DIETARY SUGARS AND THE RISK OF CARDIOVASCULAR DISEASE: AN UPDATE

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In its report *Diet, Physical Activity and Cardiovascular Disease Prevention in Europe*, published in 2011, the European Heart Network has set an interim population goal for consumption of sugars of less than 10% of energy from added sugars and to reduce as much as possible consumption of sugar-sweetened drinks. More ambitious longer-term goals were formulated as less than 5% of energy from added sugar and zero consumption sugar-sweetened drinks.[1]

This section reviews the recent scientific literature about the role of dietary sugars in CVD and their potential mechanism(s) since 2010. Between 2010 and 2016 a considerable number of additional cross-sectional, observational and randomised cross-over studies on the relationship between the consumption of sugars and cardiometabolic health and its underlying mechanism(s) have been published. In addition, extensive reviews and meta-analyses have been performed, some of which have served as background information for (inter)national dietary recommendations. The majority of studies concerned sugar-sweetened beverage consumption and fructose consumption, with less attention for total or added sugars and the potential difference between liquid and solid forms of sugar.

In this paper, first the recent dietary recommendations on consumption of sugars in the general population is reviewed. Next a summary of the systematic reviews and meta-analyses is presented and the results of any additional studies, which were not included in these systematic reviews. The last section is devoted to some newer evidence with respect to the mechanisms underlying the relationship between consumption of sugars and CVD risk.

1. Definitions

Dietary sugars are glycaemic carbohydrates and consist of all mono- and disaccharides. The main dietary sugars are the monosaccharides glucose and fructose and the disaccharides sucrose and lactose. Sucrose consists of a fructose and a glucose monomer, lactose of a glucose and galactose monomer. In this paper the term total sugars is used for all mono- and disaccharides combined. Sugars can occur naturally in foods or can be added. According to the European Food Safety Agency (EFSA)[2] 'added sugars' refers to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing. Sugar alcohols (polyols) such as sorbitol, xylitol, mannitol, and lactitol, are usually not included in the term sugars, although they are partly metabolised. The World Health Organization (WHO) uses the term 'free sugars' rather than 'added sugars'.[3] Free sugars are defined as monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.[3] This definition combines non-milk extrinsic sugars and added sugars. Extrinsic sugars are naturally occurring sugars not located in the cellular structure of

foods. Sugar-sweetened beverages (SSBs) are beverages containing added caloric sweeteners such as sucrose or high-fructose corn syrup (HFCS).

2. Dietary recommendations

Since 2010, new dietary recommendations have been published in many European countries, such as France[4], Germany[5], the Nordic countries,[6] England[7] and the Netherlands.[8] Also in the US new dietary guidelines were formulated.[9] In addition, a scientific statement about consumption of sugars in children and adolescents was been published by the American Heart Association in 2016.[10] WHO published a guideline for sugar intake in 2015.[3] A short summary of these recommendations with respect to intake of sugars is given below. It should be realised that these diet recommendations aim to maintain or improve overall health in the general population and do not specifically address CVD risk. However, apart from dental caries, most of the recommendations for consumption of sugars are based on its relationship to the risk of obesity and type 2 diabetes, which also affect CVD risk.

In France it is recommended that the consumption of sugar and foods rich in sugar such as sugar-sweetened beverages, jams, chocolate, pastries, sugar-containing desserts, ice cream[4] is limited. The German Nutrition Society recommends a reduction in the consumption of sugar-sweetened beverages.[5] In the Nordic countries the advice is to limit intake of sweetened beverages and foods with added sugars.[11] In the Netherlands the recommendation is to limit consumption of sugar-*containing* beverages, including fruit juices, as much as possible. The consumption of foods with high sugar content, such as candy, cookies and pastries, should also be limited.[8] In England the recommendation is to limit free sugar intake to less than 5% of average energy intake for age groups from 2 years upward and to minimise SSB consumption in children and adults.[7] It was estimated that a reduction of free sugar intake to 5% of energy intake would lead to a moderately lower weight in the majority of the population.[7] WHO proposes that all individuals should consume less than 10% and in appropriate national circumstances less than 5%.[12] The latter recommendation (<5%) is based on the prevention of dental caries. WHO recommends this reduced intake of free sugars throughout the life course.[12] In the US, the Dietary Guidelines Advisory Committee concluded that a healthy dietary pattern is low in sugar-sweetened foods and drinks.[13] The American Heart Association (AHA) concluded in 2009 that a prudent upper limit of consumption of sugars would be half of the discretionary calorie allowance that can be accommodated within the appropriate energy intake level of an individual to achieve or maintain a healthy weight. Thus, most American women should eat or drink no more than 100 kcal per day (or ≈ six teaspoons) from added sugars, and most American men should eat or drink no more than 150 kcal per day from added sugars[14] which in practice means no more than about 5% of energy intake. In its 2016 statement on added sugars and CVD risk in children and adolescents, the AHA recommends that children and adolescents limit their intake of SSBs to one or fewer 8-oz (=237 ml) beverages per week and states that it is reasonable to recommend that children and adolescents consume ≤ 25 g (100 kcal) of added sugars per day which is again a limit of about 10% in younger children and about 5% in adolescents.[10]

Although some of the recommendations above do not specify upper limits of intake of sugars, they do recommend maintenance of a healthy weight. In the context of a nutritionally balanced diet there is little room for energy-dense foods and drinks,

containing a high sugar or fat content, if a healthy weight is to be maintained. This is the background for the quantitative advice given. However, it has also been argued that restricting the intake of added sugar and advocating increased fruit and vegetable consumption, as in most recommendations, may not alter total sugar intake.[15]

3. Evidence for an association between sugars and cardiovascular disease

Different aspects of the association between consumption of sugars and CVD have been studied and reviewed over the past six years. Here only outcomes based on prospective cohorts and RCTs are discussed; cross-sectional studies are not included. In addition, the results of prospective studies should be interpreted with care, because they may be subject to reporting bias, and residual confounding. While the strongest evidence is usually obtained from well-designed and conducted RCTs, these also have their limitations. RCTs are usually of relatively short duration, include small numbers of participants with varying baseline characteristics and may also suffer from compliance issues. When evaluating the evidence relating to consumption of sugars with CVD mortality and risk factors, which is reviewed below, these limitations should be kept in mind.

4. Sugars and cardiovascular disease mortality

Few studies on the association between consumption of sugars and CVD mortality are available. Paganini-Hill and colleagues analysed the association between SSB consumption and all-cause mortality in the Leisure World Cohort Study including 13 624 elderly participants and 11 386 deaths.[16] The relative risk (RR) was 1.02 (95% confidence interval (CI) 0.92, 1.13) for cola and 1.03 (95% CI 0.92, 1.16) for other sugar-sweetened soft drinks, comparing >1 can/week with no consumption. Tasevska and colleagues investigated the association between consumption of sugars and CVD mortality in the NIH-AARP Diet and Health Study, a cohort of US adults aged 51-70 years at baseline.[17] The cohort included 353 751 participants and 10 894 subsequent cardiovascular events. No significant associations of total sugars, added sugars, total fructose, added fructose, total sucrose and added sucrose with CVD mortality were found. However, when consumption of sugars was divided in solid and liquid sources, there was evidence that sugars from beverages, and especially fructose from beverages, were associated with an increased CVD mortality (Hazard Ratio (HR) 1.14 (95% CI 1.02, 1.28) in women and HR 1.13 (95% CI 1.05, 1.22) in men when comparing the lowest with the highest quintile of intake). Yang et al analysed the association between added sugars and CVD mortality in the NHANES III cohort, a nationally representative sample of US adults, with 11 733 participants and 831 CVD deaths.[18] The adjusted HR was 2.03 (95% CI 1.26, 3.27) comparing the highest with the lowest quintile of consumption of added sugars. HRs were 1.30 (95% CI 1.09, 1.55) and 2.75 (95% CI 1.40, 5.42), respectively, when participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugars were compared with those who consumed less than 10.0% of calories from added sugars.

Summary on sugars and cardiovascular disease mortality

Although the latter two studies may be suggestive of an association between consumption of sugars and CVD mortality, the available evidence is currently too limited and still too heterogeneous to draw conclusions about the causal relationship of such an association.

5. Sugars and coronary heart disease

In 2012, Hauner et al reviewed the literature on the association between consumption of sugars and CHD.[5] They concluded that, due to the low number of studies, there was insufficient evidence for a significant association between the intake of mono- and disaccharides or the consumption of sugar-sweetened beverages and the risk of CHD. A systematic review by Sonestedt and colleagues[19], which informed the Nordic Nutrition Recommendations, and the report of the SACN (2012)[7] committee in the UK, came to similar conclusions. Subsequently, Huang et al[20] in 2014 and Xi et al[21] in 2015 both performed a systematic review and meta-analysis of prospective cohort studies on the association between SSB consumption and the risk of CHD. Both included four studies with 194 664 participants and 7 396 cases. Xi and colleagues used a fixed effect model to estimate the relative risk of CHD, which is unlikely to be correct. Huang et al used a more appropriate random effects model. Comparing the lowest with the highest category of SSB consumption in each study cohort a RR of 1.17 (95% CI 1.07, 1.28) was found without significant heterogeneity between studies (I^2 = 0%). The risk of CHD increased by 16% with each additional serving/day of SSBs.[20] Additionally, in 2015, Li and colleagues analysed data from the Nurses Health Study and the Health Professionals Follow-up Study (127 536 participants, 7 667 incident cases of CHD) and found that intake of carbohydrates from refined starches and added sugars was positively associated with the risk of CHD (HR 1.10, 95% CI 1.00, 1.21).[22] This category mainly included foods with relatively high glycaemic index, such as potatoes, refined grains and added sugars from beverages and foods.

Summary on sugars and coronary heart disease

The number of studies on the association between incident CHD and consumption of sugars is small (n=5). Moreover, they mainly focus on SSB consumption and studies on the association between consumption of added sugars and CHD risk are currently lacking. More studies are clearly needed before a reliable conclusion on the association between free or added sugars and CHD can be made.

6. Sugars and stroke

Xi and colleagues also did a meta-analysis of studies on the association between SSB consumption and stroke.[21] Six prospective cohorts with 259 176 participants and 10 011 cases of stroke were included. Using an inappropriate fixed effect model, the highest intake of SSB was marginally associated with the risk of total stroke (RR 1.10, 95% CI 1.00, 1.20) compared with the lowest level, with little evidence of heterogeneity (I^2 = 43 %). With a more appropriate mixed effects model the association would probably not have been significant.

Summary on sugars and stroke

So far there is no evidence that higher SSB consumption increases the risk of stroke. There are no studies on the association between total consumption of sugars and stroke.

7. Sugars and hypertension

Hypertension is a major risk factor for CVD and the effects of sugars on hypertension has been the topic of cohort studies and RCTs.

Systematic reviews and meta-analyses

Four meta-analyses[7,21,23,24] and four systematic reviews[5,19,25,26] have been performed on dietary sugars and blood pressure and/or risk of incident hypertension. The reviews by Hauner et al[5] and Sonestedt et al,[19] both in 2012, included four studies and both reported no significant association between consumption of sugars and risk of hypertension.

In 2014 Keller and colleagues included five prospective cohorts and one RCT and concluded that there was a direct association between SSB consumption and a change in blood pressure.[26] The 2014 review by Malik et al included six prospective cohort studies and six cross-sectional studies with a total of 409 707 participants.[25] The conclusion of this review was also that SSB consumption was positively associated with blood pressure and risk of hypertension.

In 2015 Jayalath and colleagues meta-analysed three studies on five prospective cohorts (240 508 participants and 79 251 cases) with respect to SSB consumption and risk of hypertension.[24] The RR was 1.12 (95% CI 1.06, 1.17; I^2 = 62%) comparing the highest quantile (≥ one serving/d) with the lowest (none). The authors indicated that collinearity of SSB consumption with other components of a Western diet could not be excluded. The meta-analysis by Xi and colleagues included one additional cohort and used a different analysis of the SUN cohorts (incident hypertension instead of the metabolic syndrome criteria for blood pressure).[21] In total 259 176 participants and 10 011 cases were included. The highest intake of SSB was positively associated with the risk of hypertension (RR 1.10, 95% CI 1.06, 1.15; I^2 = 47 %) compared with the lowest level of intake.

Randomised clinical trials on consumption of sugars and blood pressure were reviewed by the Scientific Advisory Committee on Nutrition (SACN) in the UK in 2012)[7], Ha et al in 2012[27] and Te Morenga and colleagues in 2014.[23] The meta-analysis of SACN was based on three RCTs and concluded that there was no evidence for an effect of increased consumption of sugars on systolic blood pressure (SBP) or diastolic blood pressure (DBP).[7] The systematic review and meta-analysis by Ha specifically looked at the effect of fructose consumption on BP in RCTs. Thirteen isocaloric (n = 352) trials were included. Fructose intake in isocaloric exchange for other carbohydrates significantly decreased DBP (mean difference (MD) -1.54 (95% CI -2.77, -0.32; I^2 = 47%) and mean arterial pressure (MD -1.16 (95% CI -2.15, -0.18; I^2 = 97%). There was no significant effect of fructose on systolic blood pressure (MD -1.10 (95% CI -2.46, 0.44; I^2 = 31%).[27] Te Morenga et al included 12 trials with 324 participants in their meta-analysis. Overall no effect of increased intake of sugars on SBP was found (MD 1.1 mm Hg (95% CI -1.0, 3.2; I^2= 67%), but there was a significant effect on DBP (MD 1.4 mm Hg (95% CI: 0.3, 2.5; I^2 = 41%). When only trials with a duration of 8 weeks or longer were included, the effects were more pronounced (for SBP 6.9 mm Hg (95% CI 3.4,10.3) and for DBP 5.6 mm Hg (95% CI 2.5, 8.8). Studies funded by the sugar industry (n=5) generally reported less pronounced effects of sugar on blood pressure and excluding these studies from the analysis strengthened the hypertensive effects of higher sugar intakes.[23]

Additional studies

Several additional studies, not included in the reviews summarised above, were identified. In 2010 Perez-Poso and colleagues studied the effect of adding a high dose of 200 g fructose/d in liquid form to the habitual diet but avoiding SSBs in 74

normotensive individuals during two weeks.[28] Ambulatory SBP increased by 7 ± 2 mmHg and DBP by 5 ± 2 mmHg (P = 0.004 and 0.007, respectively). Body weight increased by 0.6 ± 0.2 kg, P = 0.003. In an RCT by Teunissen-Beekman et al in 2012 94 overweight participants were randomised to a group consuming three glucose (maltodextrin)-containing drinks (60g glucose/d) or three isocaloric protein drinks/day during four weeks.[29] Body weight did not change during the intervention in either group. After four weeks SBP and DBP measured in the clinic/office were 4.9 ±1.7 mmHg (P = 0.005) and 2.7 ± 1.3 mmHg (P = 0.05) higher in the glucose group. Ambulatory daytime SBP was also 4.6 ± 1.7 mm Hg higher in the glucose group (P = 0.006), whereas ambulatory daytime DBP did not differ between groups (P = 0.37). Lowndes and colleagues performed a randomised controlled trial in 2014 in which 65 overweight and obese individuals were placed on a eucaloric (weight stable) diet for 10-weeks with sucrose- or HFCS-sweetened, low-fat milk at 10% or 20% of calories.[30] Blood pressure did not change and no differences in blood pressure changes were found among groups. In 2015 Raatz and colleagues compared the effects of 50 g/d of honey, sucrose or HFCS for two weeks in 55 adults.[31] SBP was unchanged, whereas DBP was lowered, but there were no significant differences among treatments. Lustig et al, in 2016, studied the effect of reducing consumption of sugars from the habitual 28% of total energy intake to 10% by starch substitution during nine days in 43 children.[32] No comparison with a control treatment was included in this study. SBP did not change (-1.4 mmHg (95% CI -4.9, 2.1)) over the 10 days, DBP decreased significantly by 4.9 mmHg (95% CI -8.1, -1.8). Blood pressure changes were adjusted for the reduction in weight of 0.9 ± 0.2 kg (P<0.001) that occurred over the 10-day intervention. Given the time course of the weight change it was considered unlikely that the children were in a negative energy balance at the time of the post-intervention measurements. However, since no control group was included, these results should be interpreted with care.

Summary on sugars and hypertension

Overall, the results seem to suggest that the risk of hypertension may increase with increased long term consumption of SSBs. RCTs on the BP effect of changes in consumption of sugars suggest that lowering intake of sugars may lower blood pressure, especially when maintained over a longer period of time, but the effect size appears highly variable and will need to be further explained. The association is not nearly as clear-cut as the relationship between salt intakes and blood pressure (See Chapter 2.3.2).

8. Sugars and type 2 diabetes

Type 2 diabetes is an important risk factor for CVD and the association between sugars and type 2 diabetes has been addressed in a number of studies.

Systematic reviews and meta-analyses

Three systematic reviews and meta-analyses on the association between consumption of sugars and risk of type 2 diabetes haven been published since 2010.[33–35] All three focus on the role of SSBs. The review by Malik and colleagues included eight prospective cohort studies with a total of 310 819 participants and 15 043 subsequent cases of incident type 2 diabetes.[33] A RR of 1.26 (95% CI 1.12, 1.41; I^2 = 66%) comparing the highest (most often one to two servings per day) with the lowest intake category (most often none or less than one serving/month) in each study was found. A serving was defined as a can of 330 ml. Greenwood et al[34] did a meta-analysis in 2014

of six prospective studies, only partly overlapping with those reviewed by Malik in 2010. The RR from the linear dose–response meta-analysis was 1·20 (95% CI 1.12, 1.29) per 330 ml/d of SSBs with substantial heterogeneity between the cohorts (I^2 = 80 %). The last meta-analysis by Imamura and colleagues in 2015 was based on 17 prospective cohorts (38 253 cases/10 126 754 person years).[35] The analysis showed a RR of 1.18 (95% CI 1.08, 1.28; I^2 = 89%) per serving/day of SSB. After adjustment for differences in adiposity, the association was attenuated, RR 1.13 (95% CI 1.06, 1.21; I^2=79%) per serving/day of SSB. Various sensitivity analyses supported the positive association between SSBs and type 2 diabetes. However, the association of fruit juice consumption with incident type 2 diabetes, based on 13 prospective cohorts, was not significant (RR 1.05 (95% CI 0.99, 1.11) per serving/day of fruit juice; I^2=58 %), and the RR estimate was unstable in sensitivity analyses.

Additional studies

One additional study investigated the association between intake of different types of sugars and the risk of type 2 diabetes in the EPIC-Norfolk cohort involving 749 individuals with diabetes compared with a randomly selected sub-cohort of 3 496 participants aged 40-79 years.[36] Dietary intakes of total carbohydrates, starch, sucrose, lactose or maltose were not significantly related to diabetes risk after adjustment for confounders. After additional adjustment for energy intake, however, higher intakes of fructose were inversely associated with incident type 2 diabetes (HR 0.88 (95% CI 0.78, 0.99).[36]

Summary on sugars and type 2 diabetes

The meta-analyses on the association between SSB consumption and risk of incident type 2 diabetes suggest a 20-25% increase in risk per serving (around 350 ml) per day of SSB, which seems to be at least partially mediated by increased adiposity. The only study that looked at total consumption of sugars and its different components, on the other hand, found an inverse association between a higher consumption of fructose (as percentage of total energy intake) and the risk of incident type 2 diabetes. It is currently unclear how these findings can be reconciled.

9. Sugars and body weight or adiposity

Obesity is an important risk factor for hypertension, type 2 diabetes and CVD. Over the last five years a considerable number of new studies on the association between sugars and obesity have been published.

Systematic reviews and meta-analyses on added sugars

In a review of the scientific literature published in 2012, underpinning the German recommendations on consumption of sugars, Hauner et al concluded that there was insufficient evidence for a role of sucrose or added sugars in increasing the risk of obesity in adults and children.[5] The association between SSBs and obesity risk was considered possible, especially in overweight children and adolescents. In the UK SACN concluded in 2012 that studies provided conflicting evidence concerning the relationship between sweetened beverages and BMI, with US studies tending to find small but positive associations and European studies tending to report no evidence of a statistical association.[7] In the same year Te Morenga and colleagues published a systematic review and meta-analysis on intake of free sugars and its relationship with adiposity in children and adults.[37] This review was commissioned by WHO and was

the basis for the WHO recommendation on sugars. Exposure was based on total consumption of free sugars, but also on specific sources such as sucrose, glucose, fructose, or sugar-sweetened beverages. In five randomised trials of adults without strict control of energy intake (ad libitum) a reduced intake of dietary free sugars was associated with a decrease in body weight (MD 0.80 kg, 95% CI 0.39,1.21) compared with no change in free consumption of sugars, with no evidence of heterogeneity (I^2=17%). Increased intake of dietary free sugars in the context of an ad libitum diet was associated with significantly greater weight gain (MD 0.75 kg (95% CI 0.30, 1.19)) compared with no change in consumption of free sugars in adults. Heterogeneity among studies was significant (I^2 =82%). This analysis was based on 10 studies. In contrast, when free sugars were (partly) replaced by isocaloric amounts of other carbohydrate or other macronutrient sources (12 studies), there was no evidence for a change in body weight (MD 0.04 kg (95% CI -0.04, 0.13; P=0.3) (I^2=32%).[37] Overall, Te Morenga concluded that in the context of ad libitum diets, higher intake of free sugars or SSBs is associated with higher body weight. When energy intakes are controlled then the effect is negligible implying that, the effects of sugar appear to be mediated by changes in energy intake and that there is no selective fructose effect, because isocaloric exchanges are ineffective.[37] The same conclusion was drawn in a systematic review and meta-analysis on the association between fructose intake and body weight by Sievenpiper and colleages in 2012.[38]

Additional studies on added sugars

Two additional prospective cohort studies, not included in the review by Te Morenga were identified. Pollock et al in 2012 investigated the association between fructose consumption and visceral and subcutaneous abdominal fat mass in 559 adolescents.[39] After adjustment for total fat mass and other relevant factors, fructose consumption was positively associated with visceral fat mass, but not with subcutaneous abdominal fat mass. Lee and colleagues in 2015 analysed the effects of an increase in consumption of added sugars on changes in waist circumference (WC) and BMI z-score in 9 to 10-year old girls over one year.[40] Each additional 4 g/day of liquid added sugars was associated with a 0.22 mm increase in WC ($P < 0.001$) and a 0.002 increase in BMI z-score ($P = 0.003$). Each 4 g/day of solid added sugar was associated with a 0.13 mm increase in WC ($P = 0.03$) and a 0.001 increase in BMI z-score ($P = 0.03$). There was no association between an increase in naturally occurring sugars and changes in BMI z-score or waist circumference.[40]

Systematic reviews and meta-analyses on SSBs

The specific role of consumption of sugar-sweetened beverages has been the subject of a number of additional systematic reviews and meta-analyses[41–45] since 2010. In addition two reviews of reviews on this topic have been published.[46,47]

The systematic review by Woodward-Lopez et al in 2010 included 24 prospective cohorts: 16 showed a positive association between SSB intake and body weight and eight showed no association.[41] In addition, five RCTs on increased SSB intake and four on reduced SSB intake were reviewed. The results of studies on the reduction in SSB intake were equivocal, but those on the increase in SSBs were all positive, i.e. increased consumption led to increased body weight. The results of this review were largely confirmed in the meta-analysis of Malik and colleagues in 2013.[43] Malik included 15 prospective cohorts in children (174 252 children) and seven in adults (25 745 adults). In children the BMI change was 0.06 kg/m^2 (95% CI 0.02, 0.10) per one

daily serving increment of SSBs with significant heterogeneity among studies; in adults the weight change was 0.12 kg (95% CI 0.10, 0.14) per one daily serving increment of SSBs also with significant heterogeneity. Malik et al also did a meta-analysis of five RCTs in children (2 772 children) on the effect of reducing SSB consumption and of five RCTs in adults (292 adults) on the effect of increasing SSB intake. In children there was a non-significant BMI change of -0.17 (95% CI -0.39, 0.05) per one daily serving reduction of SSBs with significant heterogeneity among studies. More BMI reduction was found in substitution studies than in studies with an education approach. Noteworthy is the result of the DRINK study, in which masked replacement of a can of SSB (104 kcal) with a sugar-free beverage per day over 18 months led to a one kg smaller increase in weight among 11-12 year old school children.[48] In adults a weight change of 0.85 kg (95% CI 0.50, 1.20) per one daily serving increment of SSBs was found with no significant heterogeneity among studies. Based on these analyses Malik concluded that SSB consumption promotes weight gain in children and adults.[43]

Another meta-analysis, only including RCTs, was performed initially by Mattes et al in 2011[42] and then updated by Kaiser and colleagues in 2013.[44] The latter meta-analysis included seven RCTs on increased and eight on reduced SSB intake. Of these, seven were not included in the meta-analysis by Malik.[43] Conversely, two trials in the meta-analysis by Malik were not included by Kaiser. The trials on increased intake showed a standardised mean difference (SMD) of 0.28 (95% CI 0.12, 0.44; I^2 = 48%), favouring an increase in weight. The studies on reduced intake of SSBs showed a non-significant SMD of 0.06 (95% CI -0.01, 0.13; I^2 = 59%). When only studies in overweight or obese individuals were included, the SMD became statistically significant (SMD 0.25 (95% CI 0.13, 0.38; I^2 = 49%)). Based on their meta-analysis Kaiser et al concluded that, although the evidence suggests that a beneficial effect of a reduction in SSB may be demonstrable in some populations, the effect size is small and of equivocal statistical significance.[44] In 2015 a systematic review on SSBs and obesity risk was published by Pereira.[45] Twelve prospective cohorts and five RCTs on reduction of SSB consumption in children were included. Pereira concluded that the totality of evidence points to an increased risk of weight gain with higher SSB consumption, but that the heterogeneity among studies and the methodological limitations of both observational and experimental studies makes it difficult to establish the strength of the association.

Additional studies on SSBs

Some additional studies not included in the systematic reviews and meta-analyses summarised above were identified. An RCT by Lowndes et al in 2014 confirms that increased sugar-containing beverage consumption leads to significant weight gain (approximately 1 kg over 10 weeks) in adults, independent of the type of sugar (HFCS, sucrose, lactose).[49] In the prospective Framingham Third Generation cohort with 1003 participants, higher SSB intake at baseline was not associated with change in BMI (P_{trend} = 0.87), but it was associated with higher visceral adipose tissue volume at 6-y follow-up (P_{trend} <0.001) after adjustment for multiple confounders including change in body weight.[50] Massougbodji and colleagues in 2014 investigated whether the scientific quality and other study characteristics were associated with conclusions of reviews on the causal relation between SSBs and body weight.[46] The investigators included five meta-analyses, three systematic reviews and 12 non-systematic reviews. Scientific quality scores were unrelated to conclusions, but industry-funded reviews

(n=4) were more likely to suggest that the evidence for a causal relation was weak in contrast to the other reviews that generally considered the evidence to be well-founded.

In 2015 Keller and colleagues also published a review of reviews on the relationship between SSBs and adiposity in children and adolescents.[47] They included 13 reviews and meta-analyses. Nine reviews concluded that there was a direct relation between SSB consumption and weight gain, overweight, and obesity; four did not. They indicated that even the two meta-analyses with the highest scientific quality score (by Malik et al[43] and Kaiser et al,[44] see above) came to discrepant conclusions, which could be related to the inclusion criteria applied but also to the funding source of the authors (non-industry and industry respectively).[46]

Summary on sugars and adiposity
The reviews and meta-analyses on the effect of sugars on adiposity in majority conclude that adiposity increases with increasing consumption of sugars or SSBs. The effects of a reduction in SSB consumption in RCTs in children are heterogeneous, which may be related to the intervention method (education or provision of beverages). No RCT data on the effect of a reduction in SSB or sugars consumption on body weight or adiposity as such in adults are available. In isocaloric exchange studies no effects of reducing or increasing consumption of sugars on adiposity are seen, suggesting that the association is mediated by increased energy intake.

10. Sugars and fatty liver

A recent meta-analysis has suggested that non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of incident cardiovascular disease.[51] In reviews by Tappy and Le in 2012[52] and Vos et al in 2013,[53] the potential contribution of dietary fructose consumption to the development of NAFLD was discussed. Tappy and Le concluded that short-term fructose overfeeding may increase hepatic triglycerides without reaching the levels seen in NAFLD. Vos et al concluded that fructose is associated with increasing hepatic fat, inflammation, and possibly fibrosis in humans. However, whether fructose alone can cause NAFLD or only when consumed excessively in the setting of insulin resistance, a positive energy balance, and a sedentary lifestyle is unclear.[53] In a recent four week RCT by Jin et al 24 overweight adolescents who had hepatic fat >8% and who were regular consumers of sweet beverages were randomised to isocaloric fructose only or glucose only beverages.[54] After four weeks, there was no significant change in hepatic fat or body weight in either group.

Currently there is therefore not enough evidence to draw conclusions about the association between consumption of sugars and NAFLD.

11. Sugars and lipids

Increased plasma concentrations of lipids and lipoproteins are associated with increased cardiovascular disease risk.[55] Several recent systematic reviews and meta-analyses have addressed the potential association between sugars and plasma lipids.

Systematic reviews and meta-analyses

In 2012 Hauner et al concluded that the results of studies on the association between the intake of sugars and LDL-cholesterol and HDL-cholesterol concentration were inconsistent.[5] They also concluded that an association between fructose intakes < 100 g/d and plasma triglycerides was improbable, but that higher intakes increase plasma triglycerides. Sonestedt and colleagues in 2012 concluded that too few studies were available for a conclusion.[19] SACN reported no effect of consumption of sugars on total, HDL- or LDL-cholesterol or triglycerides. Subsequently, two meta-analyses have reported on the association between consumption of sugars and blood lipids.[23,56]

Te Morenga and colleagues in 2014[23] undertook a meta-analysis of 37 RCTs comparing the effect of higher with lower levels of free consumption of sugars on various blood lipid parameters. Higher compared with lower free sugar intakes significantly raised triglyceride concentrations (MD 0.11 mmol/L (95% CI 0.07, 0.15; I^2 = 73%), total cholesterol (MD 0.16 mmol/L (95% CI 0.10, 0.24; I^2 = 74%), low-density lipoprotein cholesterol (MD 0.12 mmol/L (95% CI 0.05, 0.19; I^2 = 73%), and high-density lipoprotein cholesterol (MD 0.02 mmol/L (95% CI 0.00, 0.03; I^2 = 36%). The effects were most pronounced in isocaloric exchange studies.[23] These findings are in contrast with findings of two previous systematic reviews and meta-analyses that specifically examined the effects of fructose consumption compared with consumption of other carbohydrates.[57,58] A more recent meta-analysis on this topic by Chiavaroli et al in 2015 included RCTs of at least one week duration that studied the effect of fructose consumption compared to a control carbohydrate on lipids.[56] Fifty-one isocaloric trials (n=943), in which fructose was provided in isocaloric exchange for other carbohydrates, and eight hypercaloric trials (n=125), in which the fructose was supplemented in excess, were included. Fructose had no effect on LDL-cholesterol, non-HDL-cholesterol, triglycerides, or HDL-cholesterol in isocaloric trials. However, in hypercaloric trials fructose raised triglycerides (MD 0.26 mmol/L (95% CI 0.11, 0.41; I^2 = 66%). These results suggest that the increase in triglycerides in the hypercaloric studies depended on the energy surplus when feeding fructose-containing diets. Furthermore, the investigators considered that the trials were limited by short follow-ups and low quality scores.[56]

Additional studies

In 2014 Lowndes and colleagues published the results of an RCT in which intakes of isocaloric amounts of HFCS, sucrose and placebo during 10 weeks were compared in 65 overweight individuals.[30] The type of sugar did not affect the lipid response to the diets. Lustig and colleagues in 2016 studied the effect of reducing consumption of sugars from the habitual 28% of total energy intake to 10% by starch substitution during nine days in a non-controlled trial in 43 children.[32] Fasting triglycerides were reduced from 1.4 ± 0.9 to 1.0 ± 0.5 mmol/L (P=0.002), LDL from 2.4 ± 0.6 to 2.1 ± 0.6 mmol/L (P=0.003) and plasma HDL from 1.2 ± 0.2 to 1.0 ± 0.2 mmol/L (P<0.001). When adjusted for weight loss, these changes were no longer significant. Given the fact that no control group was included, these results should be interpreted with care.

Summary on sugars and lipids

The studies on the effect of consumption of sugars on lipids show highly variable outcomes and currently no clear conclusions can be drawn. It also remains unclear whether any effects are mediated by changes in adiposity, since one meta-analysis suggests that the plasma lipid increasing effects are mainly seen in studies in which

energy balance is maintained, whereas the other meta-analysis concludes that the effects are due to increased energy intake rather than the sugars (fructose) consumption per se. High intakes of fructose can be associated with increased triglyceride concentrations, but the relevance of this finding for policymaking and specifying national average dietary targets or optimum goals is unclear.

12. Mechanisms

Several mechanisms have been suggested for the association between consumption of sugars and CVD risk. There is clear evidence that consumption of sugars and especially SSB consumption may lead to excess energy intake and gain of body mass and fat mass (see above). How much of the increased cardiovascular risk by dietary sugars is explained by adiposity and its associated cardiometabolic disturbances, such as the cluster of risk factors representing the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance with or without glucose intolerance, proinflammatory state and a prothrombotic state[59]), has not fully been elucidated, but other mechanisms have been suggested as well.

Rosset et al recently reviewed the potential mechanisms underlying the effects of fructose-containing sugars on CVD.[60] A major focus was on a potential role for hyperuricemia in fructose-induced cardiovascular risk. High fructose intake induces increases in plasma uric acid levels, both acutely[61] and chronically.[62] As potential mechanisms increased synthesis of uric acid by the liver or reduced renal uric acid excretion were suggested. Hyperuricemia might induce endothelial dysfunction and indirectly insulin resistance by activating the NALP3 inflammasome. In addition, hyperuricemia may activate lipogenic enzymes. A link between elevated uric acid levels and increased subsequent rates of CVD events has been suggested and there is increasing evidence that it may be an independent risk factor.[63] Nevertheless the role of diet in promoting hyperuricaemia with the induction of subsequent cardiovascular events is still unclear.[60,64]

Hyperglycemia and high insulin levels have been suggested to lead to endothelial dysfunction.[65] Mechanisms may involve inhibition of oxidative stress-induced dysregulation of nitric oxide homeostasis and formation advanced glycation end products (AGEs).[66] Indeed, Teunissen-Beekman et al in 2015 found lower endothelial dysfunction z-scores (based on plasma concentrations of cellular adhesion molecules (ICAM, VCAM and E-selectin) and the clotting protein Von Willebrand factor) when glucose consumption (60 g/d in the form of maltodextrin) was isocalorically replaced by protein consumption for four weeks.[67] Also fructose consumption has been shown to induce expression of cellular adhesion molecules.[68] In addition, fructose may contribute to a prothrombotic state by induction of Tissue Factor, sometimes termed thromboplastin.[68]

A review by Ares and colleagues in 2015 put forward the hypothesis the fructose may interact with renal salt handling, which is important for blood pressure regulation.[69]

Finally, some recent reports suggest that polymorphisms in certain genes may influence the susceptibility of individuals to the detrimental cardiometabolic effects of SSBs.[70–72]

13. Conclusion

Over the past six years a lot of new information has become available on the potential association between consumption of sugars and the risk of CVD, especially on the contribution of SSBs. The effects are most evident when sugars are consumed in excess, i.e. when accompanied by weight gain. However, some weight-gain independent effects may also be present. Evidence suggests that the increased risk is mainly associated with fructose-containing sugars, but the role of non-fructose containing sugars is less well studied and has not been fully elucidated. Although study results are not always consistent, a linear dose-response relationship between intake and risk is suggested by most studies. However, confounding by other aspects of a Western diet cannot be fully excluded. Well-controlled studies on the effects of reducing the intake of sugars on cardiovascular risk are relatively scarce, with the strongest evidence for a beneficial effect of reducing SSB consumption on adiposity in children from two well-controlled RCTs and for some lowering of blood pressure. Limiting the consumption of free or added sugars, and especially SSBs, is likely to have positive effects on adiposity, although the effect will be moderate. Based on the meta-analysis of Malik and colleagues in 2013, adults who consume one serving of SSB per day have on average a 0.22 kg (95% CI 0.09, 0.34) greater increase in body weight after one year than those not consuming any SSBs.[43] Nevertheless, limiting free sugars consumption may have a beneficial, although small, impact on cardiovascular health of populations. Because the dose-response relationships so far do not suggest a lower threshold, the recommendation should be to limit free sugars consumption as much as possible in order to obtain the largest benefits. Major contributors to free sugars consumption are soft drinks including fruit juices and dairy products with added sugars, sweets, candies, cakes and cookies. Limiting consumption of such food products as much as possible should be recommended, especially in those struggling to maintain a healthy weight.

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