MUFA. One of the two studies found an inverse association with total PUFA and ALA (174).

Skin cancer (Appendix 5, Table 3e). One PCS in men found an inverse association between intake of total fat and risk of basal skin cancer after 8 years follow-up (175). Further statistical analysis suggested that the association was limited to MUFA. One CC found no association between risk of squamous cell carcinoma of the skin with intake of total fat, SFA, MUFA, PUFA, n-6 PUFA, or n-3 PUFA (176). There was a tendency for decreased risk in the highest (>90th percentile) compared to the lowest (<50th percentile) n-3 LCPUFA category (OR: 0.71, 95% CI. 0.49–1.00).

In summary, the evidence for an association between fat intake and esophageal, gastric, bladder, and skin cancers is limited and *inconclusive*. For renal cell cancer the available evidence indicates that an association is *unlikely*, For pancreatic cancer the evidence for an association was either *inconclusive* (SFA, n-3 PUFA) or *unlikely* (total fat, MUFA, PUFA) (Appendix 9).

Overall mortality (all cause or from major chronic diseases)

In five studies included in this SR, the effects of the amount and quality of dietary fat on overall mortality was studied (Appendix 4, Table 2b). Two moderate-quality PCS, both based on the same cohort from the USA (97, 177), examined the effect of reduced fat intake and/or modified quality of dietary fat (SFA reduction, overall SFA/MUFA/PUFA, and increased n-3 LCPUFA) on mortality over a 8–18 year follow-up period in 40,000 subjects. Results from the shorter follow-up found that both a total fat intake of ≤30 E% and a SFA intake <10 E% was associated with a 10% reduction in risk (177), but there were no significant associations at the 18 year follow-up (97). The issue was also examined in a high-quality SR and meta-analysis (67), which was based on 21 RCTs, 71,000 subjects, and 4,292 deaths. It was concluded that there was no evidence that a decreased intake of total fat, a reduction in SFA, or a substitution of unsaturated fatty acids for SFA was associated with a significant reduction in overall mortality.

Two PCS and one NCC study showed inverse association with total PUFA, n-6 PUFA or LA in serum or CE, and CVD mortality and total mortality (88, 115, 116) (Appendix 6, Table 4b).

In summary, results from RCTs and PCS do not support an association between total fat intake or fat quality with mortality risk. However, there was *suggestive* evidence of an inverse association between biomarkers of PUFA or LA intake and CVD mortality (Appendix 10, Table 4a).

Discussion

The objective of this SR was to assess all evidence published between January 2000 and February 2012 regarding the effects of the amount and type of dietary fat based on both dietary assessment methods as well as biomarkers of intake using fatty acid composition in various blood lipid fractions on risk factors for lifestyle diseases such as T2DM and CVD, BW change, and risk of clinical outcomes for CVD, T2DM, and cancer. Articles focusing solely on the effect of TFA were excluded as the intake of TFA has decreased considerably during the last decades in the Nordic countries and are well below current guidelines (2). Articles on the effects of CLA or dietary cholesterol were also excluded.

The different outcomes for total fat and fatty acid categories have been summarized in the result section. The following discussion provides an overview of the evidence regarding the major health outcomes (BW, T2DM, CVD, and cancer) in relation to each of the fat categories (total fat, SFA, MUFA and PUFA, n-6 and n-3 PUFA) along with a comparison of the conclusions of this SR with the conclusions of other recent SRs within each field.

Effect of fat intake on metabolic risk markers

Based on modern genetic studies, LDL-C has been shown to be causally related to atherosclerosis and LDL-C/HDL-C and non-HDL-C are also known to be good markers for CVD risk (178–180). Plasma/serum LDL-C has been identified as an important and causal risk factor for atherosclerosis, whereas a high HDL-C concentration and a low LDL-to-HDL-C ratio are associated with the reduced risk of atherosclerosis. Higher risk profile already in childhood has also been shown to be associated with an increased risk of atherosclerosis and CHD (181, 182). The relatively high-fat content with a high proportion of SFA in the diet in the Nordic countries during the 1960s and 1970s have been considered as contributors to the high prevalence of CVD. However, during the past decades, there has been a significant decrease in CVD morbidity and mortality in Finland, which previously had the highest rate of CVD mortality in the world. Simultaneously there has been a decrease in serum LDL-C concentration. In women, the decrease in the intake of SFA has been reported to explain 41% of the decrease in LDL-C concentration. The equivalent degree of explanation in men is 47% (183). Low HDL-C concentration and elevated TAG concentration in plasma/serum have been suggested to be independent risk factors for both T2DM and CVD (184–187), but their casual role has remained unresolved. Recent genetic studies, however, suggest a direct link of plasma/serum TAG concentration in the development of CVD (188).

In line with several SRs and recommendations (2, 189), the present SR found that a substitution of SFA with

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MUFA and/or PUFA convincingly decreases concentrations of total and LDL-C. A partial replacement of CHO with MUFA or PUFA was, however, not found to have an impact on the lipid profile. This SR also included a few studies which investigated effect of dietary fat on LDL particle size, but no firm conclusions could be drawn on this aspect.

Regarding comparisons of FO with other types of PUFA, there do not seem to be differences regarding serum/plasma total lipid or lipoprotein cholesterol concentrations. The evidence that FO lowers plasma/serum TAG concentration as compared with MUFA was considered *probable*. In the other recent SRs (190–192) n-3 LCPUFA has been shown to consistently lower plasma/serum TAG concentration. There is *suggestive* evidence that DHA increases serum/plasma LDL-C concentration compared with MUFA. Because in some of the included studies EPA and DHA were studied instead of fish oil, the specific effects of these two n-3 LCPUFA were evaluated. There is also some evidence that the effect of DHA on plasma/serum TAG concentration may differ from that of EPA. In the meta-analysis of Wei and Jacobsen (190) consisting of 33 studies, both EPA and DHA were found to decrease serum/plasma total TAG concentrations and DHA was, furthermore, found to increase the concentrations of both LDL-C and HDL-C. However, this meta-analysis also included studies on non-Caucasians and did not differentiate between studies which used MUFA or other type of PUFA as the control. Compared with the effect of n-3 LCPUFA, the effect of ALA on plasma lipid profile is not examined as thoroughly and the evidence regarding potential beneficial effects are therefore not as clear (193, 194).

When it comes to the effects on fasting serum/plasma glucose concentrations, none of the fat exposures, including substitution of SFA with MUFA and/or PUFA were found to have any effect on plasma glucose concentrations in healthy people or people at risk with quite normal fasting glucose concentrations. Furthermore, no conclusions could be drawn from comparisons of the effects of MUFA or PUFA and SFA on insulin sensitivity measured either by SI or HOMA-IR. On the contrary, when MUFA and CHO was compared with SFA, MUFA resulted in better HOMA-IR or SI or fasting serum/plasma insulin concentration when compared with SFA (24, 47–49) and this was confirmed by effects on glycated hemoglobin in a sub-study (27) of Due et al. (48). Thus, overall the evidence was considered as *probable* for a beneficial effect of MUFA and CHO versus SFA on insulin sensitivity. In two recent intervention studies in obese subjects with the metabolic syndrome no effect of reducing the intake of SFA on SI was found (195, 196). The report by FAO (2) concluded that there was a possible favorable effect of replacing CHO with MUFA on insulin sensitivity. The amount of total fat may modify the effect of the quality of fat as a study by Vessby et al. (19) found in a secondary analysis that replacing SFA with MUFA improved insulin sensitivity in particular in healthy subjects when total fat intake was below 37 E%, which may explain why no effect was observed in some of the studies that had a high-fat intake. Animal studies have indicated that n-3 PUFA have a beneficial effect on glucose homeostasis and insulin sensitivity (197, 198), but based on the studies in this SR, no conclusions can be drawn regarding the effects of n-3 LCPUFA from fish oil supplements on insulin sensitivity or serum/plasma glucose and insulin concentrations. This is in line with the conclusion in other reviews that have evaluated the evidence from studies in humans (199).

Only few of the included studies, examined the effect of the total amount of fat on BP and no conclusions could be drawn. Conclusions regarding the effect of the quality of fat on BP were *inconclusive* as well. In four included studies the one by Bos et al. (11) and the cohort study by Wang et al. (57) showed no difference, whereas in studies by Gulseth et al. (55) and Rasmussen et al. (56) a MUFA-rich diet resulted in lower BP than a SFA-rich diet. Interestingly, in a study by Rasmussen et al. (56) the response to the change in the quality of fat was only seen in those subjects whose fat intake was below 37 E%. In a study by Bos et al. (11) the intake of fat was about 40 E%. In a cross-sectional INTERMAP study, including also non-Caucasian populations, dietary total PUFA, n-3 LCPUFA as well as ALA and gamma-linolenic acids were inversely related to BP, also in normotensive subjects (200).

No conclusion could be drawn regarding the effect of n-3 LCPUFA on BP. In the meta-analysis by Geleijnse et al. (201), n-3 LCPUFA was found to reduce BP, although mostly in subjects who were >45 years or hypertensive.

New cardiovascular risk markers are emerging and several of the included studies have examined effects of dietary fat on markers of coagulation and inflammation. There are, however, generally only a few studies with the same combination of fat exposure as these risk markers so it was not possible to draw any conclusions from these studies.

One of the studies used ex vivo platelet aggregation as a method to assess coagulation, but this method may not be applicable for in vivo conditions. The results of the included studies on coagulation were quite inconsistent and some results indicate that sex may modify the effect of dietary fat (202). The n-3 PUFA are generally said to be antithrombogenic although in high doses (203). However, no conclusions could be drawn from the studies included in this SR. It is of note, that the effect of specific n-3 LCPUFA, namely EPA and DHA, on coagulation may differ (202).

Regarding inflammatory markers, plasma levels of CRP (in the lower range) has been established as an independent marker of CVD (204). Very few of the included studies examined associations between dietary fat and CRP. Unsaturated fatty acids, that is, MUFA, PUFA, or n-3 LCPUFA were not found to have beneficial effects in any of the included studies. However, SFA was not better than unsaturated fat in any of the studies. There were five studies for intima media thickness or endothelial function included in this SR and the results from these did not allow any clear conclusions to be drawn.

Body weight

Obesity is generally considered to be one of the most dominating modifiable determinants of lifestyle diseases (205). Obesity is, however, a gradually developing condition and none of the included studies examined fat intake and long-term risk of obesity, because this aspect was covered by another recent SR (206). The present SR focused on the effects of the amount and quality of dietary fat on changes in BW. The studies that investigated the effect of fat intake and dietary fatty acid composition on BW included one very large SR and meta-analysis (67) and generally show that fat quality has no impact on BW. The effect of the amount of fat on BW was variable in the included studies. A reduction in an overall intake of fat below 30 E% seemed to be associated with modestly lower BW. The high-quality SR and meta-analysis of RCTs and PCS by Hooper at al. (68) concluded that a reduction in fat intake resulted in lower weight gain of 1.4–1.6 kg on average. Baseline fat intakes in the studies were 28–43 E%, which covers ranges observed in Nordic populations. It was concluded that there is *probable* evidence for a moderate association between total fat intake and BW. However, other dietary factors such as type and amount of CHO and protein may interact as well (206).

Type 2 diabetes

No association with the risk of T2DM and n-3 LCPUFA, MUFA, or total fat intake was found. However, *probable* evidence was found that LA intake reduces the risk of T2DM, which is in agreement with the conclusion in the FAO report (2). This conclusion was based on studies where increased mainly n-6 PUFA (from 3 to around 6 E%) at the expense of SFA or CHO was found to be associated with a risk reduction of T2DM of around 20%. This association was supported by *suggestive* evidence for an inverse association between levels of LA in serum-PL and RBC and reduced T2DM risk, with a similar effect size (RR of around 20–40%). This effect is also supported as results from RCTs have suggested a moderate insulin sensitizing effect of n-6 PUFA compared with SFA (17, 207).

In long-term RCTs, a reduced intake of fat and SFA in combination with modest weight reduction, increased intake of dietary fiber, and increased physical activity has been shown to reduce the risk of T2DM in subjects with glucose intolerance even many years after the active intervention (208–212). In the Finnish Diabetes Prevention Study, increased risk of diabetes was associated with a diet high in fat and low in CHO, whereas a diet reduced in fat and higher in CHO has been found to be protective (209).

In a recent report by FAO, SFA was considered to have a possible positive relationship with increased risk of T2DM (2). However, this SR did not find any clear associations between intake of SFA and T2DM. In one of the three identified PCS, SFA intake was associated with a higher risk of T2DM, but this association was not independent of BMI (75). Increased serum SFA has recently been shown to be associated with insulin resistance, elevated serum glucose concentration, and tissue inflammation (213). In the present SR, there were limited data to draw conclusions with respect to circulating levels of major SFA, although the studies did suggest a positive association, which was however only seen with SFA in plasma lipids, and not with RBC. Data regarding circulating levels of SFA are however difficult to interpret as the correlation with intake is generally poor (214), except for the odd-chain SFA that are not synthesized endogenously. The SR found *suggestive* evidence that the minor odd-chain SFA (15:0 and 17:0), which are produced by micro-organisms in the rumen of cows and are thus found in milk fat, are inversely associated with risk of T2DM. However, 15:0 and 17:0 is also found in fish (83, 84, 214). Thus, controlled studies are needed to understand the significance of these inverse associations. High-fat dairy products, for example, butter, have not been found to have favorable effect on insulin sensitivity or β-cell function, when compared with n-6 PUFA or MUFA in short-term RCTs (19, 207). However, there might be differences between the effect of different types of dairy products on glucose metabolism and other components in dairy products may explain the association, so further studies are needed in this respect.

Some of the included PCS indicate that high intake of n-3 LCPUFA may be associated with increased risk of T2DM, which is surprising and in contrast to hypothesis based on the effect of n-3 LCPUFA on insulin resistance in rodents and the before mentioned effect on various risk markers (197, 198). However, a recent SR and meta-analysis (74) found that intake of EPA and DHA was not associated with either a favorable or a harmful effects on the risk of T2DM. The meta-analysis also showed that intake of ALA, was not associated with a reduced risk of T2DM, but circulating ALA levels were suggested to be associated with modestly lower risk of T2DM. However, the present SR did not find any evidence that plasma or RBC ALA or intake of ALA were related to T2DM risk.

The report by FAO (2) concluded that there was possible evidence that total PUFA intake was associated

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with reduced risk of diabetes. In our SR evidence for an inverse association between the major dietary n-6 PUFA, LA (in serum-PL and RBC) and the risk of T2DM was *suggestive*. A possible moderate insulin sensitizing effect of n-6 PUFA has been suggested in some RCTs, when compared with SFA (17, 207).

Cardiovascular diseases

Risk of CVD was in this SR not found to be modified by the total dietary fat intake at observed mean intakes from about 30 E% to 45 E%, but the results indicate effects of fat quality. A pooled analysis of data from PCS showed a 20% reduction in the risk of CHD in both men and women when part of SFA was replaced with PUFA, mainly n-6 PUFA, whereas the risk was increased by when SFA was replaced with CHO (93). This association seems to be dependent on type of CHO. In a PCS replacement of SFA by CHO with high glycemic index increased the risk of myocardial infarction whereas a replacement by CHO with low glycemic index did not affect the risk (92). The FAO report, however, evaluated that replacement of fat with 'refined' CHO is probably not associated with an increased risk, but may support the development of the metabolic syndrome (2). CHD is rare in populations with very low intake of both total fat and SFA (<15 E% and <5 E%, respectively) (215). This discrepancy is most likely explained by the quality of CHO in the diet and lower BMI as well as the level of physical activity (92, 216). Circulating levels of some major SFA was in a couple of studies found to be related to overall and CVD mortality, but these data should be interpreted with caution since tissue SFA is a weak dietary biomarker as previously mentioned. Thus, the SR concluded that there is *convincing* evidence that partial replacement of SFA with mainly PUFA can reduce CVD events by around 10–20%, whereas the total amount of fat did not affect the CVD risk (67, 93, 94).

A recent large NCC including both women and men found an inverse association between plasma PL n-6 PUFA (LA in particular) and CHD during a 13-year follow-up and the association was independent of sex and several other confounders (217). Similar results were seen in three studies in North European populations, the United Kingdom, Sweden, and Finland, which was included in this SR (88, 115, 116). Since LA is one of the strongest dietary fatty acid biomarker (mainly reflecting overall intake of PUFA from vegetable oils) the associations are relevant. The inverse association between LA is thus well in accordance with the results based on dietary intakes (93, 94). With respect to n-3 PUFA – ALA or n-3 LCPUFA – two of the included biomarker studies on ALA and CVD indicated a potential beneficial effect (113, 114), whereas no effect of ALA was found in three studies (99, 104, 111). In the study by Mozaffarian et al. (112), a beneficial effect of increasing ALA intakes on CHD events was only evident at concomitant low n-3 LCPUFA intake (<100 mg/day), indicating that the association with ALA may be modified by n-3 LCPUFA intake. The ratio between n-3 and n-6 PUFA was not found to have an effect on CVD risk (104, 112). This is in line with the conclusions by FAO/WHO (2).

The intake of n-3 LCPUFA of marine origin had beneficial effects on CVD incidence and mortality in several studies, but intakes >0.20–0.25 g/day had no or limited effect in most of the studies. The effect seems to be limited to specific CHD outcomes. According to the guidelines by European Society of Cardiology (189) the evidence of the efficacy of total PUFA in secondary prevention in AF was considered limited because of the controversial results. The recent SR and meta-analysis by Rizos et al. (218) concluded that n-3 LCPUFA supplementation was not associated with an overall lower risk of mortality in CHD patients but did find a significant reduction in cardiac death (RR $= 0.91$; 95% CI: 0.85–0.98).

Some major SFA was related to CVD mortality in two studies (115, 116) and overall mortality in one study (115). The data on SFA should, however, be interpreted with caution because they are much weaker dietary biomarkers than LA, ALA, and n-3 LCPUFA (EPA and DHA), as well as the minor 15:0 and C17:0 found in milk fat and fish (81, 214).

Cancer

We included two moderate-quality studies (one RCT and one PSC) that examined the association between total fat intake and total cancer incidence in women. These studies found no significant effect of either with total fat intake (97, 119) or n-3 LCPUFA intake (97). Breast cancer is the major cancer type in women, and the studies included in this SR also did not find any association between risk of breast cancer and the intake of total fat in postmenopausal women, but BMI may modify the association (123). However, a positive association was found in premenopausal women in one of the two included studies (129). Data suggest that the associations may be modified by several factors, for example, hormone replacement therapy (125), age (126), and dietary source of concomitant intake of n-3 and n-6 PUFAs (134). Results from studies using tissue markers of dietary fat intake do not show any consistent relation.

This SR found limited and *inconclusive* evidence linking intake of total fat or quality of fat with endometrial, colorectal, or pancreatic cancer. However, for ovarian cancer, the evidence for a positive association with the intake of SFA is *suggestive* as it is for prostate cancer for an inverse association with the intake of ALA. No associations were found for prostate cancer, esophageal cancer, gastric cancer, renal cell cancer, bladder cancer, lung cancer, or skin cancer by the total intake or types of dietary fat.

The findings from this SR are generally in line with the conclusions from the World Cancer Research Fund (WCRF) report (219). However, the report concluded that there is *limited-suggestive* evidence for a link between total fat and an increased risk of postmenopausal breast cancer and lung cancer and also *limited-suggestive* evidence that foods containing fat of animal origin are linked to increased colorectal cancer risk. According to the WCRF/AICR report (219) there is an indirect link between energy-dense diets and cancer and the evidence indicates a *probable* or *convincing* link between body fatness and most cancer types.

Methodological considerations

The database searches included studies published in 2000–2012. The reason for not including older articles was that we focused on new evidence that has evolved since the previous edition of NNR (10). However, several SRs and meta-analyses that included previous publications were identified and evaluated which likely adds confidence to the results. Although we used structured terms and free text in the searches, additional relevant articles were identified by the experts via 'snowballing' and reference lists, thus emphasizing the importance of expertise in the various research fields.

The use of a structured guide, which included a tool for assessing study quality and criteria for evidence grading, facilitated objective evaluation and judgment (A guide for conducting Systematic Literature Reviews for the fifth edition of the NNR). The guide builds on several other established guidelines developed by, for example, WCFR/AIRC (219), US Agency for Healthcare Research and Quality (220), and the Swedish Council on Health Technology Assessment (221). Combination with predefined inclusion and exclusion criteria of studies minimizes bias. However, criteria for both study quality and evidence grading were strict, resulting in relatively conservative estimates of the evidence, which is also to be taken into account in the discussion where the results of this SR were compared with other SRs and meta-analyses.

In general, there were very few studies graded as high quality (A). Most of the articles were graded as moderate (B), or low (C) quality. This does not mean that all of these studies were of lower quality. A common reason for lower rating was lack of details on methodological issues such as recruitment, dropout, compliance, statistical methods, and dietary intakes. This highlights the need for improved criteria and requirement for reporting in published articles.

The studies on metabolic risk markers were all RCTs except one. The number of subjects varied from 14 to 1,720. It was striking that most of the studies did not use any biomarkers for the compliance to the intervention diets. Only few conclusions can be drawn on the quality of fat on risk markers because of the heterogeneity of comparisons which leads to small number of studies per each comparison.

Many aspects of the intake of fat and the quality of dietary fat have been studied and generally there are only few articles within each of these aspects that look at the effects on hard clinical endpoints in healthy people within the period that is evaluated in this SR. In most cases studies that look at effects on hard clinical endpoints are also mostly observational and only a few of them make proper adjustments for the intake of other nutrients – specifically the intake of total energy, CHO, and protein – as specified in the research question. The endpoint of interest also affects the optimal conduction of a study. Weight maintenance and obesity are easier to investigate by an RCT, whereas the development of CVD and cancer need more long-term studies and are therefore more difficult to be examined in RCTs. For CVD, there are a number of well-characterized metabolic risk markers that are used as indicators of the risk. This is, however, not the case for cancer and there are also relatively few PCS within this field. Despite this, RCCs within this area were not included in drawing the conclusions because of a number of confounding factors typical to this study type.

The impact of dietary assessment method on clinical outcomes has been discussed, especially in epidemiological studies regarding dietary fat and breast cancer (120, 222). Results from statistical analysis of data from diet records and FFQs indicate that FFQs may result in imprecise intake estimates and thus may underestimate true associations. More recent epidemiological studies have, however, not shown any significant differences between risk estimates based on FFQs or dietary records (133).

Results from current Nordic dietary surveys show that the average total fat intake is 31–37 E% in the general adult population, with SFA contributing 12–14 E% and PUFA contributing 5–6 E%. In view of the results of the current SR, focus should be on replacing part of SFA with PUFA and/or MUFA. During the past decade, intake of TFA in the Nordic countries has decreased to 0.5–0.6 E%. It is prudent to keep the intake at a low level, as there are several documented and potential health consequences of elevated intakes (2).

This SR has reviewed a large number of studies, involving several hundred thousand participants, focusing on different health outcomes. Despite the vast research efforts, many questions remain unresolved, mainly because of conflicting results from studies and lack of high-quality controlled studies. There is thus an evident need for highly controlled RCTs and PCS with sufficient number of subjects and long enough duration on the effects of the amount and quality of fat, especially regarding insulin sensitivity, T2DM, low-grade inflammation, and BP. It is warranted to find new surrogate markers for CVD. Furthermore, using the new methodology available for

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examining lipid metabolism, for example, lipidomics and metabolomics, should be considered in the future.

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Contributions of authors

All authors participated in the quality grading of the studies. US, LL, UR, and WB prepared the manuscript. All authors commented the manuscript.

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