

### 1.1.1 *Sugars*

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#### 1.1.1.1 Background

Over the past years a role of dietary sugar intake in the pathogenesis of cardiovascular disease has been suggested.<sup>1,2,3,4,5,6</sup> This relates to the consumption of dietary sugars in general,<sup>2,4</sup> the intake of sucrose,<sup>1</sup> the consumption of sugar-sweetened beverages,<sup>7</sup> or to a specific role for fructose consumption.<sup>8,9</sup> Effects of dietary sugars on endothelial function, overweight, insulin resistance, dyslipidemia, blood pressure, uric acid and inflammation have been implied as mechanisms underlying a potential association between sugar consumption and cardiovascular disease. In its report on Food, Nutrition and Cardiovascular Disease Prevention in the European Region, published in 2002, the European Heart Network has set a population goal for sugary foods of four or fewer occasions per day for the prevention of cardiovascular disease in Europe<sup>10</sup> based on the available evidence at that time. This section reviews the evidence for a role of dietary sugars in cardiovascular disease and its potential mechanism(s) with emphasis on the new evidence that has emerged since 2002. This comes from large observational studies and from controlled studies in humans. These new data give further support to a potential negative effect of high dietary sugars—and especially dietary fructose—consumption on cardiovascular disease risk, although the evidence remains inconsistent.

#### 1.1.1.2 Definition of dietary sugars

Dietary sugars are glycaemic carbohydrates.<sup>i</sup> 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 the combination of all mono- and disaccharides. Added sugars refers to any form of sugars added during food preparation, manufacturing or consumption. When the singular sugar is used, sucrose is meant. High-fructose corn syrup is not addressed as a separate entity, because its composition is very similar to that of sucrose. Sugar-sweetened beverages contain caloric sweeteners such as sucrose or high-fructose corn syrup.

#### 1.1.1.3 Dietary sugar consumption in Europe

The European Food safety Authority (EFSA) has recently published an overview of total sugars and sucrose intake (as % of energy intake (E%)) of children and adults in European countries. In children and adolescents between five and 18 years of age the

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<sup>i</sup> The term "glycaemic carbohydrates" refers to those carbohydrates which can be digested in the small intestine and then absorbed as simple monosaccharides for metabolism in the body whereas "non glycaemic carbohydrates" pass into the lower intestine for potential fermentation to short chain fatty acids which also provide energy to the intestine itself and then the rest of the body.

average total sugars intake varied between 22 and 36 E% and sucrose intake varied between 12 and 19 E%, in adults total sugars varied between 17 and 36 E% and sucrose between 8 and 18 E% among European countries.<sup>11</sup> Reported standard deviations ranged between 5 and 7E% for both total sugars and sucrose intake.<sup>11</sup> No data on added sugars consumption in Europe have been found. However, most of the dietary sucrose consumption comes from added sucrose<sup>11</sup> and EFSA noted that the average intake of (added) sugars in some EU Member States exceeds 10 E%, especially in children.<sup>11</sup> In the US average daily added sugars consumption was estimated at around 350 kcal or 90 g/d in 2001-2004, one third came from soft drink consumption.<sup>4</sup>

#### 1.1.1.4 Dietary sugar and risk of cardiovascular disease

Since the early observation by Yudkin and Roddy<sup>12</sup> that patients with recent myocardial infarction (MI) and peripheral artery disease (PAD) had higher consumption of total dietary sucrose than control subjects (mean intake in MI, PAD and control 132, 141 and 77 g/day respectively), the role of dietary sugar in cardiovascular disease has been much debated.<sup>13</sup> Yudkin even argued that the positive association between dietary intake of fat and cardiovascular disease may well be explained by the effect of sugar intake on cardiovascular disease because of the strong correlation between dietary fat and sugar intake.<sup>1</sup> Because dietary sucrose, if it plays a role, is unlikely to be the only dietary factor that influences cardiovascular risk, cross-sectional and observational epidemiological studies cannot be expected to give clear answers to the question whether dietary sugars consumption affects cardiovascular risk. Moreover, only a limited number of observational studies have been published on this topic since the initial reports by Yudkin.<sup>14,15</sup> Bolton-Smith and colleagues<sup>14</sup> found some evidence for a U-shaped relationship between added sugars consumption and the risk for coronary heart disease in Scottish males (not in females), but concluded that in the absence of a clear dose-response relationship this could not be seen as evidence for a role of dietary sugars in cardiovascular disease. Liu and colleagues failed to find a significant association between coronary heart disease risk and total carbohydrate, starch, sucrose, lactose or fructose intake in the Nurses' Health Study.<sup>15</sup>

More studies report on the associations between sugar-sweetened beverage (SSB) consumption and cardiovascular risk factors. In the Nurses Health Study consumption of SSBs was associated with a higher risk of coronary heart disease, even after adjustment for other dietary and lifestyle risk factors in subjects consuming  $\geq 2$  SSBs per day (relative risk (95% confidence interval (95% CI)) 1.35 (1.07, 1.69)) compared to those consuming  $< 1$  SSB per month).<sup>16</sup> In middle-aged participants of the Framingham Heart Study SSB consumption ( $\geq 1$  SSB per day compared to  $< 1$  SSB per day) was associated with a higher prevalence (odds ratio (OR) (95%CI) 1.81 (1.28, 2.56)) and incidence over four years of follow-up (OR 1.62 (0.96, 2.75)) of metabolic syndrome.<sup>17</sup> The prospective ARIC study showed that SSB consumption ( $> 1$  SSB per day *vs*  $< 1$  SSB per day) at baseline tended to be associated with the prevalence of chronic kidney disease in a multivariate model (OR (95% CI) 1.46 (0.96, 2.22)), but not with the incidence over the nine year follow-up in middle-aged US adults (OR 0.82 (0.59, 1.16)).<sup>18</sup> A higher sugar-sweetened beverage consumption

in a large nationally representative sample of the US adolescents studied between 1999 and 2004 was associated with higher serum uric acid and systolic blood pressure<sup>19</sup> and with higher insulin resistance-associated metabolic parameters and anthropometrics.<sup>20</sup> Higher dietary fructose consumption was associated with a more atherogenic lipid profile (smaller LDL particle size and lower HDL cholesterol) in a relatively small study in 6-14 year-old Swiss children, independent of adiposity.<sup>21</sup> A meta-analysis, based on 11 prospective cohort studies involving 310,819 participants and 15,043 cases of diabetes, reported that higher intakes of sugar-sweetened drinks are associated with type 2 diabetes.<sup>22</sup> Individuals with the highest intake of sugar-sweetened beverages (highest quartile; usually 1-2 servings/day) had a 26% greater risk of developing type-2 diabetes than those in the lowest quartile. Three studies examining metabolic syndrome (19,431 participants) found a 20% greater risk among those in the highest quartile of soft drink intakes compared to individuals in the lowest quartile.

#### 1.1.1.5 Dietary sugars and cardiovascular risk factors: controlled studies in humans

Several papers have recently reviewed the evidence derived from controlled studies in humans on the effect of dietary sugars on cardiovascular risk.<sup>23,4,11</sup>

With respect to glucose tolerance and insulin sensitivity, the European Food Safety Authority (EFSA) concluded that most studies do not find adverse effects of predominantly added sugars (mostly sucrose) up to 20-25% of energy, provided that body weight does not increase.<sup>11</sup> Ruxton and colleagues concluded in 2010 that relevant studies all report similar or better insulin sensitivity on diets high in sugars, with most of these studies including subjects with obesity, type-2 diabetes or at risk from heart disease.<sup>23</sup>

With respect to blood lipids, EFSA indicates that high intake of sugars (> 20% of energy), mainly as added sucrose or fructose, potentially increases triglycerides and LDL-cholesterol, especially in hyperinsulinaemic individuals.<sup>11</sup> The American Heart Association (AHA) concludes based on their review of studies that high sugar (glucose, sucrose and fructose) diets (> 20% of energy) increase plasma triglycerides, but that the effects on LDL cholesterol are inconsistent. The review by Ruxton and colleagues is supportive of this view.<sup>23</sup> The negative effect on blood lipids is most clearly seen in the studies with high levels of added fructose.

With respect to the effect of consumption of sugars on body weight, EFSA concluded that the evidence was inconsistent, but that high intakes of sugars in the form of sugar-sweetened beverages might contribute to weight gain.<sup>11</sup> This conclusion is in agreement with that of other recent reviews on this topic.<sup>23,4,24,25</sup>

Very few studies have looked at the blood pressure effects of dietary sugars. EFSA does not comment on a potential effect of sugars on blood pressure,<sup>11</sup> the AHA states that the data are inconsistent,<sup>4</sup> and blood pressure is not mentioned in the review by Ruxton and colleagues.<sup>2</sup> In the literature, a number of studies on this topic were found. Israel and colleagues reported in 1983 on an increase in diastolic blood

pressure of 2-3 mm Hg in 24 subjects on a high sucrose diet (33% of energy vs 5 or 18% of energy).<sup>26</sup> Van der Schaaf and colleagues, on the other hand, found no change in ambulatory blood pressure in 13 hypertensive subjects on an isocaloric high-sucrose diet (~40% of energy).<sup>27</sup> The composition of the control diet was not reported. Sørensen and colleagues compared sucrose (125-175 g/d depending on total energy intake, ~25% of total energy) with artificial sweetener on top of an *ad libitum* diet.<sup>28</sup> The diets were not isocaloric, which resulted in significant differences in weight change between the groups. Systolic and diastolic blood pressures were significantly higher on the high sucrose diet (8 and 4.5 mm Hg respectively), although adjustment for body weight changes attenuated the difference (6 and 5mm Hg respectively).<sup>28</sup> Further studies are clearly needed to assess whether dietary sugars have an effect on blood pressure.

Inflammation is regarded as a risk factor for cardiovascular disease. Few studies so far have addressed a potential effect of sugars on inflammation. The AHA remarks that there is a clear lack of controlled studies that have assessed the effect of long-term sugar consumption on inflammation and markers of oxidative stress.<sup>4</sup>

#### 1.1.1.6 Role of fructose in cardiovascular disease

It has been suggested that it is not the overall intake of sugars (mono- and disaccharides) that leads to cardiovascular disease, but rather the intake of sucrose or fructose.<sup>29</sup>

Near equal amounts of fructose and glucose are found in all common nutritive sweeteners, including high fructose corn syrup, except for those based solely on glucose, such as pure glucose or regular corn syrup.<sup>30</sup> It is estimated that >95% of Americans aged >19 y consume <100 g/d of fructose from all sources.<sup>31</sup> Dolan and colleagues recently estimated, based on data from the NHANES study between 1999-2004, that the 95<sup>th</sup> percentile of fructose consumption in US adults is 136 g/d or 18.8 % of energy intake.<sup>32</sup> Livesey argues on the basis of similar data that intervention studies using >100 g/d of fructose for women and 150 g/d for men are of minor relevance for public health.<sup>31</sup>

In Europe the production of HFCS is restricted to protect the sugar market and is set at approximately 5% of total sugar production.<sup>33</sup> Therefore, in contrast to the US, foods and beverages with added sugars on the European market are predominantly sweetened with sucrose. However, this does not make a difference for the fructose consumption, because sucrose and high fructose corn syrup contain similar amounts of fructose per gram.

#### *Fructose metabolism*

The metabolism of fructose is different from that of the other monosaccharides. Fructose is solely metabolised in the liver, in contrast to glucose and other monosaccharides. Dietary fructose activates the fructokinase pathway in hepatocytes. It is rapidly phosphorylated, bypassing 6-phosphofructokinase, one of the rate-limiting enzymes in glycolysis.<sup>34</sup> The post-meal oxidation of fructose is therefore much more rapid and extensive than the oxidation of glucose with equal availability.

Studies suggest that fructose may be less satiating than glucose and that sweetness of sucrose increases palatability.<sup>6</sup> Both factors may contribute to over consumption. Moreover, fructose has a lipogenic effect in the liver and could potentially modify the fatty acid composition of VLDL and induce harmful secondary effects like hypertriglyceridemia or insulin resistance.<sup>6,35,36</sup> Chong and colleagues concluded that the contribution of *de novo* lipogenesis to elevated postprandial triglyceride concentrations in humans is probably small, and that they are mainly due to lower activation of LPL and thereby reduced uptake of triglycerides in adipose tissue.<sup>37</sup> The phosphorylation of fructose in the liver requires ATP, which may result in ATP depletion and, as a consequence, production of uric acid from the breakdown of ADP. Uric acid inhibits NO production, increases ROS production and inflammation, and impairs endothelial and kidney function.<sup>38,6</sup>

#### *Fructose and uric acid*

Elevated uric acid concentrations are usually found in adults with metabolic syndrome, cardiovascular and renal disease.<sup>6</sup> Few controlled studies in humans have compared the effect of fructose consumption with consumption of other sugars or starch on uric acid concentrations.<sup>6,39</sup> A study by Akhavan and Anderson<sup>40</sup> investigated the effect of acute isocaloric ingestion of glucose/fructose mixtures, with glucose and fructose in different ratios, on the area under the curve (AUC) of uric acid over 75 min after ingestion. The AUC showed a dose-dependent increase with increasing fructose content of the mixture. Data on more long-term effects of high fructose diets on uric acid in humans from controlled trials seem to be lacking.<sup>40</sup>

#### *Fructose and lipids, glucose metabolism and body mass*

Several recent reviews have addressed the association between dietary fructose and lipids, glucose metabolism and body mass.<sup>31,41,42</sup> Schaefer concluded that diets containing  $\geq 20\%$  of energy from fructose are more likely to cause lipid abnormalities (hypertriglyceridaemia in those with hyperinsulinaemia and LDL-cholesterol increases in normo-insulinaemic individuals).<sup>42</sup> Diets containing 6-12 % of energy as fructose had very little effect on lipids and may reduce glucose levels modestly.<sup>42</sup> Dolan and colleagues conclude, based on an extensive review of the literature, that there is no evidence for increased plasma triglycerides after long-term ingestion of fructose of up to ~135 g/d, when it is not consumed in calorie excess, in healthy individuals.<sup>41</sup> These authors also report that there is no evidence that fructose consumption up to approximately 100 g/d instead of glucose or sucrose is associated with an increase in body weight.<sup>41</sup>

A neutral or even beneficial effect of moderate fructose diets (0-50 g/d) and a potentially unfavourable effect of diets very high in fructose (>100 g/d) agrees with the outcome of a meta-regression analysis by Livesey on the dose-response relationships between fructose consumption and various health parameters (insulin sensitivity, blood lipids, uric acid, BMI).<sup>31</sup>

#### *Fructose and blood pressure*

Hardly any studies have specifically studied the effect of fructose consumption on blood pressure. One study showed that consumption of a fructose drink (500 ml with 60 g of fructose) increased mean blood pressure acutely, over at least two hours after

consumption, by ~4 mm Hg in comparison with an isocaloric glucose drink, due to a more pronounced increase in cardiac output in the absence of less change in peripheral resistance, in young healthy volunteers.<sup>43</sup>

#### 1.1.1.7 Current recommendations for dietary sugars with respect to cardiovascular disease prevention

The general population guidelines on added sugars consumption differ among European countries. Most countries have qualitative guidelines for consumption of sugars (e.g. use in moderation, limit intake, little portions, consume occasionally), other countries use quantitative recommendations (e.g. maximum 10 or 15% of energy, <15 g/d).<sup>23</sup>

In its 2002 report, the European Heart Network set a population goal for sugary foods of four or fewer occasions per day for the prevention of cardiovascular disease in Europe.<sup>10</sup> This recommendation was not based on a direct relationship between dietary sugars and cardiovascular disease, but was rather given in the context of preventing overweight and obesity, which are associated with increased risk for cardiovascular disease. The recommendation was derived from the prevention of caries where the frequency of sugar consumption is more relevant than the total amount.<sup>23,44</sup>

Based on a review of the available evidence, the European Food Safety Authority has concluded recently that the data are insufficient to set an upper limit for sugars based on their effects on lipids, body weight or dental caries.<sup>11</sup>

However in the United States, recommendations on intake of sugars for cardiovascular risk reduction have been issued by the American Heart Association (AHA). In its 2002 scientific statement on sugars and cardiovascular disease, it is concluded that since sugars have no nutritional value other than to provide calories, high intake of sugars should be avoided because this will help to reduce the nutrient density of the diet and the intake of excess calories.<sup>45</sup> In line with this conclusion, the 2006 Diet and Lifestyle Recommendations for Cardiovascular Risk Reduction by the AHA specifically mention dietary sugars.<sup>46</sup> the AHA advises to minimise the intake of beverages and foods with added sugars. In its most recent statement on this issue, the AHA recommends a prudent upper limit of added sugars intake of half of the discretionary calorie allowance, which is for most American women no more than 100 kcal per day and for most American men not more than 150 kcal per day, from added sugars (approximately equivalent to 35 g/d of added sugars, i.e. sugar content of 0.33 ml can of soft drink).<sup>4</sup>

#### 1.1.1.8 Conclusion

Based on this review of the recent literature on the association between dietary sugars and existing dietary recommendations it is concluded that:

1. there is limited and inconsistent evidence for an effect of consumption of sugars on cardiovascular disease risk;

2. most consistent evidence is found for an association between high intake of sugar sweetened beverages and risks of cardiovascular disease;
3. most evidence suggests that unfavourable effects of consumption of sugars on blood lipids is related to high intakes of fructose (>100-150 g/d or >15-25 E%);
4. high intakes of sugar-sweetened beverages may increase the risk of overweight;
5. a prudent recommendation would be to avoid high intakes of fructose, especially in the form of sugar-sweetened beverages, even though unequivocal evidence for such recommendation is lacking.

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