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Does high sugar consumption exacerbate cardiometabolic risk factors and increase the risk of type 2 diabetes and cardiovascular disease?

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Abstract

Consumption of sugar has been relatively high in the Nordic countries; the impact of sugar intake on metabolic risk factors and related diseases has been debated. The objectives were to assess the effect of sugar intake (sugar-sweetened beverages, sucrose and fructose) on association with type 2 diabetes, cardiovascular disease and related metabolic risk factors (impaired glucose tolerance, insulin sensitivity, dyslipidemia, blood pressure, uric acid, inflammation markers), and on all-cause mortality, through a systematic review of prospective cohort studies and randomised controlled intervention studies published between January 2000 and search dates. The methods adopted were as follows: the first search was run in PubMed in October 2010. A second search with uric acid as risk marker was run in April 2011. The total search strategy was rerun in April 2011 in SveMed+. An update was run in PubMed in January 2012. Two authors independently selected studies for inclusion from the 2,743 abstracts according to predefined eligibility criteria. The outcome was that out of the 17 studies extracted, 15 were prospective cohort studies and two were randomised controlled crossover trials. All of the studies included only adults. With respect to incident type 2 diabetes (nine studies), four of six prospective cohort studies found a significant positive association for sugar-sweetened beverage intake. In general, larger cohort studies with longer follow-up more often reported positive associations, and BMI seemed to mediate part of the increased risk. For other metabolic or cardiovascular risk factors or outcomes, too few studies have been published to draw conclusions. In conclusion, data from prospective cohort studies published in the years 2000–2011 suggest that sugar-sweetened beverages probably increase the risk of type 2 diabetes. For related metabolic risk factors, cardiovascular disease or all-cause mortality and other types of sugars, too few studies were available to draw conclusions.

Keywords: *sugar; fructose; sugar-sweetened beverages; systematic review; Nordic nutrition recommendations*

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The present literature review is a part of the fifth version of the Nordic Nutrition Recommendations (NNR) project with the aim of reviewing and updating the scientific basis of the fourth edition of the NNR issued in 2004 (1). The NNR5 project is mainly focused on a revision of those areas in which new scientific knowledge has emerged since the fourth edition, with special relevance for the Nordic setting. A number of systematic literature reviews will form the basis for establishment of dietary reference values in the fifth edition of NNR.

The present expert group was to systematically review studies regarding carbohydrate quantity and quality in association with health outcomes. To limit the scope, the group first reviewed the Dietary Guidelines from the United States Department of Agriculture (USDA) (2–4) and the Dietary Reference Values from European Food Safety Agency (EFSA) (5), both published in 2010, especially with respect to how values from those reports differ from each other and from the NNR 2004. The dietary reference values from EFSA (5) and the dietary guidelines from USDA (3, 4), which are partly based on a

series of literature reviews, and the NNR from 2004 (1) are similar with respect to total intake of carbohydrates (45–60E%, 45–65E% and 50–60E%, respectively) and fibre for adults (25, 25–35 and 25–35 g/day, respectively). Neither the opinion from EFSA nor the report from USDA found sufficient evidence to support the role of the glycaemic index and glycaemic load in maintaining weight and preventing metabolically related diseases in healthy adults. However, dietary reference values and guidelines for sugars are not consistent. The NNR from 2004 recommends limiting refined sugar intake to no more than 10% of total energy intake (E%), whereas EFSA's Scientific Opinion on Dietary Reference Values states that the scientific data are insufficient to define an upper limit and USDA Dietary Guidelines Advisory Committee suggests a maximal added sugar intake of 25% or less of total energy (3). In contrast, the USDA policy document recommends that combined added sugar and solid fat intake be limited to 5–15E% (4).

The basis for the recommendation of maximum 10E% from refined sugars in the NNR from 2004 is mainly based on association with caries in the oral cavity and lower nutrient density of the food with increasing sugar intake in the Nordic countries. In recent years, however, interest has been revived in the potential role of sugar-sweetened beverages, added sugar and total fructose intake in the development of metabolic and cardiovascular diseases and risk factors (6–11), but whether sugar plays a causal role is still much debated (8, 11). This issue was not approached in detail in the previous NNR (1).

Sugar consumption has increased dramatically in the world, including the Nordic countries, over the last decades; the increase in sugar intake from sugar-sweetened beverages has been especially prominent (6). The increase has been more pronounced among older children, adolescents and young people. In the Nordic countries, the mean intake of refined sugar was approximately 8–12E% in 1997–2009 (12–16). At the same time the prevalence of obesity and type 2 diabetes has increased dramatically in the Nordic countries.

We chose to focus on sugar intake in relation to disease development because of the relatively high sugar intake in Nordic countries and the discrepancy in recommendations. Because the World Health Organisation is performing a systematic literature review on sugar and obesity, and because a systematic review was previously performed in association with the USDA recommendations (2), this endpoint was not included in the search.

The aim of this systematic literature review was to assess the effect of sugar intake (sugar-sweetened beverages, sucrose and fructose) on association with type 2 diabetes, cardiovascular disease and related metabolic risk factors (impaired glucose tolerance, insulin sensitivity, dyslipidemia, blood pressure, uric acid, inflammation markers), and all-cause mortality, through a systematic

review of prospective cohort studies and randomised controlled intervention studies published in 2000–2010.

Methods

Eligibility criteria

We defined the literature search and criteria for inclusion and exclusion (set prior to abstract screening) based on the following aspects:

- (1) *Exposure/intervention*: We included sugar-sweetened beverages, sugars, sucrose and fructose as indicators of dietary sugar exposure. We included studies examining intrinsic, added and total sugar intake.
- (2) *Study design*: Prospective observational studies (cohort or nested case-control) with a length of follow up of 4 years or more, or randomised and controlled interventions that last at least 4 weeks were included. For randomised studies, the drop-out rate had to be less than 50%. Studies including more than one intervention in the experimental arm were not included.
- (3) *Outcome*: We included cardiovascular disease, type 2 diabetes and all-cause mortality as outcome measures. Glucose tolerance, insulin sensitivity, serum lipids, inflammation markers and blood pressure were chosen as intermediate markers. After scanning the abstracts, we found that there were several papers including uric acid, a potentially important metabolic and cardiovascular risk factor. This search term was therefore included as an additional outcome.
- (4) *Control*: The control diet in intervention trials had to include replacement of sugars with a corresponding amount of carbohydrate. In the case of fructose, the control group had to include a corresponding amount of sucrose, glucose or non-sugar carbohydrate. Studies not including a control group were not considered.
- (5) *Population*: The population was defined as the general healthy population including all age groups. We also considered studies that included individuals that were overweight. We only included studies in humans.
- (6) *Language*: English or a Nordic language.
- (7) *Article type*: Original articles and systematic reviews.
- (8) *Time period*: Main search from January 2000 to October 2010. Later updated to include November 2010 through December 2011.

Search methods and terms

The literature search was performed in collaboration with a librarian in order to ensure objectivity. Search terms are presented in Appendix 1. The first search was run in October 2010 in Medline through the PubMed platform,

supplied by United States National Library of Medicine (<http://www.ncbi.nlm.nih.gov/pubmed>). Papers from January 2000 to October 2010 were included. An additional search was done including uric acid as an outcome (April 2011) with the search terms 'Uric acid' (Mesh) and Uric* (Title/Abstract). In this search the time limits were slightly changed to include articles from January 2000 to April 2011. Furthermore, in April 2011 the whole search was rerun in a second database, SveMed+, supplied by the Karolinska Institute in Sweden (<http://micr.kib.ki.se/>) (April 2011), in order to include multiple databases in the systematic literature review. An update was run in Medline through the PubMed platform in January 2012 for the time period October 2010 through December 2011 to identify articles that would change the conclusion from the search until October 2010.

Selection of articles

After receiving the list of abstracts, two groups of two experts reviewed the same abstracts independently. The four experts individually reported to the librarian the articles to order in full text. Relevant systematic reviews and meta-analyses were also requested to ensure that all relevant studies were included in this systematic review. A paper was ordered in full text if one of the experts chose to include the paper. Abstracts not relevant for the research questions were excluded and reasons given. Papers from other sources were also ordered from the librarian after going through abstracts, full text papers and literature lists. The full text papers were again reviewed by two independent experts. The experts jointly decided which articles to include. The excluded articles were listed with reasons for exclusion (Appendix 2).

Quality assessment and grading of evidence

To assess study quality of the included studies, Quality Assessment Tools with a number of questions regarding several aspects of the study (including study design, population characteristics, exposure measure and outcome measures) were used (17). Two experts assessed the quality of the same studies independently and potential disagreement between experts was discussed in the whole group. The quality was assessed for all included studies and ranged from A to C (18). After the quality assessment of individual studies, the results of the quality assessment were summarised to evaluate the quality and strength of the evidence in relation to the research questions posed. The evidence for each outcome was categorised according to the directions given by the NNR5 committee guidelines into three categories: convincing, probable, limited-suggestive and limited-no conclusion.

Results

Description of studies

The original search resulted in 2,614 abstracts (Fig. 1). Together with the search for uric acid (68 abstracts) and the search in the SveMed+ database (61 abstracts), a total of 2,743 abstracts were identified. From these sources 85 abstracts (72 from original search, 9 from uric acid search and 4 from SveMed+ search) were selected for further consideration. From systematic reviews and other sources we identified four other articles to order in full text. Out of these, 17 articles (14 from the original search, 1 from the uric acid search and 2 from other sources) met the inclusion criteria and were included in this literature review (Tables 1 and 2). None of the included studies reached the highest level of quality (A). The majority of the 17 identified studies were prospective observational studies ($n = 15$). All of the studies included adults only; none of the studies included children or adolescents.

In the additional search (November 2010–December 2011), including 545 abstracts, 4 papers met the inclusion criteria and were considered of interest. These papers did not change the conclusion and were therefore not quality assessed or included in the paper.

Association between exposure and outcome measures

Blood lipids, glucose and insulin

Two prospective observational studies investigated the association between consumption of sugar-sweetened beverages and incident dyslipidemia (19, 20). Both studies found a positive association with high triglycerides (Table 3), as well as with low LDL cholesterol in the study including this endpoint (20). However, one of the

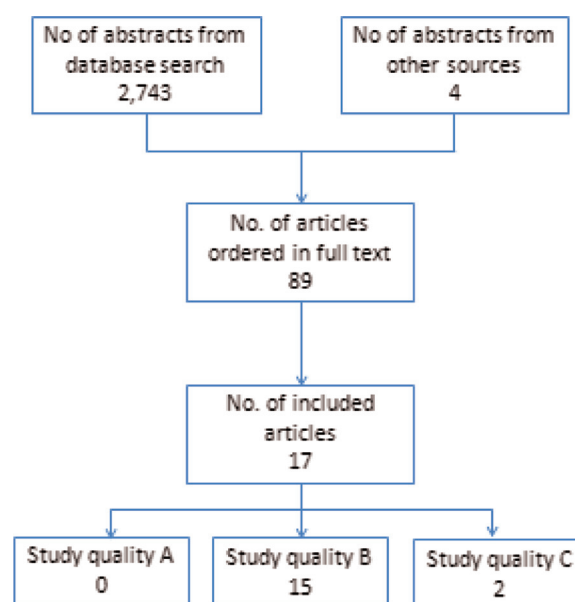


Fig. 1. Results of the search.

Table 1. Description of included prospective cohort studies.

Reference	Cohort, country	No. of participants	Age, gender	Exposure	Diet method	Outcome	Follow-up	Confounder adjustments	Quality
Bomback et al. (33)	Atherosclerosis Risk in Communities (ARIC), USA	9,451	Mean age: 52–54 y, men and women	Sugar-sweetened soft drinks	Semi-quantitative FFQ	Hyperuricemia	3 y	Age, sex, BMI, sodium intake, caloric intake, hypertension, diabetes, tobacco and alcohol use, education, field centre and race	B
de Koning et al. (28)	Health Professionals follow-up Study, USA	40,389	40–75 y, men	Sugar-sweetened beverages	Semi-quantitative FFQ	Type 2 diabetes	20 y	Age, smoking, physical activity, alcohol intake, multivitamin use, family history of type 2 diabetes, high TG at baseline, high blood pressure, use of diuretics, weight change, adherence to a low calorie diet in 1994, the alternative healthy eating index, energy intake	B
Dhingra et al. (19)	Framingham Heart Study, USA	6,039 person-observations	Mean age: 53 y, 57% women	Soft drinks (both regular and diet)	Physician-administered questionnaire	Metabolic syndrome and individual components (waist, fasting glucose, blood pressure, fasting TG, HDL-C)	4 y	Baseline levels of metabolic syndrome component, age, sex, physical activity, smoking, saturated fat, trans fat, fiber, magnesium, total calories, glycaemic index	B
Duffey et al. (20)	CARDIA, USA	up to 2,639	18–30 y, 53–66% women	Sugar-sweetened beverages (sugar-sweetened soda and fruit drinks)	Semi-quantitative interviewer-administered diet history FFQ	Blood pressure, fasting lipids, glucose and insulin	20 y	Race, age, sex, weight, smoking, physical activity, calories from food, calories from other beverages, calories from alcohol, center	B
Forman et al. (23)	Nurses Health Study I, II, Health Professionals Follow up study, USA	NHS1: 88,540; NHS2: 97,315; HPFS: 37,37	Age, women and men	Fructose	Semi-quantitative FFQ administered at baseline and every 4 y	Hypertension	NHS1: 20 y; NHS2: 14 y; HPFS: 18 y.	Age, BMI, physical activity, smoking, family history of hypertension, intake of alcohol, caffeine, folate and vitamin C	B

Table 1 (Continued)

Reference	Cohort, country	No. of participants	Age, gender	Exposure	Diet method	Outcome	Follow-up	Confounder adjustments	Quality
Fung et al. (34)	Nurses Health Study, USA	88,520	34–59 y, women	Sugar-sweetened soda and fruit drinks	Semi-quantitative FFQ administered at baseline and every 4 y	Coronary heart disease	24 y	Age, smoking, alcohol intake, family history of coronary heart disease, physical activity, aspirin use, menopausal status, postmenopausal hormone use, history of hypertension, history of high cholesterol, diet (alternate healthy eating index)	B
Hodge et al. (24)	Melbourne Collaborative Cohort, Australia	31,276	40–69 y, women and men	Sugars	121-item FFQ	Type 2 diabetes	4 y (baseline 1990–94)	Age, sex, country of birth, physical activity, family history of diabetes, education, alcohol intake, previous weight change, BMI, waist-hip-ratio	C
Janket et al. (25)	Women's Health Study, USA		Mean age: 54 y, women	Total sugars, sucrose, fructose	semi-quantitative FFQ	Diabetes	6 y	Age, smoking, alcohol intake, multivitamin use, family history of diabetes, vigorous exercise, BMI, postmenopausal hormone use, history of hypertension, history of high cholesterol	B
Meyer et al. (26)	Iowa Women's Health Study, USA	35,988	55–69 y, women	Sucrose, fructose	FFQ	Type 2 diabetes	6 y	Age, energy intake, BMI, waist:hip ratio, education, smoking, alcohol intake and physical activity	B
Montonen et al. (27)	Finnish Mobile Clinic Health Examination Survey, Finland	4,304	40–69 y, 46% women	Total sugars, sucrose, fructose, soda drinks	Dietary history interview (consumption during previous year)	Type 2 diabetes	12 y (baseline 1966–72)	Age, sex, BMI, energy intake, smoking, geographical area, physical activity, family history of diabetes and dietary pattern	B

Table 1 (Continued)

Reference	Cohort, country	No. of participants	Age, gender	Exposure	Diet method	Outcome	Follow-up	Confounder adjustments	Quality
Odegaard et al. (29)	Singapore Chinese Health Study, China	43,580	45–74 y, 46–59% women	Soft drinks	Semi-quantitative FFQ during previous year (face-to-face interview-based), eight frequency and three portion sizes.	Type 2 diabetes	6 y (baseline 1993–1998)	Age, sex, dialect, year of interview, educational level, smoking status, alcohol use, physical activity, saturated fat, dietary fiber, dairy, juice/soft drink, coffee BMI and energy intake	B
Paganini-Hill et al. (35)	Leisure World Cohort, USA	13,624	44–101 y, 63% women	Sugar-sweetened soft drinks (cola beverages with sugar; other soft drinks with sugar)	FFQ	Mortality	23 y (baseline 1981)	Age, sex, smoking, exercise, BMI, alcohol, histories of hypertension, angina, heart attack, stroke, diabetes rheumatoid arthritis, cancer	C
Palmer et al. (32)	Black Women's Health Study, USA	43,960	21–69 y, women	Sugar-sweetened soft drinks; other fruit drinks (80% are sweetened)	FFQ (frequency and three portion sizes)	Type 2 diabetes	10 y (baseline 1995)	Age, family history of diabetes, physical activity, cigarette smoking, education, the other drinks, red meat, processed meats, cereal fiber, coffee, glycaemic index	B
Paynter et al. (31)	Atherosclerosis Risk in Communities (ARIC), USA	12,204	45–64 y, 56% women	Sweetened beverages	Interview-administered semi-quantitative FFQ	Type 2 diabetes	3, 6 or 9 y	Study center, age, race, education, family history of diabetes, BMI, waist-hip ratio, energy intake, dietary fiber, smoking, alcohol consumption, physical activity and hypertension	B
Schulze et al. (30)	Nurses Health Study II, USA	91,249	26–46 y, women	Sugar-sweetened soft drinks	Semi-quantitative FFQ	Type 2 diabetes	8 y (baseline 1991, updated 1995)	Age, alcohol intake, physical activity, family history of diabetes, smoking, postmenopausal hormone use, oral contraceptive use, fiber, magnesium, trans fat, PUFA: SFA ratio and consumption of diet soft drinks, fruit juice and fruit punch	B

Table 2. Description of included intervention studies

Reference	Country	Study design	No. of participants	Age	BMI ^a	Intervention diet	Control diet	Outcome	Follow-up	Dropout/ Compliance	Quality
Bantle et al. (21)	USA	Randomised crossover	24 (12 men)		<32 (average 25)	17E% fructose	14E% glucose, 3E% fructose	Plasma lipids, plasma glucose, serum insulin	6 weeks	No information	B
Black et al. (22)	UK	Randomised crossover	13 men	Mean age: 33 y	<35 (average 26.6)	25E% sucrose	10E% sucrose	Plasma glucose, serum insulin, insulin sensitivity, blood pressure, serum lipids	6 weeks	1 dropout	B

studies also found a positive association to HDL cholesterol (19), while the other study found no significant association to this marker (20). Furthermore, both of these studies investigated the association between sugar-sweetened beverages and incidence of impaired fasting glucose. One found a positive association (19) while the other found no association (20) (Table 4). A 6-week randomised cross-over trial in 12 men and 12 women comparing high fructose vs. glucose intake (17E%), found adverse effects of the high-fructose diet on triglyceride concentrations in men but not in women and on no other marker of blood lipids, i.e. total cholesterol, LDL cholesterol or HDL cholesterol. Day-long serum insulin values were lower on the fructose diet while there was no difference in plasma glucose (21). In a 6-week randomised cross-over trial in 13 men comparing high (25E%) vs. moderate (10E%) sucrose intake in diets otherwise matched for macronutrient and fibre composition, total cholesterol and LDL cholesterol concentrations were higher after the high sucrose intake, but no difference in concentration of triglycerides or HDL cholesterol or insulin and glucose were found (22).

Blood pressure

Four studies were identified on the association between intake of sugars and blood pressure (Table 5). Of the three prospective cohorts, one found a small increased risk of hypertension with intake of sugar-sweetened beverages (20) while the other two, investigating soft drinks (19) and fructose (23) did not find a significant association. No significant differences in blood pressure were found in a 6-week randomised cross-over trial comparing high (25E%) vs. moderate (10E%) sucrose intake (22).

Type 2 diabetes

Nine prospective cohort studies were identified for incidence of type 2 diabetes (Table 6). The results from the four studies on the association between intake of total sugars, sucrose or fructose and type 2 diabetes were inconclusive (24–27). Two of three studies found significant positive associations with total fructose intake (26, 27). None of the three studies reporting sucrose intake (25–27) and none of the three studies reporting total sugar intake (24, 25, 27) found a positive association with incident diabetes; three of them (24–26) even found an inverse association. The six studies reporting on sugar-sweetened beverages and type 2 diabetes are more conclusive. Four studies reported a significant increased relative risk of type 2 diabetes with increasing intake of sugar-sweetened beverages (27–30). Of the two studies that found no association (31, 32), one study observed a significant positive association in the model not adjusting for BMI (32).

Table 3. Intake of sugars and blood lipids.

Reference	Study design	Exposure	Outcome	No of participants (incident cases)	Effect/association
Bantle et al. (21)	Randomised crossover	17E% fructose diet (14E% added sugar) vs. glucose diet (14E% glucose, 3E% naturally occurring fructose)	Fasting cholesterol, HDL, TG, calculated LDL, measured LDL, apoB, 24 h metabolic profile of TG	24	Fructose vs. glucose diet: Cholesterol: 4.30 vs. 4.22, $P=0.17$ LDL: 2.49 vs. 2.49, $P=0.76$ HDL: 1.30 vs. 1.30, $P=0.97$ Plasma TG: in women: 0.93 vs. 0.97, $P=0.63$; in men: 1.25 vs. 0.95, $P<0.001$ 24 h metabolic profiles of plasma TG: women: 31 vs. 30 $P=0.72$, men: 46 vs. 35 $P<0.001$
Black et al. (22)	Randomised crossover	25E% sucrose vs. 10E% sucrose diets	total cholesterol, LDL, HDL, TG	13	10E% sucrose vs. 25E% sucrose diet: Total cholesterol: 4.01 vs. 4.62 $p<0.01$ LDL 2.25 vs. 2.78 $p<0.01$ HDL 1.2 vs. 1.2 NS TG 0.92 vs. 0.95 NS.
Dhingra et al. (19)	Prospective cohort	Soft drinks	Incidence of hypertriglyceridemia (≥ 1.7 mmol/L); low HDL (< 1.03 mmol/L)	TG: 6,382 (1,093), HDL: 5,763 (739)	OR for ≥ 1 servings/day vs. none: TG: = 1.25 (1.04–1.51) HDL: OR = 1.32 (1.06–1.64)
Duffey et al. (20)	Prospective cohort	Sugar-sweetened beverages	High TG (≥ 1.7 mmol/L or medication); low HDL-C (< 1.04 mmol/L if male and 1.3 mmol/L if female or medication); high LDL (> 130 mg/dL or medication)	TG: 2,627 (542), HDL: 1,837 (252), HDL: 2,640 (94)	RR for increase in each exposure quartile: TG: 1.06 (1.01–1.13) HDL: 1.06 (0.97–1.16) LDL: 1.18 (1.02–1.36)

Other endpoints

No study was identified examining the effect on sugar consumption on inflammation markers as defined in this systematic review. One prospective observational study on consumption of sugar-sweetened soft drinks and uric

acid was identified reporting no association (33) (Table 7). The only study identified on cardiovascular disease, found a positive association with consumption of sugar-sweetened beverages (34) (Table 8). Only one prospective cohort study on mortality was identified (35) (Table 9).

Table 4. Intake of sugars and glucose tolerance and insulin sensitivity.

Reference	Study design	Exposure	Outcome	No of participants	Effect/association
Bantle et al. (21)	Randomised crossover	17E% fructose diet (14% added sugar) vs. glucose diet (14E% glucose, 3E% naturally occurring fructose)	Plasma glucose, serum insulin	24	Fructose vs. glucose diet: 24 h metabolic profiles of plasma glucose: 139 vs. 141, $P=0.45$; serum insulin 3486 vs. 4243 $P=0.01$
Black et al. (22)	Randomised crossover	25E% sucrose vs. 10E% sucrose diets	Plasma glucose, serum insulin, insulin sensitivity, (two-step euglycaemic-hyperinsulinemic clamp), fasting plasma glucose, glucose level over 24 h	13	10E% sucrose vs. 25E% sucrose diet: Interstitial glucose 5.9 vs. 6.1 mmol/L, NS Fasting plasma glucose 5.6 vs. 5.6, NS Fasting serum insulin 8.6 vs. 9.6. NS
Dhingra et al. (19)	Prospective cohort	Soft drinks	Incidence of impaired fasting glucose (> 5.5 mmol/L or diabetes).	6,459 (1,426 cases)	OR = 1.25 (1.05–1.48) for ≥ 1 servings/day vs. none
Duffey et al. (20)	Prospective cohort	Sugar-sweetened beverages	Incidence of impaired fasting glucose (> 6.1 mmol/L or diabetes medication)	2,160 (267 cases)	RR = 1.03 (0.95–1.12) moving across quartiles

Table 5. Intake of sugars and blood pressure.

Reference	Study design	Exposure	Outcome	No of participants	Effect/association
Black et al. (22)	Randomised crossover	25E% sucrose vs. 10E% sucrose diets	Blood pressure	13	10E% sucrose vs. 25E% sucrose diet: Systolic/diastolic: 125/72 vs. 122/71 (no significant difference)
Dhingra et al. (19)	Prospective cohort	Soft drinks	Incidence of high BP (>135/85 mmHg or medication). Measured blood pressure (average of 2 readings)	4,752 (1,004 cases)	OR = 1.18 (0.96–1.44) for ≥ 1 servings/day vs. none
Duffey et al. (20)	Prospective cohort	Sugar sweetened beverages	Incidence of high BP (>130/85 mmHg or medication)	2,639 (609 cases)	RR = 1.06 (1.01–1.12) moving across quartiles
Forman et al. (23)	Prospective cohort	Fructose	Hypertension (self-reported clinician-diagnosed)	NHS1: 88,540 (31,107 cases) NHS2: 97,315 (15,863 cases) HPFS: 37,375 (11,982 cases)	RR for highest vs. lowest quintiles NHS: 1.02 (0.99–1.06) NHS2: 1.03 (0.98–1.08) HPFS: 0.99 (0.93–1.05)

This study found no association between sugar-sweetened soft drinks and mortality. We are therefore not able to state anything about the association between sugar intake and mortality, cardiovascular disease, uric acid or inflammation markers.

Reporting and summarising the evidence

Table 10 presents summary of the evidence. The quality of evidence was graded *limited-no conclusions* for the associations between intake of sugars and blood lipids, sugar intake and glucose tolerance/insulin sensitivity, sugar intake and blood pressure, sugar intake and uric acid, sugar intake and incidence of cardiovascular disease and sugar intake and type 2 diabetes. The quality of evidence was graded *probable* for the association between intake of sugar-sweetened beverages and type 2 diabetes.

Four relevant papers were identified in the last update until December 2011 (36–39). A prospective cohort study conducted in the Netherlands investigating carbohydrate quality found no association between intake of total sugars and incident type 2 diabetes (36). One intervention study (divided into two papers) investigated the effects of very-high fructose and very-high glucose diets during 4 weeks, and found no association with insulin sensitivity (38), while cholesterol and triglycerides were positively associated with fructose intake (37). One study that examined the effect of sucrose-sweetened soft drinks with those of isocaloric milk and non-caloric soft drink during 6 months found stronger adverse effects for sucrose-sweetened soft drinks on blood triglycerides and total cholesterol compared to the other groups (39). As the results of these studies would not have changed the overall conclusion of the paper, but further support a negative role of sugar-sweetened beverages, they were not included.

Discussion

In this systematic review of prospective cohort studies and randomised controlled trials published during 2000–2011, data from prospective cohort studies suggest that sugar-sweetened beverages probably increases the risk of type 2 diabetes. The results were limited or inconsistent on the adverse effect of intake of total sugars, glucose or fructose on the incidence of type 2 diabetes. For other metabolic and cardiovascular outcomes and mortality, too few studies were available to draw conclusions.

Four of six prospective cohort studies found a positive association of sugar-sweetened beverage intake with type 2 diabetes. In general, larger studies more often reported a significant association. Other systematic reviews of prospective cohort studies have also found relatively consistent associations of sugar-sweetened beverages with type 2 diabetes (40). Part of the risk of sugar-sweetened beverage intake with incident type 2 diabetes seems to be mediated by obesity, as suggested by several of the prospective cohort studies in this systematic review and by a meta-analysis (40). For example, Palmer et al. (32) observed that the positive association between sugar-sweetened beverage intake and type 2 diabetes was no longer significant in a model adjusting for BMI. Schulze and co-workers (30) found that, after adjustments for BMI, the risk estimate for the association between intake of sugar-sweetened drinks and type 2 diabetes was halved, although still significant. Obesity was not included as an outcome in this systematic review. In other systematic reviews of prospective studies, sugar-sweetened beverage intake has been associated with a higher BMI or obesity in adolescents and adults (41).

Dietary intake of total sugars, sucrose or fructose was not consistently associated with development of type 2 diabetes in this systematic review of prospective

Table 6. Association between intake of sugar and incidence of type 2 diabetes.

Reference	Exposure	Outcome	No of participants	Effect/association
Hodge et al. (24)	Sugars (not specified)	Type 2 diabetes (self-reported and confirmed from medical practitioners)	31,276 (365 cases)	OR for difference between the 87.5th and 12.5th intake percentile: 0.72 (0.56–0.93), $P=0.01$
Janket et al. (25)	Total sugar, sucrose, fructose	Diabetes (self-reported)	38,480 (918 cases)	RR for highest vs. lowest quintile: Total sugar: 0.77 (0.52–1.15), P -trend = 0.26 Sucrose: 0.59 (0.39–0.88), P -trend = 0.05 Fructose: 1.24 (0.84–1.85) P -trend = 0.30
de Koning et al. (28)	Sugar sweetened beverages (caffeinated colas, caffeine-free colas, other carbonated sugar-sweetened beverages and non-carbonated sugar-sweetened beverages)	Type 2 diabetes (self-reported)	40,389 (2,680 cases)	RR of highest vs. lowest quartile: 1.24 (1.09–1.40), P -trend < 0.01
Meyer et al. (26)	Sucrose, fructose	Type 2 diabetes	35,988 (1,141 cases)	RR of highest vs. lowest quintile: Sucrose: 0.81 (0.67–0.99), P -trend = 0.027 Fructose: 1.27 (1.06–1.54), P -trend = 0.0015
Montonen et al. (27)	Total sugar; sucrose; fructose; soda drinks	Type 2 diabetes (from drug register and medical records)	4,304 (177 cases)	RR of highest vs. lowest quartile: Total sugars: 1.56 (0.99–2.46), P -trend = 0.10 Sucrose: 1.12 (0.71–1.76), P -trend = 0.61 Fructose: 1.90 (1.20–3.01), P -trend = 0.004 Soft drinks: 1.60 (0.93–2.76), P -trend = 0.01
Odegaard et al. (29)	Soft drinks; other fruit and vegetable juices (80% were sweetened)	Type 2 diabetes (self-reported diagnosis and validated through hospital records and detailed telephone interview)	43,580 (2,273 cases)	RR for 2 or more drinks/week vs. rarely consumed: Soft drinks: 1.34 (1.17–1.52) P -trend < 0.0001 Juice: 1.24 (1.01–1.53), P -trend = 0.09
Palmer et al. (32)	Sugar sweetened soft drinks; sweetened fruit drinks	Type 2 diabetes (self-reported; validated by in 229 subjects by physician)	43,960 (2,713 cases)	IRR of ≥ 2 drinks/day vs. < 1 drink/month: Soft drinks: 1.05 (0.90–1.23) (not adjusting for BMI); 1.24 (1.06–1.45); P -trend = 0.002 Fruit drinks: 1.31 (1.13–1.52); P -trend = 0.001
Paynter et al. (31)	Sweetened beverage (fruit punch, non-diet soda, orange or grapefruit juice)	Type 2 diabetes	12,204 (1,437 cases)	HR of 2 or more/day vs. less than 1 drink/day: Men: 1.03 (0.82–1.28), P -trend = 0.94 Women: 1.01 (0.79–1.29), P -trend = 0.58
Schulze et al. (30)	Sugar-sweetened soft drinks	Type 2 diabetes (self-reported; 98% were confirmed by medical record review in substudies)	91,249 (741 cases)	RR of ≥ 1 drink/day vs. < 1/month: 1.39 (1.07–1.76), P -trend = 0.01

epidemiological evidence published between 2000 and October 2010. One reason for this might be that a significant part of the consumed sugars are not added sugar but naturally occurring sugars in for example fruits. Studies have not associated intake of fruit in the recommended quantities with increased risk of type 2 diabetes (42).

For the association between sugar-sweetened beverages and type 2 diabetes, the dose where the risk of type 2 diabetes increased significantly was at consumption of two or more servings of sugar-sweetened beverages per week (29), or at several servings per week or more (27, 28, 30) in the studies finding a positive association. Interestingly, in one of the paper not finding an

Table 7. Intake of sugars and uric acid.

Reference	Study design	Exposure	Outcome	No of participants	Effect/association
Bombback et al. (33)	Prospective cohort	Sugar-sweetened soft drinks	Hyperuricemia (>5.7 mg/dl for women, >7.0 mg/dl for men)	9,451 (3,288 cases)	OR for >1 vs. <1 soda/day: 1.17 (0.95–1.43)

Table 8. Intake of sugars and incidence of cardiovascular disease.

Reference	Study design	Exposure	Outcome	No of participants	Effect/association
Fung et al. (34)	Prospective cohort	Sugar-sweetened soda and fruit drinks	Incident coronary heart disease (reported with subsequent confirmation by medical records)	88,520 (3,105 cases)	RR for ≥ 2 /day vs. < 1 /month: 1.35 (1.07–1.69)

association they compared one can per day or less with two cans or more a day (31). This might be too small of a difference in sugar-sweetened beverage intake, and it is clearly different from the other studies that compare the high consumers (>1 or 2 cans) with those not consuming sugar-sweetened beverages or only rarely or use lowest compared to highest quartiles. This discrepancy in dietary studies has been discussed in papers pointing at the need to use a different approach when evaluating evidence-based medicine and evidence-based nutrition (43).

In observational studies, the sugar intake might be a marker of other dietary and lifestyle characteristics also associated with sugar intake. Most of the prospective cohort studies used validated semi-quantitative FFQs to assess dietary intakes. Although useful for epidemiological studies, these dietary assessment methods are often imprecise and prone to bias. Most of the observational cohort studies attempted to control for potential bias and confounding by adjustment for energy, other dietary factors, BMI, lifestyle factors and other variables in the multivariable analyses, but some residual confounding may remain. In addition, adjustments were made for BMI in some papers while others did not do this. The duration of the follow up period among the prospective cohort studies varied widely, from 4 to 24 years. It might be considered whether a follow up period of more than 10 years is too long as the diet may change during this period. For several of the prospective cohort studies, this was dealt with by repeated assessment of diet at varying frequencies during the follow-up.

The quality of evidence regarding the relation between sugar-sweetened beverages and risk of type 2 diabetes based on the prospective cohort studies was graded *probable*, meaning that the evidence is strong enough to support a judgement of a probable relationship. There are, according to the NNR systematic literature review

manual, four criteria required for this grade. First, there must be evidence from at least two independent cohort studies. This review includes four prospective cohort studies showing a positive association. Second, there should be no substantial unexplained heterogeneity between or within study types of an association, or the direction of effect. Third, several of the studies need to be of good quality (graded A or B). All of the four prospective cohorts were graded B. Fourth, a biological plausibility of the observed association might be found. Some researchers have postulated that sugar-sweetened beverages, or calories consumed as beverages, have smaller effects on satiety, resulting in higher energy intake and more weight gain than with other dietary sources high in sugars (8, 44, 45). In addition, the frequency of consumption and the amount absorbed at any given time has been discussed (6, 8–10, 46). However, it cannot be excluded that the association of sugar-sweetened beverages is mediated by factors other than sugars. Increased fructose intake has been postulated as another biological mechanism explaining the increased risk for diabetes associated with sugar-sweetened beverage intake. Both sucrose (50% fructose) and high-fructose corn syrup (55% fructose), frequently used to sweeten soft drinks, contain similar amounts of fructose and glucose. Relative to glucose, fructose may increase liver triacylglycerol formation, fatty liver, visceral adiposity and insulin resistance (46). Nonetheless, the current evidence in humans indicating that high-fructose sweeteners have more adverse metabolic effects than sucrose on insulin resistance, fat distribution and other metabolic outcomes is limited or at best, suggestive.

Surprisingly, medium-to-long term randomised controlled trials on the metabolic effects of fructose, glucose and sucrose intake meeting the eligibility criteria were largely lacking. In addition, the trials included had rather few subjects. Six other intervention studies on sugar

Table 9. Intake of sugars and incidence of mortality.

Reference	Study design	Exposure	No of participants	Effect/association
Paganini-Hill et al. (35)	Prospective cohort	Cola with sugar; other soft drinks with sugar	13,624 (11,386 cases)	RR for > 1 cans/week vs. none: Cola with sugar: 1.02 (0.92–1.13) Other soft drinks with sugar: 1.03 (0.92–1.16)

Table 10. Summary table on the association between intake of sugars and outcomes.

Outcome	Exposure	Number of participants (studies)	Association/ effect	Number of studies rated as A, B, C	Strength of evidence
Type 2 diabetes	Sugar-sweetened beverages	Cohorts: 235,666 (6)	Positive (4) or NS (2)	6 rated B	Probable
Type 2 diabetes	Total sugars	Cohorts: 74,405 (3)	Inverse (1) or NS (2)	2 rated B, 1 rated C	Limited-no conclusion
Type 2 diabetes	Sucrose	Cohorts: 78,752 (3)	Inverse (2) or NS (1)	3 rated B	Limited-no conclusion
Type 2 diabetes	Fructose	Cohorts: 78,752 (3)	Positive (2) or NS (1)	2 rated B, 1 rated C	Limited-no conclusion
Cardiovascular disease	Sugar-sweetened beverages	Cohorts: 88,520 (1)	Positive	1 rated B	Limited-no conclusion
Total mortality	Sugar-sweetened beverages	Cohorts: 13,978 (1)	NS	1 rated C	Limited-no conclusion
Eight Glucose intolerance or insulin resistance	Sugar-sweetened beverages	Cohorts: 8,619 (2)	Cohorts: Positive (1) or NS (1)	2 rated B	Limited-no conclusion
Glucose intolerance or insulin resistance	Sucrose	Interventions: 13 (1)	NS	1 rated B	Limited-no conclusion
Glucose intolerance or insulin resistance	Fructose	Interventions: 24 (1)	Inverse	1 rated B	Limited-no conclusion
Blood pressure	Sugar-sweetened beverages	Cohorts: 7,391 (2)	Cohorts: Positive (1) or NS (1)	3 rated B	Limited-no conclusion
		Interventions: 32 (1)	Interventions: NS		
Blood pressure	Sucrose	Interventions: 13 (1)	NS	1 rated B	Limited-no conclusion
Blood pressure	Fructose	Interventions: 24 (1)	NS	1 rated B	Limited-no conclusion
Cholesterol	Sucrose	Interventions: 13 (1)	Positive	1 rated B	Limited-no conclusion
Cholesterol	Fructose	Interventions: 24 (1)	NS	1 rated B	Limited-no conclusion
Triglycerides	Sugar-sweetened beverages	Cohorts: 9,009 (2)	Positive (2)	2 rated B	Limited-no conclusion
Triglycerides	Sucrose	Interventions: 13 (1)	NS	1 rated B	Limited-no conclusion
Triglycerides	Fructose	Interventions: 24 (1)	Positive in men, NS in women	1 rated B	Limited-no conclusion
LDL	Sugar-sweetened beverages	Cohorts: 2,640 (1)	Positive	1 rated B	Limited-no conclusion
LDL	Sucrose	Interventions: 13 (1)	Positive	1 rated B	Limited-no conclusion
LDL	Fructose	Interventions: 24 (1)	NS	1 rated B	Limited-no conclusion
HDL	Sugar-sweetened beverages	Cohorts: 7,600 (2)	Inverse (1) or NS (1)	2 rated B	Limited-no conclusion
HDL	Sucrose	Interventions: 13 (1)	NS	1 rated B	Limited-no conclusion
HDL	Fructose	Interventions: 24 (1)	NS	1 rated B	Limited-no conclusion
Hyperuricemia	Sugar-sweetened beverages	Cohorts: 9,451 (1)	NS	1 rated B	Limited-no conclusion

intake were excluded because of not having an appropriate control group. Overall, the findings suggest that fructose-sweetened beverage intake may have more adverse effects than glucose-sweetened beverage intake. Also, high sucrose intake may increase LDL cholesterol levels, but data are limited and in part inconsistent, and do not allow conclusions to be drawn. In a matched double-blind parallel-arm trial in 32 middle-aged overweight and obese men and women found adverse effects of 10 weeks of fructose beverage intake on visceral adiposity, insulin sensitivity and dyslipidemia (47). This study, although well carried out, carefully controlled and

otherwise meeting eligibility criteria, was not included in this review because it was not randomised.

Extending the time frame for the systematic review to the 1980s for example would increase the number of studies. However, earlier reviews (6, 11) indicate that trial evidence on high fructose or sucrose intake on metabolic outcomes in the medium and long-term are inconsistent. A number of these are reviewed in the EFSA opinion on carbohydrates.

The heterogeneity in study designs and the problems induced by the composition of the diets could lead to discrepancies in results. For example, there may be

differences in effects of added sugars in intervention studies in relation to the background diet. Regarding observational studies, we only included prospective studies. Many studies have examined the cross-sectional associations between sugar intake and risk markers and diseases. However, these studies are an even weaker measure of causality than prospective cohort studies (11). Furthermore, there is always a risk of publication bias as research with significant findings is more likely to get published.

This review focused on individuals that were considered generally healthy at baseline. However, it cannot be excluded that intake of sugars especially in individuals at risk might have more negative effect than the same amount in a healthy individual (11).

The recent reports from USDA and EFSA arrived at different conclusions in their evidence based approach regarding dietary added sugars. As our systematic review also suggests, data supporting an association of high intake of total sugars, sucrose or fructose with adverse health outcomes is only suggestive, and data for specific cut-offs is even more limited. A recent review found no evidence of adverse effects of normal dietary consumption of fructose on triglyceride concentrations or body weight in healthy, normal weight individuals (48). However, the USDA dietary guidelines take a more pragmatic, but less evidence-based approach. Because the epidemic of obesity is in simplistic terms based on excessive energy intake coupled with insufficient energy expenditure, the USDA recommended limiting energy intake from added sugars and saturated fat to no more than 15E%. This is also based on dietary surveys indicating that dietary added sugar contribute to a large part of the energy intake in the US population overall, and many of the most commonly consumed foods in the US population were high in added sugar with little nutrient value otherwise (3, 4). In the Nordic countries, intake of refined sugars is approximately 8–18E% depending on age, and marked segments of the population consume at least 20E%. Given the growing obesity epidemic and excess energy intake relative to energy expenditure also in Nordic countries, limiting added sugars also in Nordic countries might be one target for decreasing energy intake.

Conclusion

Data from prospective cohort studies published during 2000 to December 2011 suggest that sugar-sweetened beverages probably increase the risk of type 2 diabetes. For other metabolic and cardiovascular outcomes, or other sources of sugars, too few prospective cohort studies were available to draw conclusions. Evidence from medium and long-term studies on the metabolic effects of high-fructose or high sucrose intake is also too limited to draw conclusions. Although only one of the

studies included in this systematic review is actually conducted in a Nordic setting, the Finnish Mobile Clinic Health Examination Survey with baseline 1966–1972, we feel that the results can reasonably be transferred to the Nordic setting. The exposure range in most of the studies is similar to the Nordic setting, and most were conducted in cohorts of mainly well-educated individuals with largely European background. Overall, specific cut-offs for sugar intake based on strong scientific evidence cannot be made (5), but pragmatic interpretation of the evidence as was done by the USDA (3) would support limiting added sugars and sugar-sweetened beverage intake to, e.g. 10E% as recommended in the NNR4. Specific recommendations regarding sugar-sweetened beverage intake in particular may be warranted.

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Appendix 1. Search terms with regard to exposure, outcome and study design

Exposure	Outcome	Study design
“Fructose”[Mesh] OR “Sucrose”[Mesh] OR “Dietary Sucrose”[Mesh] OR “sugar sweetened drinks” [Title/Abstract] OR soft drink*[Title/Abstract] OR refined sugar*[Title/Abstract] OR Sugar*[Title/Abstract]	Glucose tolerance and insulin sensitivity “Hyperglycemia”[Mesh] OR “Glucose Intolerance”[Mesh] OR “Blood Glucose”[Mesh] OR “impaired fasting glucose”[Title/Abstract] OR “high fasting glucose”[Title/Abstract] OR “fasting plasma glucose”[Title/Abstract] OR “Hemoglobin A”[Mesh] OR “Hemoglobin A, Glycosylated”[Mesh] OR “glycosylated”[Title/Abstract] OR “Insulin Resistance”[Mesh] OR “Hyperinsulinism”[Mesh] OR “hyperinsulinemia”[Title/Abstract] OR “insulin sensitivity”[Title/Abstract] OR Insulin [Title/Abstract] OR Serum lipids “Lipoproteins”[Mesh] OR “Lipoproteins, HDL”[Mesh] OR “Lipoproteins, LDL”[Mesh] OR “Triglycerides”[Mesh] OR “Cholesterol”[Mesh] OR “serum lipids”[Title/Abstract] OR Low density lipoprotein* [Title/Abstract] OR High density lipoprotein* [Title/Abstract] OR AND LDL [Title/Abstract] OR AND HDL [Title/Abstract] OR Inflammation markers “Inflammation Mediators”[Mesh] OR “Inflammation”[Mesh] OR “C-Reactive Protein”[Mesh] OR “Leukocyte Count”[Mesh] OR Blood pressure “Blood pressure”[Mesh] OR “Hypertension”[Mesh] OR Uric acid	“Randomized Controlled Trial” [Publication Type] OR randomized[Title/Abstract] OR “randomized clinical trial”[Title/Abstract] OR “Cohort Studies”[Mesh] OR “Prospective Studies”[Mesh] OR “Epidemiologic Studies”[Mesh] OR controlled[Title/Abstract] OR cohort[Title/Abstract] OR prospective[Title/Abstract] OR observational[Title/Abstract] OR risk[Title/Abstract] OR incidence[Title/Abstract] OR incident[Title/Abstract] OR “Risk Factors”[Mesh]

Appendix 1 (Continued)

Exposure	Outcome	Study design
	"Uric acid"[Mesh] OR Uric*[Title/Abstract] OR Type 2 diabetes "diabetes"[Title/Abstract] OR "Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR Cardiovascular disease "Cardiovascular Diseases"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Coronary Disease"[Mesh] OR All-cause mortality "Mortality"[Mesh] OR "Survival"[Mesh] OR "Fatal Outcome"[Mesh] OR "Cause of Death"[Mesh]	

Appendix 2. Exclusion criteria for ordered articles

Article	Reason for exclusion
[No authors listed] (2000). "Side effects. Metformin for blood sugar problems." <i>TreatmentUpdate</i> 12 (7): 5–6.	Did not examine sugar
Assy, N., et al. (2008). "Soft drink consumption linked with fatty liver in the absence of traditional risk factors." <i>Can J Gastroenterol</i> 22 (10): 811–816.	Cross-sectional study
Berg, C. M., et al. (2008). "Food patterns and cardiovascular disease risk factors: the Swedish INTERGENE research program." <i>Am J Clin Nutr</i> 88 (2): 289–297.	Dietary pattern
Brown, C. M., et al. (2008). "Fructose ingestion acutely elevates blood pressure in healthy young humans." <i>Am J Physiol Regul Integr Comp Physiol</i> 294 (3): R730–737.	Acute effects
Brynes, A. E., et al. (2003). "A randomised four-intervention crossover study investigating the effect of carbohydrates on daytime profiles of insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men." <i>Br J Nutr</i> 89 (2): 207–218.	Too short (24 days)
Buyken, A. E., et al. (2010). "Carbohydrate nutrition and inflammatory disease mortality in older adults." <i>Am J Clin Nutr</i> 92 (3): 634–643.	Foods high in sugars or refined starch
Charlton, K. E., et al. (2005). "Micronutrient dilution associated with added sugar intake in elderly black South African women." <i>Eur J Clin Nutr</i> 59 (9): 1030–1042.	Cross-sectional
Chen, L., et al. (2010). "Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults." <i>Circulation</i> 121 (22): 2398–2406.	Too short (18 months followup)
Choi, H. K., et al. (2010). "Fructose-rich beverages and risk of gout in women." <i>JAMA : the journal of the American Medical Association</i> 304 (20): 2270–2278.	Gout as endpoint
Cowin, I. S., et al. (2001). "Associations between dietary intakes and blood cholesterol concentrations at 31 months." <i>Eur J Clin Nutr</i> 55 (1): 39–49.	Diet (18 months of age), lipid (31 months)
Culling, K. S., et al. (2009). "Effects of short-term low- and high-carbohydrate diets on postprandial metabolism in non-diabetic and diabetic subjects." <i>Nutr Metab Cardiovasc Dis</i> 19 (5): 345–351.	Too short (3 days)
Curhan, G. C., et al. (2010). "Sugar-sweetened beverages and chronic disease." <i>Kidney Int</i> 77 (7): 569–570.	Review (not a systematic review)
Davis, J. N., et al. (2007). "Associations of dietary sugar and glycemic index with adiposity and insulin dynamics in overweight Latino youth." <i>Am J Clin Nutr</i> 86 (5): 1331–1338.	Cross-sectional

Appendix 2 (Continued)

Article	Reason for exclusion
Davis, J. N., et al. (2007). "Reduction in added sugar intake and improvement in insulin secretion in overweight latina adolescents." <i>Metab Syndr Relat Disord</i> 5(2): 183–193.	Intervention groups combined, reported change in sugar consumption used
Davis, J. N., et al. (2005). "The relation of sugar intake to beta cell function in overweight Latino children." <i>Am J Clin Nutr</i> 82(5): 1004–1010.	Cross-sectional study
Dolan, L. C., et al. (2010). "Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals." <i>Crit Rev Food Sci Nutr</i> 50(1): 53–84.	Review (not a systematic review)
Erkkila, A. T., et al. (2007). "Moderate increase in dietary sucrose does not influence fasting or postprandial serum lipids regardless of the presence of apolipoprotein E2 allele in healthy subjects." <i>Eur J Clin Nutr</i> 61(9): 1094–1101.	No control group
Gohgi, Y., et al. (2005). "[Risk factors for requiring long-term care among middle-aged and elderly people]." <i>Nippon Koshu Eisei Zasshi</i> 52(3): 226–234.	Not in English
Harrington, S. (2008). "The role of sugar-sweetened beverage consumption in adolescent obesity: a review of the literature." <i>J Sch Nurs</i> 24(1): 3–12.	SLR on obesity and Sugar Sweetened Beverages
Heinig, M., et al. (2006). "Role of uric acid in hypertension, renal disease, and metabolic syndrome." <i>Cleve Clin J Med</i> 73(12): 1059–1064.	Review (not a systematic review)
Hofmann, S. M., et al. (2009). "Dietary sugars: a fat difference." <i>J Clin Invest</i> 119(5): 1089–1092.	Comment on Stanhope
Johnson, R. J., et al. (2009). "Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes?" <i>Endocr Rev</i> 30(1): 96–116.	Review (not a systematic review)
Johnson, R. J., et al. (2007). "Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease." <i>Am J Clin Nutr</i> 86(4): 899–906.	Review (not a systematic review)
Johnson, R. K., et al. (2009). "Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association." <i>Circulation</i> 120(11): 1011–1020.	AHA statement
Kirkwood, L., et al. (2007). "Effects of advice on dietary intake and/or physical activity on body composition, blood lipids and insulin resistance following a low-fat, sucrose-containing, high-carbohydrate, energy-restricted diet." <i>Int J Food Sci Nutr</i> 58(5): 383–397.	High carbohydrate, high sugar diet
Knight, J., et al. (2010). "Metabolism of fructose to oxalate and glycolate." <i>Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme</i> 42(12): 868–873.	Kidney stone as endpoint
Konstantinova, S. V., et al. (2008). "Dietary patterns, food groups, and nutrients as predictors of plasma choline and betaine in middle-aged and elderly men and women." <i>Am J Clin Nutr</i> 88(6): 1663–1669.	Cross-sectional study
Kopp, W. (2006). "The atherogenic potential of dietary carbohydrate." <i>Prev Med</i> 42(5): 336–342.	Review (not a systematic review)
Lairon, D., et al. (2007). "Digestible and indigestible carbohydrates: interactions with postprandial lipid metabolism." <i>J Nutr Biochem</i> 18(4): 217–227.	Review (not a systematic review)
Lancaster, K. J., et al. (2006). "Dietary intake and risk of coronary heart disease differ among ethnic subgroups of black Americans." <i>J Nutr</i> 136(2): 446–451.	Descriptive
Lau, C., et al. (2005). "Dietary glycemic index, glycemic load, fiber, simple sugars, and insulin resistance: the Inter99 study." <i>Diabetes Care</i> 28(6): 1397–1403.	Cross-sectional study
Le, K. A., et al. (2006). "A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans." <i>Am J Clin Nutr</i> 84(6): 1374–1379.	No control group
Le, K. A., et al. (2006). "Metabolic effects of fructose." <i>Curr Opin Clin Nutr Metab Care</i> 9(4): 469–475.	Not a randomized control study or prospective cohort
Lichtenstein, A. H., et al. (2006). "Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee." <i>Circulation</i> 114(1): 82–96.	American Heart Association statement
Liese, A. D., et al. (2010). "Food intake patterns associated with carotid artery atherosclerosis in the Insulin Resistance Atherosclerosis Study." <i>Br J Nutr</i> 103(10): 1471–1479.	Food intake patterns, not clear exposure
Lim, J. S., et al. (2010). "The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome." <i>Nat Rev Gastroenterol Hepatol</i> 7(5): 251–264.	Review (not a systematic review)
Malik, V. S., et al. (2010). "Sugar Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A Meta-analysis." <i>Diabetes Care</i> .	A meta-analysis

Appendix 2 (Continued)

Article	Reason for exclusion
Marckmann, P., et al. (2000). "Ad libitum intake of low-fat diets rich in either starchy foods or sucrose: effects on blood lipids, factor VII coagulant activity, and fibrinogen." <i>Metabolism</i> 49 (6): 731–735.	No control. Only 2 weeks of exposure, comparing sugar with fiber and starch.
McNaughton, S. A., et al. (2008). "Dietary patterns, insulin resistance, and incidence of type 2 diabetes in the Whitehall II Study." <i>Diabetes Care</i> 31 (7): 1343–1348.	Dietary pattern, not clear exposure.
McNaughton, S. A., et al. (2009). "Food patterns associated with blood lipids are predictive of coronary heart disease: the Whitehall II study." <i>Br J Nutr</i> 102 (4): 619–624.	Dietary pattern, not clear exposure.
Michels, K. B., et al. (2002). "A prospective study of variety of healthy foods and mortality in women." <i>Int J Epidemiol</i> 31 (4): 847–854.	Dietary pattern, not clear exposure.
Miller, A., et al. (2008). "Dietary fructose and the metabolic syndrome." <i>Curr Opin Gastroenterol</i> 24 (2): 204–209.	Review (not a systematic review)
Mirmiran, P., et al. (2008). "Effect of nutrition intervention on non-communicable disease risk factors among Tehranian adults: Tehran Lipid and Glucose Study." <i>Ann Nutr Metab</i> 52 (2): 91–95.	Many dietary changes made, not only sugar
Montonen, J., et al. (2007). "Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence." <i>J Nutr</i> 137 (6): 1447–1454.	
Mølgaard, C., et al. (2003). "The impact of sugar on health." <i>Ugeskrift for Læger</i> 165 (44): 4207–4210.	Review (not a systematic review)
Nakagawa, T., et al. (2005). "Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome." <i>Nat Clin Pract Nephrol</i> 1 (2): 80–86.	Review (not a systematic review)
Nandorf, R. (2002). "Coca-Cola vending-machines in schools are grounding for diabetes among young people." <i>Lakartidningen</i> 99 (43): 4296.	Review (not a systematic review)
Nettleton, J. A., et al. (2009). "Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA)." <i>Diabetes Care</i> 32 (4): 688–694.	Diet soda, not sugar sweetened beverages
Noel, S. E., et al. (2009). "A traditional rice and beans pattern is associated with metabolic syndrome in Puerto Rican older adults." <i>J Nutr</i> 139 (7): 1360–1367.	Dietary pattern, no clear exposure.
Okuno, M., et al. (2010). "Palatinose-blended sugar compared with sucrose: different effects on insulin sensitivity after 12 weeks supplementation in sedentary adults." <i>Int J Food Sci Nutr</i> 61 (6): 643–651.	No control group. Comparing to palatinose blended sugar with sugar
Pala, V., et al. (2006). "Associations between dietary pattern and lifestyle, anthropometry and other health indicators in the elderly participants of the EPIC-Italy cohort." <i>Nutr Metab Cardiovasc Dis</i> 16 (3): 186–201.	Dietary pattern, no clear exposure (sweets and dairy)
Palou, A., et al. (2009). "On the role and fate of sugars in human nutrition and health. Introduction." <i>Obes Rev</i> 10 Suppl 1: 1–8.	An overview of many reviews (not a systematic review)
Pereira, C., et al. (2005). "Application of cluster analysis in prevention of coronary heart disease." <i>Rev Port Cardiol</i> 24 (3): 381–394.	Comparing coronary patients (N = 30) with healthy controls (N = 30), no clear exposure.
Raben, A., et al. (2001). "Diurnal metabolic profiles after 14 d of an ad libitum high-starch, high-sucrose, or high-fat diet in normal-weight never-obese and postobese women." <i>Am J Clin Nutr</i> 73 (2): 177–189.	No control group, short intervention (14d)
Raben, A., et al. (2002). "Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects." <i>The American journal of clinical nutrition</i> 76 (4): 721–729.	Body weight as endpoint
Ruottinen, S., et al. (2009). "Carbohydrate intake, serum lipids and apolipoprotein E phenotype show association in children." <i>Acta Paediatr</i> 98 (10): 1667–1673.	Cross sectional study
Ruxton, C. H., et al. (2010). "Is sugar consumption detrimental to health? A review of the evidence 1995–2006." <i>Crit Rev Food Sci Nutr</i> 50 (1): 1–19.	Review (not a systematic review)
Rössner, S. (2004). "Diabetes caused by sugar? High intake of soft drinks increases the risk of type 2 diabetes." <i>Lakartidningen</i> 101 (49): 3982.	Review (not a systematic review)
Sorensen, L. B., et al. (2005). "Effect of sucrose on inflammatory markers in overweight humans." <i>Am J Clin Nutr</i> 82 (2): 421–427.	No control group

Appendix 2 (Continued)

Article	Reason for exclusion
Stanhope, K. L., et al. (2009). "Fructose consumption: considerations for future research on its effects on adipose distribution, lipid metabolism, and insulin sensitivity in humans." <i>J Nutr</i> 139 (6): 1236S–1241S.	Review (not a systematic review)
Stanhope, K. L., et al. (2009). "Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans." <i>The Journal of clinical investigation</i> 119 (5): 1322–1334.	Matched control, not randomized
Sun, S. Z., et al. (2010). "Lack of association between dietary fructose and hyperuricemia risk in adults." <i>Nutr Metab (Lond)</i> 7 : 16.	Cross sectional study
Swarbrick, M. M., et al. (2008). "Consumption of fructose-sweetened beverages for 10 weeks increases postprandial triacylglycerol and apolipoprotein-B concentrations in overweight and obese women." <i>Br J Nutr</i> 100 (5): 947–952.	No control group
Tappy, L., et al. (2010). "Fructose and metabolic diseases: New findings, new questions." <i>Nutrition</i> 26 (11–12): 1044–1049.	Review (not a systematic review)
Taylor, E. N., et al. (2008). "Fructose consumption and the risk of kidney stones." <i>Kidney Int</i> 73 (2): 207–212.	Kidney stones as endpoint
Valensi, P. (2005). "Hypertension, single sugars and fatty acids." <i>J Hum Hypertens</i> 19 Suppl 3: S5–9.	Review (not a systematic review)
Vasankari, T., et al. (2006). "Effect of dietary fructose on lipid metabolism, body weight and glucose tolerance in humans." <i>Scandinavian Journal of Food & Nutrition</i> 50 (2): 55–63.	Review (not a systematic review)
Ventura, E., et al. (2009). "Reduction in risk factors for type 2 diabetes mellitus in response to a low-sugar, high-fiber dietary intervention in overweight Latino adolescents." <i>Arch Pediatr Adolesc Med</i> 163 (4): 320–327.	Both low sugar and high fiber i.e., no clear exposure
Williams, C. L., et al. (2008). "Childhood diet, overweight, and CVD risk factors: the Healthy Start project." <i>Prev Cardiol</i> 11 (1): 11–20.	Only one 24 hour recall
Visvanathan, R., et al. (2005). "The effects of drinks made from simple sugars on blood pressure in healthy older people." <i>Br J Nutr</i> 93 (5): 575–579.	Postprandial measurements
Vogt, J. A., et al. (2006). "L-rhamnose and lactulose decrease serum triacylglycerols and their rates of synthesis, but do not affect serum cholesterol concentrations in men." <i>J Nutr</i> 136 (8): 2160–2166.	Intervention using L-rhamnose, Lactulose or Glucose
Vos, M. B., et al. (2009). "Fructose and oxidized low-density lipoprotein in pediatric nonalcoholic fatty liver disease: a pilot study." <i>Arch Pediatr Adolesc Med</i> 163 (7): 674–675.	Not a healthy population
Yaghoobi, N., et al. (2008). "Natural honey and cardiovascular risk factors; effects on blood glucose, cholesterol, triacylglycerole, CRP, and body weight compared with sucrose." <i>ScientificWorldJournal</i> 8 : 463–469.	Not healthy at baseline
Yoshida, M., et al. (2007). "Surrogate markers of insulin resistance are associated with consumption of sugar-sweetened drinks and fruit juice in middle and older-aged adults." <i>J Nutr</i> 137 (9): 2121–2127.	Cross sectional study