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# The Shape of the Dose-Response Relationship between Sugars and Caries in Adults

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## ABSTRACT

Dental caries is considered a diet-mediated disease as sugars are essential in the caries process. However, some gaps in knowledge about the sugars-caries relationship still need addressing. This longitudinal study aimed to explore (i) the shape of the dose-response association between sugars intake and caries in adults; (ii) the relative contribution of frequency and amount of sugars intake to caries levels; and (iii) whether the association between sugars intake and caries varies by exposure to fluoride toothpaste. We used data from 1702 dentate adults who participated in at least two of three surveys in Finland (Health 2000, 2004/05 Follow-Up Study of Adults' Oral Health and Health 2011). Frequency and amount of sugars intake were measured with a validated food frequency questionnaire. The DMFT index was the repeated outcome measure. Data were analysed using fractional polynomials and linear mixed effects (LME) models. None of the 43 fractional polynomials tested provided a better fit to the data than the simpler linear model. In a mutually adjusted LME model, the amount, but not the frequency of sugars intake was significantly associated with DMFT throughout the follow-up period. Furthermore, the longitudinal association between amount of sugars intake and DMFT was weaker in adults who used fluoride toothpaste daily than in those using it less often than daily. The findings of this longitudinal study among Finnish adults suggest a linear dose-response relationship between sugars and caries, with amount of intake being more important than frequency of ingestion. Also, daily use of fluoride toothpaste reduced, but did not eliminate the association between amount of sugars intake and dental caries.

## INTRODUCTION

Dental caries is considered a diet-mediated disease as sugars are essential in the caries process (Burt and Pai 2001; Moynihan and Petersen 2004; Moynihan and Kelly 2014; Sheiham 2001; Zero 2004). A question that needs urgent attention is the shape of the dose-response relationship between sugars and caries, as it is central to decisions about the level of sugars compatible with low levels of dental caries (Moynihan and Kelly 2014). Studies in Japanese children during World War II reported a linear (ecological) relationship between the log of annual caries incidence rate and national sugars consumption per capita per year (Koike 1962; Takeuchi 1961). Later, Newbrun (1982) suggested a sigmoid dose-response curve, based on evidence from animal studies, which became the accepted basis for establishing a limit on sugars intake (Sheiham 2001). A reappraisal of the Japanese ecological data suggested a curvilinear dose-response relationship between annual per capita sugars consumption and annual caries incidence (Sheiham and James 2014a; b).

Another question that needs addressing is the relative importance of frequency versus amount of sugars intake for caries development. The answer to that question will influence health education advice on how to reduce caries. Some believe that the frequency of intake influences the sugars-caries relationship more than the amount (Anderson et al. 2009; Touger-Decker and van Loveren 2003). However, two longitudinal studies showed that caries increment in children was more strongly related to amount of sugars intake than to frequency (Burt et al. 1988; Rugg-Gunn et al. 1984; Rugg-Gunn 1993; Szpunar et al. 1995), although in both studies amount and frequency of sugars intake were modelled separately. A strong positive correlation ( $r=0.77$ ) between amount and frequency of sugars intake was also reported in one of those studies (Rugg-Gunn et al. 1984).

It has been suggested that the relationship between sugar intake and caries is much weaker in populations with widescale fluoride exposure than in those prior to fluoride toothpaste being widely available (Burt and Pai 2001; Touger-Decker and van Loveren 2003). Fluoride alters the dose-response relationship between sugars and caries as it delays when cavitation occurs for a given level of sugars (Zero 2004). The use of fluoride toothpaste may reduce the strength of the association between frequency of sugars intake and caries incidence (Bernabé et al. 2014; Duggal et al. 2001), but nothing is known in terms of amount of sugars intake. Therefore, a third important question to address is whether the dose-response relationship between sugars and caries is affected by fluoride

in adults. A recent review only identified three prospective studies in adults. All were conducted before fluoride toothpaste was widely available (Moynihan and Kelly 2014).

To fill these gaps in knowledge this longitudinal study explored (i) the shape of the association of frequency and amount of sugars intake with caries in adults, (ii) the relatively contribution of frequency and amount of sugars intake to caries levels; and (iii) whether the association of frequency and amount of sugars consumption with caries varies according to exposure to fluoride.

## **METHODS**

The present study adheres to the Strengthening the Reporting of Observational Studies (STROBE) statement (Vandenbroucke et al. 2007).

### **Data source**

We used data from three surveys in Finland (Figure 1). The Health 2000 Survey conducted in 2000-01 was a national survey of the Finnish population including 8028 adults aged 30 years and over, recruited via stratified two-stage cluster sampling (Aromaa and Koskinen 2004). A total of 6335 subjects (79%) had clinical oral examinations. Of them, 5389 (85%) were dentate with complete data on dental status. A follow-up study in 2004-05 included 2000 adults randomly selected from the list of participants who had attended the oral examinations in the Health 2000 Survey. People who died or were edentate, and for logistic reasons, those in health centre districts where less than 15 subjects had been sampled, were excluded. The final sampling frame comprised 1248 subjects who were invited to a clinical oral re-examination; 1049 participated (84%). The Health 2011 Survey was a follow-up study of the Health 2000 Survey. All participants of the Health 2000 Survey alive and living in Finland were invited. The sample of those aged 30 years or over in 2011 consisted of 7964 adults, of whom 5806 (73%) participated in at least one part of the study and 4221 (53%) in the health examination. Only those adults living in Southern or Northern Finland (2 of the 5 examination areas, n=3713) were invited to participate in a new oral examination and 1496 agreed (40%).

There were 1889 dentate adults (aged 30 to 89 years at baseline) who had caries data in at least two of three surveys (baseline plus 2004/5 and/or 2011), of which 187 (10%) were excluded for missing data on covariates. Caries data were available for 1702, 902 and 1009 participants in 2000, 2004 and 2011, respectively. Furthermore, 1493 (88%) contributed to 2 waves of caries data and 209 (12%) to all 3 waves.

## Variable selection

Food consumption was measured in the Health 2000 Survey (baseline data) using a validated food frequency questionnaire (FFQ) including 128 commonly used or nutritionally important food items and mixed dishes (Mannisto et al. 1996; Paalanen et al. 2006). Participants were asked to estimate the consumption frequency of each food item on a nine-point scale from 'never or rarely' to '6 times a day or more often' during the past 12 months. A standard portion size was assigned to each FFQ item and specified using natural units (piece, slice, glass, tablespoon, etc.). When returned, questionnaires were checked for unreliable answers by a nutritionist. The overall frequency of sugars intake (times/day) was estimated by adding the weighted responses (e.g. 0.143 for 'once a week', 2.5 for '2-3 times a day' and 6 for '6 times a day or more often') for 15 sugary items (coffee bread, Danish pastries, sweet pies, cakes, biscuits/cookies, fruit curd, pancakes, ice cream, chocolate, liquorice, candies, sugared coffee/tea, cocoa, fruit juices and sweetened soft drinks). The amount of sugars intake (grams/day) was estimated by multiplying the food consumption frequency by fixed portion sizes. The ingredients of mixed foods were broken down into their components as well as the contents of different nutrients using the Finnish Food Composition Database (Fineli®, National Institute for Health and Welfare, Finland).

Demographic, socioeconomic and behavioural factors at baseline were considered as potential confounders. Socioeconomic position was indicated by participants' education (basic, secondary and higher). Dental behaviours were dental attendance pattern that was reported on a 3-point scale (regularly for check-ups, only for emergencies or never), toothbrushing frequency on a 5-point scale (more often than twice a day, twice a day, once a day, less often than every day or never) and use of fluoride toothpaste on a 4-point scale (daily, weekly, less often or never).

Identical clinical oral examinations were conducted at baseline and follow-ups and were independent of participants' completion of questionnaires. Clinical examinations were performed by dentists with participants seated on a dental chair and using headlamps, fibre optic light, mouth mirror and a WHO periodontal probe. Teeth were blown dry before inspection and cotton rolls were used to keep them dry while inspected. A tooth was recorded as decayed if there was evidence of a carious lesion clearly extending into dentine on any coronal or root surface. The carious lesion had to be cavitated, to have penetrated the fissure and undermined the enamel, or the dentine walls to be clearly softened. All the examiners (in 2000/01, 2004/05 and 2011) received similar training given by the same experienced

dentists. The overall Kappa value for inter- and intra-examiner reliability at the baseline survey was 0.87 and 0.95 at tooth level, respectively (Suominen-Taipale et al. 2004; Suominen-Taipale et al. 2008). The sum of decayed, missing and filled teeth or DMFT index was estimated from each wave and used as a repeated outcome measure.

### **Statistical analysis**

Linear mixed effects (LME) models were used to estimate the longitudinal association between sugars intake at baseline and DMFT levels over 11 years. LME models use all available data over the follow-up, handle unequally spaced observations over time and take into account the fact that repeated measures on the same individual are correlated (Singer and Willett 2003; Twisk 2013). We fitted both the intercept and the slope as random effects, allowing individual differences both in DMFT level at baseline and rate of DMFT increment. All analyses were run in Stata 13 using the *mixed* command.

We first explored the shape of the dose-response relationship of frequency and amount of sugars intake with DMFT levels using fractional polynomials, a flexible family of parametric models that allows modelling curvilinear associations (Royston and Altman 1994; Royston et al. 1999). Briefly, the model deviance of each of 8 powers (-2, -1, -0.5, 0, 0.5, 1, 2 and 3, where a power of 0 is the log function and a power of 1 the straight line) was used to identify the best fitting first-order polynomial. All 36 combinations of pairs of these powers were then examined, and again the model deviance was used to select the best-fitting second-order polynomial. Next, the best fitting second-degree polynomial was compared with the linear model using the difference in model deviances. If the second-degree model provided a better fit to the data than the linear one ( $p < 0.05$ ), the former was then compared to the best fitting first-order model. Otherwise, the linear model was preferred (Sauerbrei et al. 2007). The method is similar with multilevel models (Long and Ryoo 2010).

We then explored the relative contribution of the frequency and amount of sugars intake to variations in DMFT levels. First we estimated a model without any covariates (null model) to establish the rate of change in DMFT within the observed period. Survey years (2000, 2004 and 2011) were used as the underlying time scale in all models. Next, we tested the crude effects of frequency and amount of sugars intake on DMFT in Model 1 and subsequently adjusted for socio-demographic factors (sex, age and education) in Model 2 and dental behaviours (toothbrushing frequency and dental attendance pattern and use of fluoride toothpaste) in Model 3. Frequency and amount of sugars intake were

mutually adjusted in Model 4 to evaluate their relative contribution to explaining variations in DMFT levels conditional on each other.

Finally, the moderating role of use of fluoride toothpaste on the effects of frequency and amount of sugars intake was examined by testing the significance of the statistical interaction between use of fluoride toothpaste and each indicator of sugars intake in models also adjusted for confounders (Model 3). We also tested the three-way interactions between toothbrushing frequency, use of fluoride toothpaste and each indicator of sugars intake. The significance level was set at 0.10 to increase power when testing interactions (Aiken and West 1991; Marshall 2007).

## RESULTS

We used data from 1702 adults, with a mean age of 47.6 years (SD: 11.4). No differences in socio-demographic characteristics and DMFT levels were found between the study sample and those excluded for missing data on covariates. The mean amount of sugars intake was 110.9 g/day (SD: 47.8; range: 13.7-442.3) with significant differences by sex and age. The mean frequency of sugars intake was 3.2 times/day (SD: 2.4, range: 0-15.6) with significant differences by sex, education, toothbrushing frequency and use of fluoride toothpaste (Table 1). The frequency and amount of sugars intake were positively correlated ( $r=0.64$ ,  $R^2=0.41$ ,  $p<0.001$ ). The mean DMFT at baseline was 21.91 (SD: 6.4; range: 0-32), with only 3 participants (0.2%) having no caries experience.

Table 2 shows the results from fitting first- and second-order polynomials to the data in order to test for curvilinear dose-response relationships between sugars intake and DMFT levels. The best fitting first-order polynomial had a power 3 whereas the best fitting second-order polynomial had powers (-2 3) in frequency of sugars intake. Neither model was significantly better, in terms of model fit to data, than the straight line model. For amount of sugars intake, the best fitting polynomials of degree 1 and 2 had powers 2 and (3 3), respectively. Again, the fit of those polynomials was not significantly better than that of the simpler linear model. Consequently, the associations of frequency and amount of sugars intake with DMFT levels were modelled as linear effects.

The null LME model showed that the mean DMFT increased by 0.47 units (95%CI: 0.37-0.58) in 2004 and 0.74 units (95% CI: 0.64-0.84) in 2011. Neither the frequency nor the amount of sugars intake was significantly associated with DMFT in unadjusted models (Table 3). However, both indicators became, and remained significant after adjustment for socio-demographic and behavioural factors.



The DMFT throughout the follow-up period increased by 0.15 (95%CI: 0.04-0.25) and 0.10 units (95%CI: 0.04-0.15) for every additional occasion of sugars consumption and every 10 grams of sugars consumed, respectively. In addition, only the amount of sugars intake remained significantly associated with DMFT levels in the mutually adjusted model (0.09 DMFT units, 95%CI: 0.02-0.15).

The use of fluoride toothpaste moderated the association between amount of sugars intake and DMFT levels ( $p=0.064$ ) but not that between frequency of sugars intake and DMFT levels ( $p=0.129$ ). The slope of the longitudinal association between amount of sugars intake and DMFT levels was less pronounced in adults using fluoride toothpaste on a daily basis (0.08, 95%CI: 0.03-0.14) than in those using it less often than daily (0.26, 95%CI: 0.07-0.45) (Figure 1). Although the same pattern was observed for frequency of sugars intake in adults using fluoride daily (0.12, 95% CI: 0.04-0.23) and less often than daily (0.43, 95%CI: 0.01-0.75), the two coefficients were not significantly different. The three-way interactions of toothbrushing frequency and use of fluoride toothpaste with frequency and amount of sugars intake were not significant ( $p=0.712$  and  $0.307$ , respectively).

## DISCUSSION

This study first found that both the frequency and amount of sugars consumption were linearly related to dental caries in adults. None of the 43 alternative curvilinear models, including the logarithmic, quadratic and cubic transformations among others, provided a significant improvement from the straight line model. A linear dose-response relationship between sugars and caries implies that even the small amount of sugars will lead to caries development in adults. This finding challenges previously held assumptions on the shape of the sugars-caries relationship based on ecological data from Japanese children. The difference between the original and re-analysis of the Japanese data is explained by the scale used to model caries incidence. While Takeuchi (1961) and Koike (1962) used the log of annual caries incidence, Sheiham and James (2014a; b) used annual caries incidence. A curvilinear relationship in crude scale becomes linear when log-transformed.

Second, the amount of sugars consumed was more relevant to caries levels than the frequency of ingestion. In the mutually adjusted model, the DMFT increased by 0.09 units (95%CI: 0.02-0.15) for every 10 additional grams of sugars consumed while the coefficient for frequency of intake was not significant. The strongest evidence on the role of frequency of sugars intake in adults comes from the Vipeholm study (Gustafsson et al. 1954). However, our finding agrees with two prospective studies in

children (Burt et al. 1988; Rugg-Gunn et al. 1984). Collinearity could not explain these findings since amount of intake only explained around 40% of the variation in frequency and vice-versa. This finding also implies that frequency cannot be used as a proxy for amount of sugars ingestion. Indeed, one could exceed the recommended energy intake from sugars in a single occasion. This finding supports the view that population nutrient goals should be set in terms of amount of sugars so as to monitor population's diets and evaluate the outcomes of health promotion initiatives against clear milestones (Moynihan 2014). Focusing on amount of sugars intake will also be consistent with current guidelines to reduce the risk of other non-communicable diseases related to excess sugars (WHO 2015).

Third, the association between amount of sugars intake and dental caries varied depending on adults' exposure to fluoride toothpaste. A weak, although significant relationship between amount of sugars intake and dental caries persisted with regular exposure to fluoride toothpaste. Importantly, sugars were related to dental caries even in a population with slow caries progression (DMFT increment lower than 1 tooth over 11 years), low levels of fluoride in water—in 98% of water from waterworks and 95% of single well waters the concentration of fluoride is <0.1mg/l (Ahonen et al. 2008)—but high exposure to fluoride toothpaste (92% reported using fluoride toothpaste daily).

Some limitations need to be addressed. First, although the study sample was large and drawn from a national survey, those who participated in the follow-ups were younger and more educated, had more favourable dental behaviours and lower DMFT than participants at the baseline survey. Thus, the present results reflect valid relationships between the variables of interest, but are not generalisable to the entire Finnish adult population. Second, sugars consumption was collected using a FFQ with 12-month recall period and single average portion sizes. Thus, there can be some measurement error due to under- and over-reporting (Shim et al. 2014; Thompson and Byers 1994). Furthermore, FFQs do not distinguish between food items that are consumed together or in separate occasions during the day, which may overestimate the frequency of intake for some individuals. However, an advantage of FFQs is that they evaluate the usual long-term diet, which is conceptually more important in epidemiological studies than absolute intake over a few days (as derived from food records). The FFQ used in this study was calibrated against a 16-day food record and it was found to meet the requirements of epidemiological studies (Paalanen et al. 2006). Third, we assessed sugars consumption at a single point in time (baseline). This is the simplest scenario in longitudinal research and unlikely to represent the complex interplay of factors influencing caries development (individuals'

diet may have changed during the follow-up period). Further studies, using alternative methods to assess sugars intake over multiple times, are therefore encouraged. Fourth, although caries was diagnosed for each tooth surface, it was recorded by tooth and reported with the DMFT due to time constraints during comprehensive clinical examinations. The DMFT shows lower variation (and weaker associations) than the DMFS and is affected by the inclusion of teeth extracted for conditions other than caries, particularly among old groups. However, the DMFT is well established as the key measure of caries experience in dental epidemiology.

In conclusion, the association between sugars intake and dental caries in this group of Finnish adults was best described using a linear dose-response relationship. Second, the amount of sugars intake was more relevant to caries development than frequency. The effect of frequency on dental caries was fully attenuated after accounting for amount of sugars ingested. Third, sugars were related to caries in adults using and not using fluoride toothpaste daily, although the association was stronger in those using fluoride toothpaste less often than daily.

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The authors declare no conflicts of interest in relation to this work.

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**Table 1.** Frequency (times/day) and amount (g/day) of sugars consumed according to baseline characteristics (n=1702 adults)

Baseline characteristics	n	(%)	Frequency	Amount
			Mean (SD)	Mean (SD)
<i>Sex</i>				
Men	750	44%	3.8 (2.6)	114.9 (49.6)
Women	952	56%	2.7 (2.1)	107.8 (46.1)
			<i>P value</i> <sup>a</sup>	
			<0.001	0.002
<i>Age groups</i>				
30-34 years	241	14%	3.2 (2.4)	109.1 (44.1)
35-44 years	508	30%	3.3 (2.3)	116.4 (46.8)
45-54 years	498	29%	3.0 (2.5)	108.5 (49.2)
55-64 years	307	18%	3.1 (2.7)	107.3 (49.5)
65+ years	148	9%	3.2 (2.3)	110.6 (47.4)
			<i>P value</i>	
			0.331	0.042
<i>Education</i>				
Basic	417	25%	3.3 (2.5)	108.9 (46.3)
Secondary	606	36%	3.4 (2.6)	114.6 (52.0)
Higher	679	40%	2.8 (2.2)	108.9 (44.6)
			<i>P value</i>	
			<0.001	0.066
<i>Dental attendance pattern</i>				
Only for emergency/never	637	37%	3.3 (2.5)	110.3 (48.0)
Regularly for check-ups	1065	63%	3.1 (2.4)	111.3 (47.7)
			<i>P value</i>	
			0.107	0.662
<i>Toothbrushing frequency</i>				
Once a day or less	539	32%	3.7 (2.7)	112.3 (49.3)
Twice or more a day	1163	68%	2.9 (2.3)	110.3 (47.1)
			<i>P value</i>	
			<0.001	0.429
<i>Use of fluoride toothpaste</i>				
Less often than daily	128	8%	3.9 (2.9)	112.1 (49.3)
On a daily basis	1574	92%	3.1 (2.4)	110.8 (47.7)
			<i>P value</i>	
			<0.001	0.768

<sup>a</sup> t-test and analysis of variance were used to compare 2 and 3+ groups, respectively

**Table 2.** Comparison of model fit between different specifications for the effect between frequency and amount of sugars consumption and DMFT levels over 11 years using fractional polynomials

Variable	Model	df	Deviance	Deviance difference	p value	Powers
Frequency	omitted	0	17830.23	10.978	0.052	
	linear	2	17823.03	3.776	0.287	1
	m = 1	3	17819.42	0.168	0.919	3
	m = 2	5	17819.26	0	--	-2 3
Amount	omitted	0	17830.23	14.595	0.006	
	linear	1	17817.28	1.64	0.651	1
	m = 1	2	17817.08	1.44	0.486	2
	m = 2	4	17815.64	0	--	3 3

df: degrees of freedom

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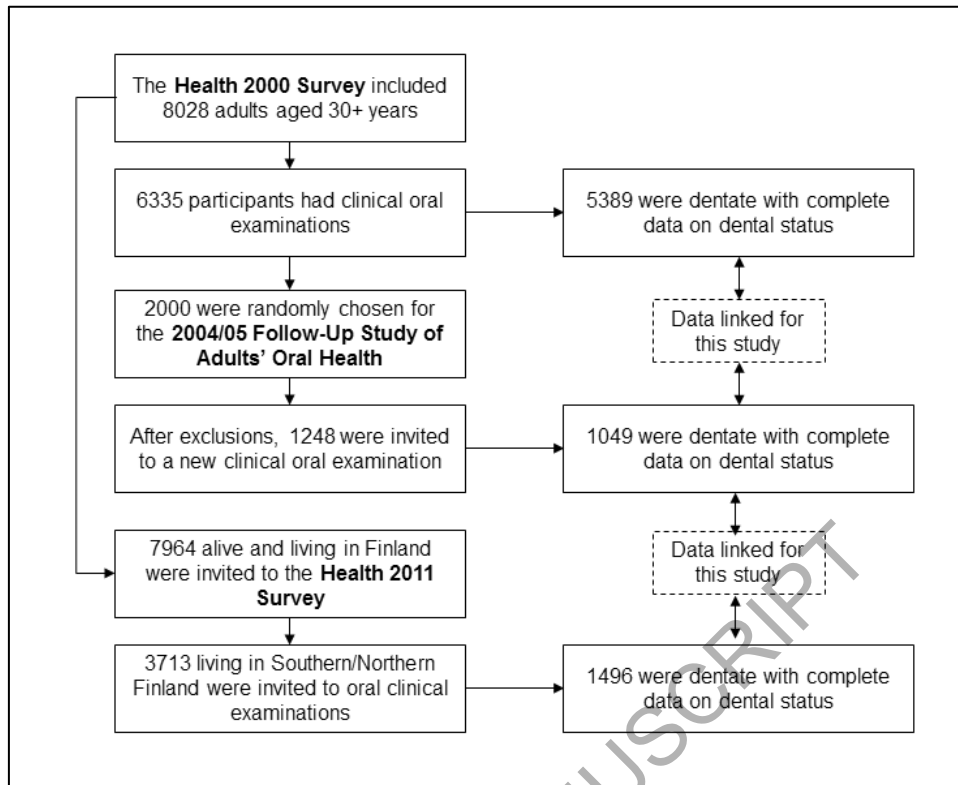


**Table 3.** Linear mixed effects models for the associations of frequency and amount of sugars intake with DMFT levels over 11 years (n=1702 adults)

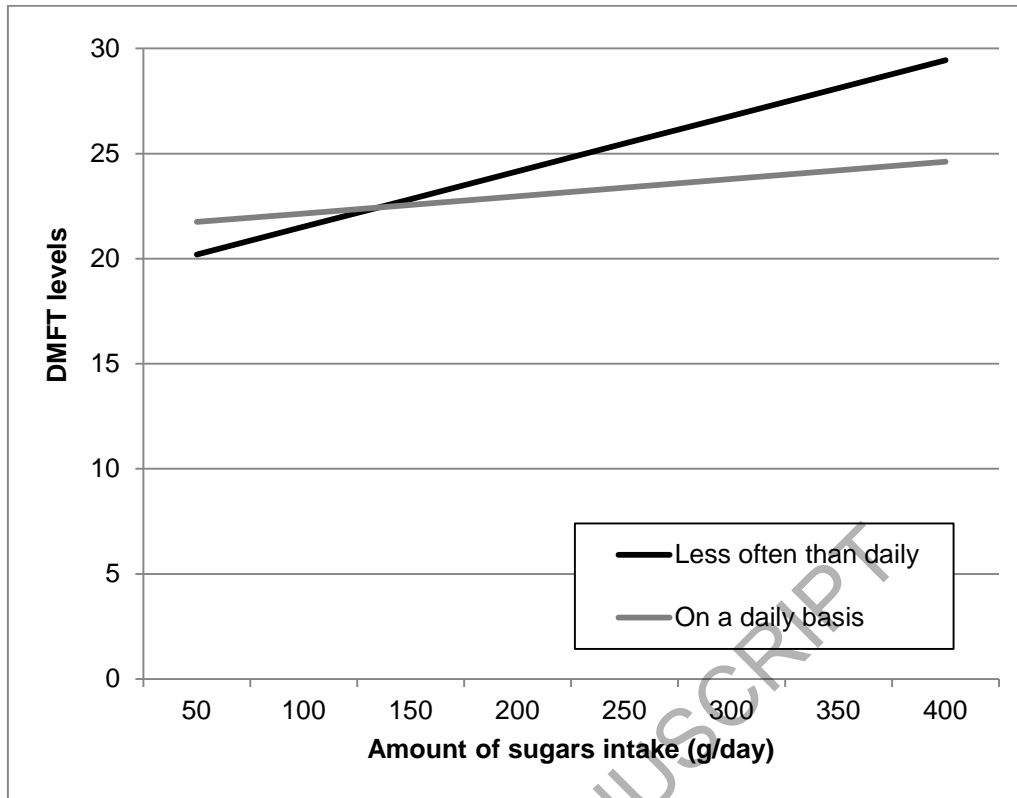
<b>Sugars</b>	<b>Model 1<sup>a</sup></b>	<b>Model 2<sup>a</sup></b>	<b>Model 3<sup>a</sup></b>	<b>Model 4<sup>a</sup></b>
<i>Frequency of sugars intake (times/day)</i>				
Coefficient	0.10	0.14	0.15	0.03
[95% CI]	[-0.02, 0.22]	[0.03, 0.24]	[0.04, 0.25]	[-0.10, 0.17]
<i>P value</i>	0.101	0.011	0.007	0.628
<i>Amount of sugars intake (10g/day)</i>				
Coefficient	0.06	0.10	0.10	0.09
[95% CI]	[0.00, 0.12]	[0.04, 0.15]	[0.04, 0.15]	[0.02, 0.15]
<i>P value</i>	0.055	<0.001	<0.001	0.014

<sup>a</sup> Model 1 was unadjusted, Model 2 adjusted for sociodemographic factors (sex, age and education), Model 3 also adjusted for dental behaviours (toothbrushing frequency and dental attendance pattern and use of fluoride toothpaste) and Model 4 further adjusted for the other indicator of sugars intake.

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**Figure 1.** Flow chart of participation and data linkage for the Health 2000 Survey, the 2004/05 Follow-Up Survey of Adults' Oral Health and the Health 2011 Survey.



**Figure 2.** Association between amount of sugars intake and DMFT levels over 11 years in adults with daily exposure to fluoride and those with exposure less often than daily. Estimates were derived from a linear mixed model regressing DMFT levels on sex, age, education, toothbrushing frequency, dental attendance pattern, use of fluoride toothpaste, amount of sugars intake and the two-way interaction between amount of sugars intake and use of fluoride toothpaste.