9.3.3. Fruit juices

9.3.3.1. Intervention studies

No RCTs were available for sQ3.A.

9.3.3.2. Observational studies

LoE1. Standalone (main): Incidence of GDM. PCs. Two PCs (ALSWH, NHSII) report on the relationship between the intake of FJs and incidence of GDM. The evidence table can be found in **Annex J**.

Preliminary UA

In the ALSWH cohort (Looman et al., 2018), the relationship between the intake of FJs (from fresh fruits and ready-to-eat) and incidence of GDM was negative and borderline significant in the most adjusted model (RR = 0.89; 95%CI = 0.80, 1.00 for each 100 g/day increase in intake). Fruit juice intake was adjusted for TEI using the nutrient residuals model (RoB tier 3), keeping TEI constant.

In the NHS II cohort, no association between the intake of FJs and incidence of GDM was reported. Analyses were performed by quintiles of absolute FJs intake and models were not adjusted for TEI (RoB tier 2).

The Panel considers that the available evidence does not suggest a positive relationship between the intake of fruit juice and risk of GDM. **No comprehensive UA is performed**.

Complementary LoE2: Risk of obesity and LoE 3: T2DM. PCs. There is evidence from PCs for a positive and causal relationship between the intake of FJs and risk of obesity (very low certainty sQ5.1, Section 8.2.5.1) and T2DM (moderate certainty, sQ5.3, Section 8.4.5.1).

Conclusion sQ3.A. PCs. The available BoE does not suggest a positive relationship between the intake of fruit juices and risk of GDM.

9.3.3.3. Overall conclusion sQ3.A

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of fruit juice and risk of GDM.

9.4. Birthweight-related endpoints

9.4.1. Total sugars

9.4.1.1. Intervention studies

No RCTs we available for sQ1.B.

9.4.1.2. Observational studies

LoE1. Standalone (main). **Incidence of LBW, SGA, HBW and LGA. PCs**. The relationship between the intake of total sugars and LBW and SGA was investigated in one PC (Cadmen, (Lenders et al., 1997)).

A total of 594 pregnant female adolescents between 12 and 19 years of age without history of diabetes or GDM in current pregnancy were recruited from two clinics at the time they attended for prenatal care (time not specified). Total sugar intake was assessed through a 24-h dietary recall at entry, 28 and 36 weeks of gestation. For data analysis, the sample was divided in two groups, being > or < the 90th percentile (cut-off = 206 g/day) for absolute intake of total sugars, and thus, TEI was not held constant before categorisation. The evidence table is in **Annex J**.

Preliminary UA

The risk of having infants SGA was double in the group consuming > 206 g/day of total sugars as compared to the reference group (OR = 2.01; 95% CI: 1.05,7.53) after adjusting for TEI and BMI, among other relevant covariates. Although it is stated that low birth weight (LBW) was also an endpoint for the study, logistic regression analyses were done on SGA only. It is reported that the percentage of infants with LBW was also higher in the group consuming more total sugars (13% vs. 7%) although not significantly so. This PC was at moderate RoB (tier 2), critical domains being

exposure, attrition and other sources of bias (e.g. statistical analysis on the extreme percentiles of intake, incomplete reporting).

The Panel notes that only one PC at moderate RoB was available for this LoE. The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars and risk of SGA or LBW. **No comprehensive UA is performed**.

LoE2. Standalone (surrogate). **Birthweight. PCs**. In the HSS-USA cohort (Crume et al., 2016), 1,040 pregnant women older than 16 years with no history or diabetes or GDM were recruited between 8 and 24 weeks of gestation (median 17 weeks). Birth weight was measured by trained nurses within 72h from birth (median 1 day). Total sugars intake was assessed monthly through pregnancy by repeated 24-h diet recalls. 82% of participants completed at least two 24-h recalls.

Preliminary UA

Non-significant (negative) relationships were reported between the intake of total sugars during pregnancy and birthweight in both energy substitution (for each 1E% increase in total sugars in isocaloric exchange with other macronutrients, TEI held constant) and energy partition models (for each 100 kcal/day increase in total sugars adjusting for the intake of other macronutrients, TEI not held constant) after adjusting for relevant covariates, including pre-pregnancy BMI. This PC was at low RoB (tier 1).

The Panel notes that the only PC available was at low RoB and reports non-significant associations between the intake of total sugars, either per se or in isocaloric exchange with other macronutrients and birthweight. The Panel considers that the available BoE does not suggest a positive relationship between the intake of total sugars and adverse effects on birthweight. **No comprehensive UA is performed**.

Conclusion sQ1.B. **PCs**. The available BoE does not suggest a positive relationship between the intake of total sugars and risk of adverse effects on birthweight.

9.4.1.3. Overall conclusion on sQ1.B

Since no standalone LoE passed the screening step (preliminary UA), the Panel considers that the available BoE cannot be used to conclude on a positive and causal relationship between the intake of total sugars and risk of adverse effects on birthweight.

9.4.2. Sugar-sweetened beverages

9.4.2.1. Intervention studies

No RCTs we available for sQ2.B.

9.4.2.2. Observational studies

LoE1. Standalone (main). **LBW, SGA, HBW, LGA**. Two PCs (MoBA, (Grundt et al., 2017); GeliS, (Günther et al., 2019)) report on the relationship between the consumption of SSBs during pregnancy and these endpoints. In the MoBA cohort, the relationship between carbonated SSBs consumption during pregnancy (mean intakes during weeks 15, 22 and 30) and adverse effects on birthweight-related endpoints was investigated in those that, not being diabetic at baseline, either developed or not GDM during pregnancy. In the GeliS cohort, the relationship between SSBs consumption in early (≤ 12th week of gestation) and late (> 29th week of gestation) pregnancy and adverse effects on birthweight-related endpoints was investigated. Both studies adjusted for pre-pregnancy maternal BMI and neither adjusted for TEI in the multivariable models.

The Panel notes that, whereas the cut-off for LBW was the same in both studies (birthweight < 2,500 g), the cut-off for HBW was higher in the MoBA than in the GeliS cohort (birthweight > 4,500 g and > 4,000 g, respectively). The evidence table can be found in **Annex J**.

Preliminary UA

In the MoBA cohort, in women who did not develop GDM during pregnancy, there was a non-significant higher risk of having infants with LBW (OR = 1.05; 95%CI: 0.99, 1.10, per 100 mL/day increase in intake) and a significantly lower risk of having infants with HBW (OR = 0.94; 95%CI: 0.90, 0.97, per 100 mL/day increase in intake) associated with the consumption of SSBs. Results are reported to be similar for SGA and LGA, respectively, but not provided in the publication. Similar results were obtained for SSBs (carbonated, cordials, fruit juices and nectars combined) in mL/day and for energy from added sugars (all sources), but not when volume or energy from carbonated SSBs,

respectively, was subtracted (data not shown in the publication). The relationship between consumption of carbonated SSBs and birthweight-related outcomes was in the opposite direction for women with GDM (higher risk of having infants with HBW) but not statistically significant. The Panel notes the high birthweight cut-off used to define HBW in this study (> 4,500 g) may have attenuated the strength of this association. This study was at low RoB (tier 1), with no critical domains.

In the GeliS cohort, SSBs consumption in early pregnancy was also non-significantly associated with increased risk of having a neonate with LBW (OR = 1.04; 95%CI: 0.99, 1.09 per 200 mL/day increase in intake) and with a decreased risk of having neonates with HBW (OR = 0.95; 95%CI: 0.88, 1.02 per 200 mL/day increase in intake). Similar results were reported for SSBs consumption in late pregnancy and risk of having neonates with HBW, whereas the association with having neonates with LBW was null. A similar pattern of results was reported for SSBs consumption in both early and late pregnancy and risk of having neonates SGA and LGA, respectively. The Panel notes that, in this cohort, 10.8% of the women developed GDM and 8% developed hypertension during pregnancy. Taking into account that both these variables could have been associated with both the exposure and the endpoints, and that the relationship between the intake of SSBs and birthweight in women with GDM was in the oppositive direction in the MoBA cohort, the Panel considers that not excluding women with GDM from data analysis may have attenuated the observed relationship. This study was at moderate RoB (tier 2). Critical domains were confounding and outcome assessment.

Consistent with the results obtained for dichotomous outcomes, both studies report a statistically significant inverse relationship between SSBs consumption and neonate birthweight analysed as a continuous endpoint **(LoE2. Standalone (surrogate))**. In the MoBA cohort, in women with no GDM, each additional 100 mL/day increase in carbonated SSBs consumption was associated with a mean neonate birthweight of −7.8 g (95%CI: −10.3, −5.3). Consumption of carbonated ASBs and of combined ASBs was also negatively and significantly associated with lower birthweight in this population of women with no GDM, although the magnitude of the association is reported to be 25 and 50% lower than that of carbonated SSBs, respectively (data not shown in the publication). In women who developed GDM (n = 432), mean birthweight per each 100 mL/day increase in carbonated SSBs consumption was in the opposite direction (+25.1 g, 95%CI: −2.0, 52.2). In the GeliS cohort, mean birthweight was −10.9 g (95%CI: −18.17, −3.64) and −8.19 g (95%CI: −16.26, −0.11) per each additional serving of SSBs (200 mL/day) consumed in early and late pregnancy, respectively.

The MoBa cohort was at RoB tier 1. The GeliS cohort was at RoB tier 2, critical domains being confounding and outcome assessment. The heat map for the RoB assessment is in **Annex K**.

The Panel considers that the available BoE suggests a positive relationship between the intake of SSBs and adverse effects on birthweight (i.e. a decrease in birthweight, leading to a higher risk of low birthweight and being small for gestational age) in women not developing GDM during pregnancy.

Comprehensive UA

The Panel considers that it would be inappropriate to proceed with a comprehensive UA because several downgrading factors cannot be assessed with less than three independent studies. The initial level of certainty assigned to the relationship is **very low** (0–15% probability) to reflect the limited BoE available (see Section 8.1.3). The Panel did not identify any reason to increase this level of certainty.

Conclusion sQB2. PCs. The level of certainty in a positive and causal relationship between the intake of SSBs and risk of adverse effects on birthweight is **very low**. The relationship is observed while not keeping TEI constant in the analysis.

9.4.2.3. Overall conclusion on sQ2.B

There is evidence from PCs for a positive and causal relationship between the intake of SSBs and risk of adverse effects on birthweight (**very low** level of certainty).

9.5. Overall conclusions on hazard identification: pregnancy endpoints

The Panel notes the scarcity of studies available on the relationship between the intake of dietary sugars and their sources and the pregnancy-related endpoints investigated in this assessment. Still, there is some evidence that habitual consumption of SSBs by women in child-bearing age could increase the risk of GDM during pregnancy (low certainty, > 15–50% probability), possibly through

excess energy intake leading to an increase in body weight, although a specific effect of the sugar fraction on glucose tolerance cannot be excluded.

There is also some evidence (very low certainty, 0–15% probability) that consumption of SSBs during pregnancy could increase the risk of having infants SGA in women not developing GDM during pregnancy. In women developing GDM, the risk appears to be having infants LGA. In women not developing GDM, the relationship could be mediated by lower intakes of other macronutrients (e.g. protein, fat), whereas an excess energy intake and the impaired glucose metabolism could play a role in women with GDM. However, TEI was not considered in the multivariable models used for data analysis in the two PCs that investigated these endpoints, and the limited data available preclude exploring these hypotheses.

9.6. Pregnancy endpoints: data gaps and research needs

The following major data gaps were identified in the BoE regarding the relationship between dietary sugars and their sources and risk of adverse effects on pregnancy-related endpoints:

[a] Lack of studies investigating the relationship between added and free sugars from all sources, and fructose, and incidence of GDM and adverse birthweight-related endpoints.
[b] Paucity of studies on total sugars, SSBs and FJs and incidence of GDM and adverse birthweight-related endpoints.

The data gaps identified in the BoE regarding the relationship between dietary sugars and risk of adverse pregnancy-related endpoints lead to the following research needs:

a) PCs that assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars; both habitual intakes and intakes during pregnancy) and their sources, and incidence of GDM.
b) PCs that assess the relationship between quantitative intakes of dietary sugars and their sources during pregnancy and birthweight in women developing and not developing GDM during pregnancy, accounting for factors that may confound the association (e.g. intake of other macronutrients, gestational age, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia).
c) Studies that measure the impact of interventions to reduce the amount of dietary sugars (habitual intakes, intake during pregnancy) on the development of GDM.
d) Studies that measure the impact of interventions to reduce the amount of dietary sugars during pregnancy on birthweight in women developing and not developing GDM.

10. Hazard identification: dental caries

10.1. Principles applied to assess the body of evidence

Ever since the pathogenesis of dental caries was elucidated, there is wide consensus among the scientific community that the intake of dietary sugars is causally related to the development of dental caries at all ages (Jepsen et al., 2017). For this reason, few human intervention studies investigating the effects of different doses of dietary sugars on the incidence of dental caries were undertaken over the years, owing to ethical considerations.

The BoE eligible for this assessment is presented below for the purpose of describing dose-response relationships between the exposure and the endpoint and possibly identifying a level of sugars intake that is/it is not associated with an increased risk of dental caries. The conclusions will be used for hazard characterisation.

To this end, EFSA requested all the authors of the observational studies potentially eligible for this assessment to share individual data. The purpose was to perform pooled analyses in order to identify dose-response relationships if possible.

10.2. Body of evidence

10.2.1. Intervention studies

Only one human intervention study met the inclusion criteria for this assessment (Scheinin et al., 1976).

The Turku sugar study is an open-label intervention in which free-living, healthy participants (mean age 27.7 years, age range 12–53 years) were allocated to three groups, half based on individual preference and half at random. Participants (n = 125) were asked to consume, for 2 years, all added sugars in the diet as either sucrose (n = 35), fructose (n = 38) or xylitol (n = 52).

Food products were given free of charge and were specifically manufactured for the trial (Mäkinen and Scheinin, 1976). Compliance with the dietary regimen was assessed through diaries and interviews when clarifications were needed through the 2-year period. Clinical and radiological evaluation of primary and secondary dental caries with and without defect, and of filled surfaces, was performed at baseline, and at months 3, 7, 13, 20 and 24 of the study. Details on the inter-observer variability in clinical and radiological diagnosis are thoroughly discussed in the publication. From these, several caries indices were derived for analysis.

A 25% dropout rate was foreseen, but only 10 participants (8%) discontinued participation or were removed from the trial, leaving 115 subjects for analysis (33, 35 and 47 in the sucrose, fructose or xylitol groups, respectively).

No significant differences were found between the groups for age, sex, number of primary and secondary carious surfaces with and without defect, number of filled surfaces and extracted teeth, or the decayed, missing and filled tooth surfaces (DMFS)-index. Mean intake of sucrose, fructose and xylitol was 2.2, 2.1 and 1.5 kg/month, respectively, corresponding to 73.5, 70 and 50 g/day, respectively.

After 2 years the mean (SD) increment in the DMFS-index was 7.2 (5.67), 3.8 (4.14) and 0.0 (5.35) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p < 0.01$ for sucrose vs. fructose). The mean (SD) increment in the modified DMFS-index (sum of increment in the DMFS-index and all secondary caries reversals) was 10.5 (7.97), 6.1 (5.44) and 0.9 (6.66) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p < 0.05$ for sucrose vs. fructose). The mean (SD) increment in the caries activity index (sum of increment in the DMFS-index, all secondary caries reversals and increase in size of total clinical and radiographic reversals) was 12.5 (9.35), 8.5 (6.26) and 1.9 (6.59) in the sucrose, fructose and xylitol groups, respectively ($p < 0.005$ for sucrose and fructose vs. xylitol; $p = 0.052$ for sucrose vs. fructose). No significant differences were observed in the number of filled surfaces among groups during the study. This study was at RoB tier 2, critical domains being randomisation, allocation concealment, blinding and exposure assessment (**Annex K**).

The Panel notes that full replacement of added sucrose and fructose in the diet led to a significant decrease in the incidence of dental caries over 2 years, and that fructose appeared to be less cariogenic than sucrose. The Panel also notes that, although this study confirms the cariogenic potential of sucrose and fructose, it does not allow investigating a potential dose-response relationship between the intake of these dietary sugars and the risk of developing dental caries.

10.2.2. Observational studies

A total of 11 publications reporting on seven cohorts met the inclusion criteria. One cohort included adults of both sexes (Finnish cohort, (Bernabé et al., 2016)), one was in adult and older adult men (VA-DLS, (Kaye et al., 2015)), two were in adolescents of both sexes (UK cohort (Rugg-Gunn et al., 1984; Rugg-Gunn et al., 1987); Michigan cohort (Burt et al., 1988) (Burt and Szpunar, 1994; Szpunar et al., 1995)) and three were in children, again of both sexes (IFS (Chankanka et al., 2011); STRIP-1 (Ruottinen et al., 2004); STRIP-2 (Karjalainen et al., 2001, 2015).

All children in the STRIP-1 and 2 cohorts participated in the STRIP trial, an RCT designed to restrict the intake of total fat and cholesterol for atherosclerosis prevention. The overlap between the two STRIP cohorts investigating the relationship between the intake of sucrose and dental caries is limited to one child, and thus, both cohorts are included in this assessment.

Five PCs report on total sugars (of which two also report on SSBs and one on FJs) and two cohorts (STRIP-1 and STRIP-2, Finland) report on sucrose. At the time these studies were conducted, sucrose was the major source of added sugars in Finland. Cohorts were very heterogeneous regarding the outcome of interest, consistently with the demographic characteristics of their participants. The Finnish cohort measured Decayed Missing and Filled Teeth (DMFT) including coronal and root lesions that were cavitated or extended into dentine. The VA-DLS study focused on root caries (adjusted root caries increment) only, a type of lesion that is more commonly encountered as age progresses and tooth root becomes exposed. The UK and Michigan cohorts visually assessed and reported not only the number of decayed teeth, but also tooth surfaces, and subclasses of tooth surfaces (i.e. fissure,

approximal, smooth) with cavitated carious lesions. The two studies based on data from the STRIP cohort measured the number of primary and permanent teeth with cavitated carious lesions, confirmed by radiographic assessment. The IFS measured pre-cavitated and cavitated carious surfaces in primary and permanent dentition by visual examination. The evidence table is in **Appendix M**.

Individual data were obtained for three cohorts (STRIP, IFS and VA-DLS). However, data from the VA-DLS cohort could not be used for the EFSA analysis because of difficulties in reproducing the outcome as in the original study due to lack of full information. The database was used to provide descriptive statistics on intakes for sugars in g/day (per quartiles of E%) and SSBs.

The STRIP-2 (Karjalainen et al., 2001, 2015) and IFS cohorts (Chankanka et al., 2011) were included at full-text screening because they were potentially eligible for the assessment, although the results as reported in the original publications were not (i.e. daily intakes of sugars and/or their sources were either not quantified or not used as independent variables in prospective analyses). However, authors provided individual data for EFSA to perform the analyses of interest for this opinion. A technical report with details on the statistical analysis conducted by EFSA using individual data from the STRIP and IFS cohorts can be found in **Annex N**.

The summary assessment of the RoB is in **Annex K**. Two cohorts were at low RoB (tier 1; Finnish cohort and Michigan cohort), and the remaining were at moderate RoB (tier 2) except for the VA-DLS cohort for total sugars (tier 3). Critical domains across the BoE were confounding, attrition and exposure assessment.

10.2.2.1. Total sugars

In the Finnish cohort (Bernabé et al., 2016), a positive linear dose-response relationship was observed between the intake of total sugars (in g/day) and the increment of cavitated caries in permanent dentition during the 11-year follow-up over a wide range of sugars intake (13.7 to 442.3 g/day). None of the 43 alternative curvilinear models tested improved the prediction of the linear model significantly. Mean intakes of total sugars (SD) at baseline were 110.9 g/day (47.8). After adjustment for relevant covariates, including frequency of sugars consumption, the relationship was stronger than in the crude model (**Appendix M**). Vice-versa, frequency of consumption was not associated with dental caries when the amount of total sugars was included in the model. Upon EFSA's request for additional information, the authors report that a level of total sugars associated with a zero increment in the DMFT index could not be identified in this study. The Panel also notes that the lowest intake of total sugars was low, corresponding to about 2.7 E% for a diet of 2,000 kcal/day. This PC was at low RoB (tier 1).

In the VA cohort (Kaye et al., 2015), no significant relationship was observed between quartiles of total sugars intake (E%; sum of sucrose, fructose and lactose) and adjusted root caries increment over the 11-year follow-up. Total sugars intake ranged from 3.8 to 36.7 E%. The study was at high RoB (tier 3) for total sugars. Critical domains were confounding, attrition and exposure.

In the UK cohort (Rugg-Gunn et al., 1984, 1987), there was a low but statistically significant correlation between the DMFS increment, measured over a 2-year period, and total sugars intake in g/day ($r = +0.105$ for the crude model, without adjusting for potential confounders; $p < 0.05$). When the analysis was controlled for tooth brushing frequency, the correlation between total sugars intake and caries increment was higher than in the bivariate analysis. The correlation was significant for the 2-year fissure caries increment (DFS; $r = +0.143$; $p < 0.02$) after adjusting for age, sex, gingival index, frequency of sugars intake and starch intake, but not for the caries increment for approximal or smooth tooth surfaces. Regression of DMFS increment on the amount of total sugars intake indicated that there was an average increase of 0.36 DMFS (95%CI −0.07, 0.80) over 2 years with each rise of 30 g of sugars per day in the most adjusted model. The 31 children with the highest intake of total sugars (> 163 g/day) developed 0.9 more DMFS per child per year than the 31 children with the lowest intake of total sugars (< 78 g/day, $p = 0.07$). The Panel notes that this study reports a linear dose-response relationship between the intake of total sugars and incidence of dental caries and does not allow identifying a level of intake at which the risk is not increased. The study was at moderate RoB (tier 2). Critical domains were confounding and other sources of bias (statistical analysis).

In the Michigan cohort (Burt et al., 1988; Burt and Szpunar, 1994; Szpunar et al., 1995), a higher proportion of energy intake from total sugars increased the probability of developing cavitated lesions in the permanent dentition over the 3-year follow-up period. Those in the highest quartile of total sugars intake (mean intake 29.5E%, 175 g/day) had a relative risk (95%CI) of 1.22 (1.04, 1.46) of developing caries compared with the lowest quartile (mean intake 23E%, 109 g/day). This risk rose to 1.80 (1.06, 3.10) for approximal caries. Models were adjusted for age and baseline DMFS. In most

adjusted models (including sex, age, history of previous residence in a fluoridated community, use of fluoride tablets, frequency of topical fluorides, toothbrushing frequency, antibiotic use, parental education and family income as covariates), E% from total sugars significantly correlated with total, approximal and fissures caries incidence, whereas the correlation was only significant for total caries when total sugars intake was expressed in g/day. Frequency of sugars intake did not correlate with caries risk. From these most adjusted models, it was estimated that the risk of cavitated caries increased by 1.6 times in those at +1SD of total sugars intake vs. those at −1SD, either expressed as E% or g/day. It was calculated that each additional 8 g/day of total sugars intake was associated with a 1% increase in the probability of developing cavitated lesions. In this study, the relationship between total sugars intake and caries risk appeared to be linear and it does not allow identifying a level of intake at which the risk is not increased. The Panel notes that the intake of total sugars in this population group was high. The study was at low RoB (tier 1).

In the IFS (Chankanka et al., 2011), the relationship between the intake of total sugars over the study period and risk of cavitated, non-cavitated and dental caries between the ages of 5 and 9 years in the mixed dentition was assessed. No relationship between the intake of either total sugars and risk of dental caries was observed after controlling for relevant confounders, including sex, SES, age at the dental exam at follow-up, prevalence of dental caries at baseline, mean daily toothbrushing frequency and composite water fluoride concentration (ppm). Similar results were obtained when the analyses were restricted to children free of caries at 5 years. Mean intakes of total sugars was 114 g/day (range 53 to 216 g/day). The study was at moderate RoB (tier 2). Critical domains were exposure assessment and attrition. The Panel notes that intakes of total sugars were high in this population group.

10.2.2.2. Added sugars

In the STRIP-1 cohort of Finnish children followed from infancy to age 10 (Ruottinen et al., 2004), the mean sucrose intake in a 'high' sucrose group was 48.4 g per day, and in the 'low' sucrose group, it was 22.5 g/day. The high sucrose group has a higher sucrose intake every year of the study. The sucrose consumption of the high sucrose group exceeded 10% of energy intake after 13 months of age. In the low sucrose group, the intake of sucrose did not exceed 7% of energy intake at any age. The mean dmft (primary dentition) was 2.7 (SD 3.3) in the 'high' sucrose intake group and 1.19 (SD 1.2) in the 'low' sucrose intake group ($p = 0.177$). The mean dmft+DMFT (mixed dentition) was 1.9 (SD 2.5) in the 'high' sucrose intake group and 0.5 (SD 1.1) in the 'low' sucrose intake group ($p = 0.032$). The mean DMFT (permanent dentition) in the 'high' sucrose intake group was 1.4 (SD 2.0) compared with 0.5 (SD 1.1) in the 'low' sucrose group ($p = 0.01$). Potential confounders were not included as covariates in the analysis. However, confounding by tooth brushing frequency was considered by comparing sucrose intake and dental health in different tooth brushing frequency groups. The association between sucrose intake and toothbrushing frequency was not significant, but this may have been due to the small size of the groups compared. The study was at moderate RoB (tier 2), critical domains being confounding and exposure assessment.

In the STRIP-2 (Karjalainen et al., 2001, 2015), the relationship between sucrose intakes (g/day) at years 3 and 12 and new cavitated caries in primary dentition at age 6 years and in permanent dentition at age 16 years, respectively, was investigated. Data on sex, STRIP study group, caries-free age (years), cavitated caries at baseline for each period and daily toothbrushing (yes/no) were available as covariates. The risk of developing cavitated caries in primary dentition at 6 years (yes/no) was about four times higher in the highest (mean intake = 44 g/day, range = 34.5–65.9 g/day) vs. the lowest quartile (mean intake = 15.9 g/day, range = 7.4–20.9 g/day) of sucrose intake at 3 years (OR = 4.32; 95%CI = 1.31, 14.25). Assuming an energy requirement of 1100 kcal/for a 3-year-old child, mean sucrose intakes in the highest and the lowest quartiles would correspond to 16E% (range 12.5 to 24E%) and 5.8E% (range 2.6 to 7.6E%), respectively. The risk increased by 1.64 (95%CI = 1.13, 2.37) for each 10 g/day increase in sucrose intake at 3 years. Mean intake (SD) of sucrose in the whole sample at 3 years was 28.5 g/day (11.3). The relationship between sucrose intake at 3 years and new cavitied caries in primary dentition at 6 years was not significant when new caries was expressed as counts (dmft increment). The relationship between sucrose intake at 12 years and new cavitied caries in permanent dentition at 16 years was not significant in any analyses. Mean intake (SD) of sucrose in the whole sample at 12 years was 34.7 g/day (11.3). The Panel notes that the number of children with data available from 12 to 16 years was lower (n = 81 vs. n = 128). The study was at moderate RoB (tier 2), critical domains being confounding and exposure assessment.

10.2.2.3. SSBs and FJs

In the VA cohort of adult and older adult men (Kaye et al., 2015), a significant positive linear trend ($p < 0.05$) was observed across quartiles of SSBs intake (servings per week) for adjusted root caries increment (the dental outcome variable) during the 11-year follow-up including years at risk of root caries, baseline age, smoking status, number of teeth at risk for root caries, existing root caries or restorations, subgingival calculus, dental prophylaxis in past year and removable denture status as covariates. Median intakes of SSBs ranged from 0 mL/week in the lowest quartile to 1,407 mL/week in the highest. In this PC the relationship between SSBs intake and adjusted root caries increment appears to be linear and a level of intake at which the risk is not increased cannot be identified [mean (95%CI) = 2.86 (2.28, 3.60) and 2.17 (1.68, 2.79) for the highest vs. the lowest quartile of intake]. The study was at moderate RoB for SSBs (tier 2). Critical domains were confounding and attrition.

In the IFS (Chankanka et al., 2011), the relationship between the intake of SSBs and FJs over the study period and risk of cavitated, non-cavitated and dental caries between the ages of 5 and 9 years in the mixed dentition was assessed. No relationship between the intake of SSBs or FJs and risk of dental caries was observed after controlling for relevant confounders. Similar results were obtained when the analyses were restricted to children free of caries at 5 years. Mean intakes of SSBs and FJs were 271 mL/day (range 0–1,079 mL/day) and 87 mL/day (0–525 mL/day), respectively. The study was at moderate RoB (tier 2). Critical domains were exposure assessment and attrition. The Panel notes that intakes of sugar-containing beverages were high in this population group.

10.2.2.4. Dose-response relationships

Most PCs (Finnish cohort, UK cohort, Michigan cohort) suggest a positive linear dose-response relationship between the intake of total sugars and risk of dental caries in permanent dentition across a wide range of sugars intakes. However, the Panel notes that the shape of the dose-response relationship was rather assumed in the UK and Michigan cohorts, where non-linear relationships were not explored. Two of these PCs were at low RoB (tier 1) and adequately controlled for confounding factors, including frequency of sugars intake (Finnish cohort, Michigan cohort). In these two PCs, frequency of sugars intake was either not significantly associated with risk of dental caries (Michigan cohort) or was no longer associated with the risk of caries when the amount of sugars was accounted for (Finnish cohort).

Limited data (STRIP-2 study, RoB tier 2) indicate a positive linear dose-response relationship between the intake of sucrose (a proxy for added sugars) and dental caries in primary dentition across a wide range of intakes, whereas no relationship was observed between sucrose intake and dental caries for permanent dentition in the same study.

Limited data were also available for the relationship between the intake of dietary sugars and sugar-containing beverages (SSBs and FJs) and risk of dental caries in mixed dentition (STRIP-1, IFS cohort) and in the older adults (root caries, VA cohort). No significant relationship was observed in these studies between the intake of dietary sugars and caries risk.

The low number of PCs for all age groups and the heterogeneity in available data with respect to both the measures of intake of dietary sugars and the indices used to assess the risk of dental caries (incidence (yes/no) vs. severity (counts)) did not allow pooled analyses or meta-analysis to characterise dose-response relationships between the intake of dietary sugars and caries risk across the body of evidence.

10.3. Overall conclusions on hazard identification: dental caries

The Panel notes that the relationship between the intake of dietary sugars and the development of dental caries in humans is well established. Positive linear dose-response relationships have been observed between the intake of total sugars and risk of dental caries in permanent dentition (endpoint most relevant for adults and children older than 12 years) and between the intake of sucrose (a proxy for added sugars) and risk of dental caries in primary dentition (endpoint most relevant for children younger than 6 years of age) in individual PCs across a wide range of total sugars and sucrose intakes.

However, the Panel also notes that dose-response relationships across the BoE could not be explored with the data available, that dose-response relationships between the intake of total sugars and risk of dental caries in permanent dentition were assumed to be linear in two cohorts (UK and Michigan cohorts) but tested for non-linearity only in one (Finnish cohort) and that the available data for other population groups (primary dentition in children, root caries in the older adults) and exposures (added and free sugars including sucrose and their sources) are scarce. In this context, the Panel considers that, although it is well established that dietary sugars are involved in the development

of dental caries at all ages, the available BoE does not allow conclusions on the shape of the relationship between the intake of dietary sugars and risk of dental caries for any age group, or to identify a level of sugars intake at which the risk of dental caries is not increased.

10.4. Dental caries: data gaps and research needs

The low number of PCs for all age groups and the heterogeneity in available data with respect to both the measures of intake of dietary sugars and the indices used to report dental caries counts (severity) did not allow pooled analyses or meta-analysis to characterise dose-response relationships between the intake of dietary sugars and caries risk across the body of evidence. This problem is compounded by deficits in method of nutritional assessment (e.g. lack of validation of reported intakes, use of retrospective and semi-quantitative approaches) and failure to measure and/or account for (also in the statistical analysis) factors that probably confound the relationship between the intake of dietary sugars and the development of dental caries (including indices of socio-economic status, exposure to fluoride and measures of oral hygiene).

Therefore, the data gaps identified in the BoE regarding the relationship between dietary sugars and risk of dental caries lead to the following research needs:

a Prospective cohort studies that assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars) and the development of dental caries (both incidence and severity) in all age groups, including root caries in older adults, using validated methods of nutritional assessment and accounting for factors that may confound the association.

b Studies that measure the impact of interventions to reduce the amount of dietary sugars on the development of dental caries in all age groups.

11. Hazard characterisation: dose-response assessment and derivation of a Tolerable Upper Intake Level for sugars

The UL for (total/added/free) sugars is the maximum level of chronic daily intake of sugars from all sources judged to be unlikely to pose a risk of adverse health effects to humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. The UL is not a recommended level of intake (SCF SCoF, 2000). The underlying assumption is that a 'threshold' can be identified below which no risk from consumption of dietary sugars is expected for the general population, and above which the risk of adverse health effects, including risk of disease, increases.

If there are no, or insufficient, data on which to base a UL, an indication may be given on the highest level of chronic daily intake from all sources where there is reasonable confidence in data on the absence of adverse effects (i.e. a science-based cut-off value for a daily exposure which is not associated with adverse health effects, or a safe level of intake). This requires the identification of a level of sugars intake up to which no adverse health effects are observed.

11.1. Total sugars

The available BoE from PCs does not support a positive relationship between the intake of total sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases (Section 8.9.1) or pregnancy-related endpoints (Section 9.5) considered in this assessment.

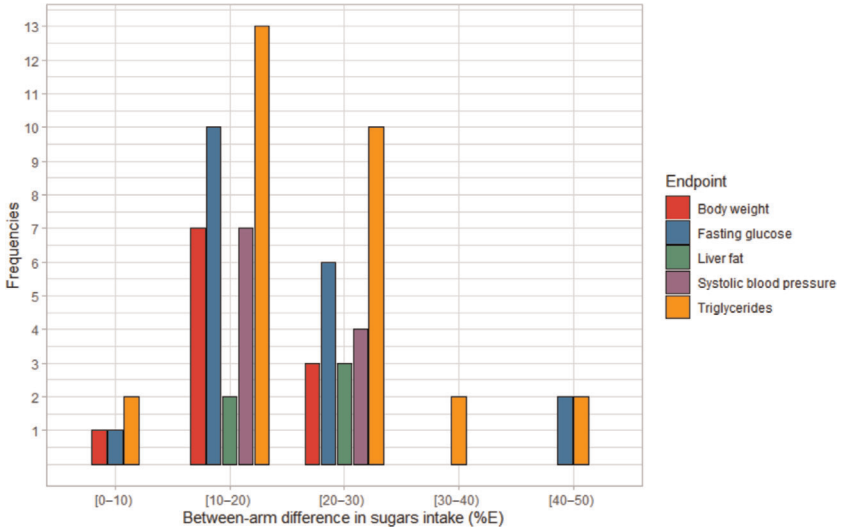
The relationship between the intake of dietary sugars and the development of dental caries in humans is well established. Positive and linear dose-response relationships between the intake of total sugars and risk of dental caries in permanent dentition have been reported in observational studies, with no evidence for non-linearity in the only cohort in which this hypothesis was tested (Finnish cohort, (Bernabé et al., 2016)). The data available, however, did not allow exploring dose-response relationships across the BoE, or to identify a level of total sugars intake at which the risk of dental caries is not increased (Section 10.3).

11.2. Added and free sugars

The available BoE from PCs does not support a positive relationship between the intake of added and free sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases (Section 8.9.2) or pregnancy-related endpoints (Section 9.5) considered in this assessment.

The level of certainty for a positive and causal relationship between the intake of added and free sugars and risk of chronic metabolic disease is considered to be moderate for obesity and dyslipidaemia (> 50–75% probability), low for NAFLD/NASH and T2DM (> 15–50% probability) and very low for hypertension (0–15% probability), based on data from RCTs which investigated the effect of 'high' vs. 'low' sugars intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and SBP (Section 8).

Figure 18 shows the distribution of RCTs addressing different endpoints by ranges of added or free sugars intake, corresponding to between-arm differences in intake. The Panel notes the limited number of measurements available for intakes of added and free sugars below 10 E% and above 30 E % for all endpoints investigated.



Legend to Figure 18. Since each randomised controlled trial (RCT) can investigate more than one endpoint, the total number of studies in the figure is higher than the number of RCTs included in the assessment.

Figure 18: Distribution of randomised controlled trials addressing different endpoints by ranges of added or free sugars intake, corresponding to between-arm differences in intake

Dose–response relationships between the intake of added and free sugars and the above-mentioned endpoints were characterised as part of the hazard identification step, where possible:

Body weight: Based on meta-regressive dose-response analysis, no dose–response relationship could be established between the intake of added and free sugars (dose range 6–24 E%) and body weight (Section 8.2.2). Dose-response was not investigated in individual studies (Section 8.2.2).

Liver fat: A dose–response relationship between the intake of added sugars and liver fat could not be established in the single study which tested it using three sugar doses (8, 18 and 30 E% in the respective study arms) (Lowndes et al., 2014b). The dose-response relationship between the intake of added and free sugars and liver fat could not be explored by meta-regression analysis owing to the limited number of RCTs available and the narrow range of sugars intakes investigated (between-arm difference range 18–22 E%) (Section 8.3.2).

Fasting glucose: A linear dose-response relationship was observed between the intake of sucrose (2, 15 and 30 E% in the respective study arms) in isocaloric exchange with starch and fasting glucose and insulin levels in the RCT by Israel et al. (1983) conducted in men and women with hyperinsulinaemia. Meta-regression analysis of the relationship between the intake of added and free sugars (between-arm difference range 8–28 E%) and fasting glucose concentrations across the BoE from RCTs identified a positive and linear dose-response (see Section 8.4.2.1 and **Annex L**).

Fasting triglycerides: A dose-response relationship between the intake of sucrose (2, 15 and 30 E% in the respective study arms) in isocaloric exchange with starch and fasting triglycerides was observed in the RCT by Israel et al. (1983) conducted in men with hyperinsulinaemia. A dose-response relationship between the intake of fructose (0, 7.5 and 15 E% in the respective study arms) in isocaloric exchange with starch and fasting triglycerides was also reported in the RCT by Hallfrisch et al. (1983a) conducted in men with hyperinsulinaemia. A meta-regressive dose-response relationship

across the BoE from RCTs was identified between the intake of added and free sugars (between-arm difference range 6–30 E%) and fasting triglycerides. The relationship was positive and linear, with no evidence for non-linearity. Most of the heterogeneity in the data set could not be explained. In this context, the Panel considers that no quantitative prediction of the effect of added (or free) sugars on fasting triglycerides can be made based on this model. The Panel notes that, for the same difference in added and free sugars intake, a higher absolute difference in fasting triglycerides was found in individuals with obesity, hypertriglyceridaemia or hyperinsulinaemia compared to other population subgroups (see Section 8.5.2.1 and **Annex L**).

Blood pressure: Dose-response was not investigated in individual RCTs. No meta-regression analysis could be performed owing to the small number of RCTs available. Visual inspection of the forest plots did not suggest a dose-response relationship (between-arm difference range 10–28E%) (Section 8.6.2).

Regarding the risk of dental caries, positive relationships with the intake of sucrose (a proxy for added sugars) have been reported in the STRIP cohort (STRIP-1; (Ruottinen et al., 2004); STRIP-2; (Karjalainen et al., 2001, 2015). A positive and linear dose-response relationship between the intake of added sugars and risk of dental caries in primary dentition was identified in the STRIP-2 cohort. The data available, however, did not allow exploring dose-response relationships across the BoE, or to identify a level of added sugars intake at which the risk of dental caries is not increased.

11.3. Conclusions on hazard characterisation

Overall, the Panel concludes that available data do not allow the setting of a UL or a safe level of intake for either total, added or free sugars. The Panel notes that the BoE considered in this opinion does not allow comparison of health effects based on the classification of dietary sugars as added or free (sections 8.1.1 and 8.1.2).

- The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. The data available, however, did not allow identifying a level of (total/added/free) sugars intake at which the risk of dental caries is not increased over the range of observed intakes.
- There is evidence from RCTs for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases, with levels of certainty ranging from moderate (50–75% probability) to very low (0–15% probability) depending on the disease. The data available, however, did not allow identifying a level of added/free sugars intake at which the risk of chronic metabolic disease is not increased over the range of observed intakes. The Panel notes that the relationship between the intake of added and free sugars and risk of chronic metabolic diseases could not be adequately explored at levels of intake $<$ 10 E% owing to the low number of RCTs available, and that the uncertainty about the shape and direction of the relationship at these levels of intake is higher than at intakes $\geq$ 10 E%.
- The available BoE from PCs does not support a positive relationship between the intake of dietary (total/added/free) sugars and any of the chronic metabolic diseases or pregnancy-related endpoints considered in this assessment. Dietary sugars were mostly assessed keeping TEI constant (i.e. in isocaloric exchange with other macronutrients).

Based on the available BoE and related uncertainties, the Panel considers that the intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. The Panel notes that decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent.

The information provided in this opinion can assist EU Member States in setting goals for populations and/or recommendations for individuals in their country, taking into account the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed (see Section 6). The Panel notes that the lowest amount of added/free sugars that is compatible with a nutritionally adequate diet in Europe may vary across population groups and countries.

12. Assistance to Member States when developing food-based dietary guidelines

Owing that the available data did not allow the setting of a UL or a safe level of intake for dietary sugars (total/added/free) from all sources, scientific advice is provided in relation to intakes of individual sugar types (e.g. fructose) and food sources of dietary sugars in order to assist Member States when developing FBDGs, as foreseen in the protocol.

12.1. Sugar types: fructose

The level of certainty for a positive and causal relationship between the intake of fructose and risk of chronic metabolic diseases is considered to be moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability), based on PCs. However, the external validity of the findings for European populations is unclear (see Section 8.9.3). In the eligible RCTs, the effects of fructose and glucose on body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure did not appear to be different, whereas fructose appeared to increase hepatic insulin resistance and uric acid levels more than equivalent amounts of glucose.

The Panel notes that fructose is a component of added and free sugars in mixed diets i.e. containing comparable amounts of fructose and glucose. The Panel considers that the conclusions for added and free sugars also apply to fructose in that context. In addition, the Panel notes that limiting the intake of added and free sugars in mixed diets would also limit the intake of fructose. This may not be the case if pure fructose or isoglucose with high fructose content (> 55%) are used to replace sucrose in foods and beverages (Section 4.2).

12.2. Sources of dietary sugars

12.2.1. Sugar-sweetened beverages

The level of certainty for a positive and causal relationship between the intake of SSBs and risk of chronic metabolic disease is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability), based on data from RCTs and PCs. When dose-response relationships between the intake of SSBs and incidence of disease (i.e. T2DM, hypertension and CVD) could be investigated using data from PCs, these were positive and linear, with no evidence for non-linearity. Whereas the relationship between the intake of SSBs and risk of obesity, NAFLD, T2DM, dyslipidaemia and gout could be attributed, at least in part, to the sugars fraction of the beverage, this is more questionable in relation to the risk of hypertension and CVD (see Section 8.9.4). In addition, the external validity of the findings in relation to the risk of gout for European populations is unclear. Based on data from PCs, there is low certainty (> 15–50% probability) that habitual consumption of SSBs by women of child-bearing age could increase the risk of GDM, and very low certainty (0–15% probability) that consumption of SSBs during pregnancy by women not developing GDM increases the risk of having infants SGA (Sections 9.3.2.2 and 9.4.2.2).

The proportion of consumers of SSBs (SSSD+SSFD) in Europe varied widely across population groups and countries, ranging from 0% to 97% of the dietary survey's sample. Intakes of added and free sugars from all sources were higher in consumers of SSBs than in consumers of any other non-core food group significantly contributing to sugars intake (fine bakery wares, confectionery, sugar and similar, fruit and vegetable juices) in virtually all countries and population groups (Section 4.3, **Annex E**).

In consumers, the mean contribution of added and free sugars in SSBs (SSSD+SSFD) to total energy intake ranged from 1 to 8 E%, depending on the survey. With few exceptions, the contribution of SSBs to the mean intake of added and free sugars ranged from 15% to about 50% (**Annex E**).

12.2.2. Fruit juices

The level of certainty for a positive and causal relationship between the intake of FJs and risk of chronic metabolic diseases is considered to be moderate for T2DM and gout (> 50–75% probability) and very low for obesity (0–15% probability), based on data from PCs. The dose-response relationship between the intake of FJs and incidence of T2DM was positive and linear, with no evidence for non-linearity. The external validity of the findings in relation to the risk of gout for European populations is

unclear. The Panel notes that the levels of intake of FJs are lower than for SSBs in prospective cohort studies and that the BoE on FJs is restricted to a lower number of studies compared to SSBs.

The proportion of consumers of fruit juices varied widely across population groups and countries, ranging from 15% to 96% of the sample. In toddlers, intakes of free sugars from all sources were higher in consumers of fruit juices than in consumers of any other non-core food group in most countries (Section 4.3, **Annex E**). In consumers, the mean contribution of free sugars in fruit juices to total energy intake ranged from 1 to 11 E% depending on the survey (**Annex E**). With few exceptions, the contribution of fruit juices to the mean intake of free sugars ranged from 15% to about 50%.

12.2.3. Other sources of dietary sugars

Data from PCs on other sources of dietary sugars were not extracted (Section 7.3.2). However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDGs.

In addition to SSBs and FJs, food groups contributing the most to the intake of added and free sugars in European countries were 'sugars and confectionery' (i.e. table sugar, honey, syrups, confectionery and water-based sweet desserts) and fine bakery wares, as well as sweetened 'milk and dairy' products in young consumers, with high variability among population groups and countries (Section 4.3, **Annex E**).

Conclusions

Based on the available scientific evidence and related uncertainties, the Panel concludes that:

Dietary sugars

- A UL or a safe level of intake for either total, added or free sugars could not be established.
- The health effects of added vs. free sugars could not be compared.
- The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. However, a level of (total/added/free) sugars intake at which the risk of dental caries is not increased over the range of observed intakes could not be identified.
- There is evidence for a positive and causal relationship between the intake of added and free sugars and risk of some chronic metabolic diseases. The level of certainty in the relationship is considered to be moderate for obesity and dyslipidaemia ($>$ 50–75% probability), low for NAFLD/NASH and T2DM ($>$ 15–50% probability) and very low for hypertension (0–15% probability), based on data from RCTs which investigated the effect of 'high' vs. 'low' sugars intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and SBP. However, a level of added/free sugars intake at which the risk of chronic metabolic disease is not increased over the range of observed intakes could not be identified.
- The relationship between the intake of added and free sugars and risk of chronic metabolic diseases could not be adequately explored at levels of intake $<$ 10 E% owing to the low number of RCTs available. The uncertainty about the shape and direction of the relationship at these levels of intake is higher than at intakes $\geq$ 10 E%.
- PCs do not support a positive relationship between the intake of dietary (total/added/free) sugars and chronic metabolic diseases or pregnancy-related endpoints. Dietary sugars were mostly assessed keeping TEI constant (i.e. in isocaloric exchange with other macronutrients).
- Excess energy intake leading to positive energy balance and body weight gain appears to be the main mechanism by which the intake of dietary sugars may contribute to the development of chronic metabolic diseases in free living conditions. Mechanisms which are specific to sugars as found in mixed diets (i.e. *de novo* lipogenesis leading to ectopic fat deposition, increased hepatic insulin resistance and impaired glucose tolerance in the long term; increase in uric acid levels) may also play a role, particularly in positive energy balance.
- The intake of added and free sugars should be as low as possible in the context of a nutritionally adequate diet. Decreasing the intake of added and free sugars would decrease the intake of total sugars to a similar extent.
- Food groups contributing most to the intake of added and free sugars in European countries were 'sugars and confectionery' (i.e. table sugar, honey, syrups, confectionery and water-based sweet desserts), followed by beverages (SSBs, fruit juices) and fine bakery wares, with high variability across countries. The main difference between the intake of added and free sugars

was accounted for by fruit juices. In infants, children and adolescents, sweetened 'milk and dairy' products were also major contributors to mean intakes of added and free sugars.
- The information provided in this opinion can assist EU Member States in setting goals for populations and/or recommendations for individuals in their country, taking into account the nutritional status, the actual composition of available foods and the known patterns of intake of foods and nutrients of the specific populations for which they are developed. The lowest amount of added/free sugars that is compatible with a nutritionally adequate diet in Europe may vary across population groups and countries.

Sugar types

- There is evidence for a positive and causal relationship between the intake of fructose and risk of some chronic metabolic diseases, based on data from PCs. The level of certainty in the relationship is considered to be moderate for gout (> 50–75% probability) and low for CVDs (> 15–50% probability), although the external validity of the findings for European populations is unclear. In the eligible RCTs, fructose appeared to increase hepatic insulin resistance and uric acid levels more than equivalent amounts of glucose. The effects of fructose and glucose on body weight, liver fat, measures of glucose tolerance, blood lipids and blood pressure did not appear to be different.
- Fructose is a component of added and free sugars in mixed diets i.e. containing comparable amounts of fructose and glucose. Therefore, the conclusions for added and free sugars also apply to fructose in that context. Limiting the intake of added and free sugars in mixed diets would also limit the intake of fructose. This may not be the case if pure fructose or isoglucose with high fructose content (> 55%) are used to replace sucrose in foods and beverages.

Sugars from specific sources

- There is evidence for a positive and causal relationship between the intake of SSBs and risk of some chronic metabolic diseases, based on data from RCTs and PCs. The level of certainty in the relationship is considered to be high for obesity, T2DM, HTN and CVD (> 75–100% probability), moderate for gout (> 50–75% probability) and low for NAFLD/NASH and dyslipidaemia (> 15–50% probability).
- There is also evidence for a positive and causal relationship between the intake of fruit juices and risk of some chronic metabolic diseases, based on data from PCs. The level of certainty in the relationship is considered to be moderate for T2DM and gout (> 50–75% probability) and very low for obesity (0–15% probability).
- The external validity of the findings in relation to the risk of gout for European populations is unclear.
- Based on data from PCs, there is low certainty (> 15–50% probability) that habitual consumption of SSBs by women of child-bearing age could increase the risk of GDM, and very low certainty (0–15% probability) that consumption of SSBs during pregnancy by women not developing GDM increases the risk of having infants SGA.
- In PCs, SSBs and FJs were mostly assessed not keeping TEI constant in the analysis, thus allowing for the possible contribution of energy to the associations.
- No conclusions could be drawn on specific sources of dietary sugars other than SSBs and FJs. However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDG.

Recommendations for research

Main data gaps and recommendations for research are addressed in Sections 8.10, 9.6 and 10.4 of this scientific opinion.

The Panel considers that the priorities for research in order to inform the setting of an UL for dietary sugars are as follows:

1) To develop and validate reliable methods and (bio)markers for the assessment of intake for dietary sugars.
2) To make individual data collected in human studies available for reanalyses and pooled analyses.

3) To improve the reporting of the methods and results of research studies by following international quality and transparency guidelines.[17]
4) To use standardised definitions for the characterisation of dietary sugars, their fractions (added and free sugars) and their sources (food groups in which they are contained).
5) To measure the impact of interventions to reduce the amount of added and free sugars from all sources (especially to below 10 E%) in controlled settings on the development of chronic metabolic diseases and surrogate endpoints thereof in all age groups. The impact of potential effect modifiers and the mechanisms involved should be further investigated.
6) To assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars), and the risk of developing GDM, and birthweight-related endpoints in women developing and not developing GDM.
7) To use reliable methods to measure possible mediators and confounders of the relationship between the intake of dietary sugars and the incidence of chronic metabolic diseases, in particular energy intake, body fatness, diet quality and physical activity.
8) To define appropriate data analysis strategies (i.e. choice of energy adjustment models, selection of covariates, testing of potential mediators) and formally evaluate and report the robustness of results (e.g. through sensitivity analysis).
9) To measure the impact of interventions in clinical and community settings to reduce the amount of dietary sugars (as E% and in g/day) on the development of dental caries in all age groups.
10) To assess the relationship between quantitative intakes of dietary sugars (characterised as the amount of total, added and free sugars) and the development of dental caries (both incidence and severity) in all age groups, including root caries in older adults, accounting for factors that may confound the association, in order to allow the characterisation of the hazard.

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Glossary, abbreviations and acronyms

100% FJs	100% fruit juices, with no added sugars
24-h DR	24-h dietary recall
24uSF	Urinary sucrose and fructose in 24-h urine samples
Added sugars	Mono- and disaccharides added to foods as ingredients during processing or preparation at home, and sugars eaten separately or added to foods at the table
AGAHLS	Amsterdam Growth and Health Longitudinal Study
AI	Adequate intake
AIC	Akaike Information Criteria
ALSPAC	Avon Longitudinal Study of Parents and Children
ALSWH	Australian Longitudinal Study on Women's Health
AMP	Adenosine monophosphate
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AOAC	Association of Official Analytical Chemists
ARIC	Atherosclerosis Risk in Communities Study
ASBs	Artificially sweetened beverages
ASSDs	Artificially sweetened drinks
ATP	Adenosine triphosphate
AUC	Area under the curve
BF	Body fat
BIA	Bioelectrical impedance analysis
BMES	Blue Mountain Eyes Study
BMI	Body mass index
BoE	Body of evidence
BP	Blood pressure
BW	Body weight
BWHS	Black Women's Health Study
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
CI	Confidence interval
CoSCIS	Copenhagen School Child Intervention Study
CTS	California Teachers Study
CVD	Cardiovascular disease
Daily-D	Daily-D Health Study
DBP	Diastolic blood pressure
DCH	Diet, Cancer and Health Study
DDHP	Detroit Dental Health Project
DFS	Decayed, filled surfaces
DMFS	Decayed, missing and filled tooth surfaces
DMFT	Decayed, missing and filled teeth
DNL	De novo lipogenesis
DONALD	Dortmund Nutritional and Anthropometric Longitudinally Designed Study
DRI	Dietary Reference Intake
DRV	Daily reference values
E%	Percent energy intake
EC	European Commission
EFSA	European Food Safety Authority
EKE	Expert Knowledge Elicitation
ELEMENT	Early Life Exposure in Mexico to Environmental Toxicants
EPIC-Diogenes	European Prospective Investigation into Cancer and Nutrition-Diet, Obesity and Genes project
EPIC-E3N	European Prospective Investigation into Cancer and Nutrition-French cohort

EPIC-InterAct	European Prospective Investigation into Cancer and Nutrition-InterAct project
EPIC-Morgen	European Prospective Investigation into Cancer and Nutrition-Morgen cohort
EPIC-Multicentre	European Prospective Investigation into Cancer and Nutrition-Multicentre
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition-Norfolk cohort
EPICOR	European Prospective Investigation into Cancer and Nutrition-Italian cohort
EPIC-Utrecht	European Prospective Investigation into Cancer and Nutrition-Utrecht cohort
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EU	European Union
FBDG	Food-based dietary guidelines
FCD	Food composition database
FFQ	Food frequency questionnaire
FJ	Fruit juice
FMCHES	Finnish Mobile Clinic Health Examination Survey
Framingham-3Gen	Framingham third Generation cohort
Framingham-Offspring	Framingham offspring's cohort
Free sugars	Added sugars plus sugars naturally present in honey, syrups, fruit juices and juice concentrates
GDM	Gestational diabetes mellitus
GeliS	Healthy living in pregnancy study
Generation R	Generation R Study
GI	Glycaemic index
GL	Glycaemic load
GLP1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
GUTS	Growing Up Today Study
GUTS II	Growing Up Today Study II
HBW	High birth weight
HDL	High-density lipoprotein
HFCS	High fructose corn syrup
HHS	U.S. Department of Health and Human Services
HOMA	Homeostatic model assessment
HPFS	Health Professionals Follow-up study
HPAEC-PAD	High Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection
HPLC	High Performance Liquid Chromatography
HPP	Harvard Pooling Project of Diet and Coronary Disease
HR	Hazard ratio
HSS-DK	Healthy Start Study-Denmark
HSS-USA	Healthy Start Study-USA
HTN	Hypertension
IFS	Iowa Fluoride Study
IGT	Impaired glucose tolerance
IL6	Interleukin 6
Inter99	Inter99 study
IoM	Institute of Medicine
IR	Insulin resistance
ISI	Insulin sensitivity index
IUGR	Intrauterine growth retardation
iv	Intravenous
IVGTT	Intravenous glucose tolerance test
IVITT	Intravenous insulin tolerance test
JPHC	Japan Public Health centre-based study Cohort
KoCAS	Korean Child–Adolescent cohort Study
KoGES	Korean Genome and Epidemiology Study
LBW	Low birth weight
LDL	Low-density lipoprotein
LF	Liver fat

LGA	Large-for-gestational age
Linking category	Categories established based on the distribution of total sugar values within each FoodEx2 level in order to match the total sugar content from the EFSA Nutrient Composition Database with the foods reported in the EFSA Comprehensive European Food Consumption Database
LoE	Line of Evidence
MDCS	Malmo Diet Cancer Study
MIT-GDS	Massachusetts Institute of Technology Growth and Development Study
MoBa	Norwegian Mother and Child Cohort Study
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MOVE	MOVE project
Mr and Ms OS	Mr and Ms OS of Hong Kong
MTC	Mexican Teachers' Cohort
Na^+/K^+ ATPase	Sodium–potassium adenosine triphosphatase
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PCC	Prospective case-cohort
NDA Panel	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NGHS	National Lung, Heart and Blood Institute's Growth and Health Study
NGT	Normal glucose tolerance
NHS	Nurses' Health Study
NHS-II	Nurses' Health Study-II
NIH-AARP	National Institutes of Health-American Association for Retired Persons Diet and Health Study
NK cells	Natural killer cells
NPAAS	Nutrition and Physical Activity Assessment Study
NSHDS	Northern Sweden Health and Disease Study
NTP	National Toxicology Program
OGTT	Oral glucose tolerance test
OHAT	Office of Health Assessment and Translation
OPEN	Observing Protein and Energy Nutrition
P/S	Polyunsaturated/Saturated fat
PCs	Prospective cohort studies
PHHP	Pawtucket Heart Health Program
PHI	Planet Health Intervention
ppm	parts per million
Project Viva	Project Viva
PROMETHEUS	PROmoting METHods for Evidence Use in Scientific assessments
PYY	Peptide YY
QUALITY	Quebec Adipose and Lifestyle InvesTigation in Youth
RCS	Restricted cubic splines
RCTs	Randomised controlled trials
REGARDS	Reasons for Geographic and Racial Differences in Stroke study
RI	Reference intake
RoB	Risk of bias
RR	Relative risk
SACN	Scientific Advisory Committee on Nutrition
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SCES	Sydney Childhood Eye Study
SCF	Scientific Committee on Food
SCHS	Singapore Chinese Health Study
SD	Standard deviation
SE	Standard error
SES	Social economic score
SFFQ	Semi-quantitative food frequency questionnaire
SGA	Small-for-gestational age

SGLT1	Sodium-Glucose-coTransporter 1
SLIVGTT	Stable labelled intravenous glucose tolerance test
sQ	Subquestion
SSBs	Sugar sweetened beverages
SSFDs	Sugar sweetened fruit drinks
SSFJs	Sugar sweetened fruit juices
SSSDs	Sugar sweetened soft drinks
STRIP	Special Turku Coronary Risk Factor Intervention Project
SUN	Seguimiento Universidad de Navarra
T2DM	Type 2 diabetes mellitus
Table sugar	Sucrose
TEI	Total energy intake
TFJ	Total fruit juice
TG	Triglyceride
TLGS	Teheran Lipid and Glucose Study
TNF-α	Tumour necrosis factor alpha
Total sugars	All mono- and disaccharides found in mixed diets i.e. glucose, fructose, sucrose, galactose, lactose, trehalose and maltose
TRL	Triglyceride rich lipoprotein
UA	Uncertainty analysis
UK	United Kingdom
UL	Tolerable Upper Level of Intake
US	United States
USDA	U.S. Department of Agriculture
VA-DLS	Department of Veterans Affairs-Dental Longitudinal Study
VAT	Visceral adipose tissue
VLDL	Very low-density lipoprotein
WAPCS	Western Australia Pregnancy Cohort (Raine) Study
WC	Waist circumference
WGHS	Women's Genome Health Study
WHI	Women's Health Initiative
WHO	World Health Organisation
WHS	Women's Health Study

Appendix A – Summary results_intake and percent contribution_whole population

Table A.1: Intake of total, free and added sugars across EU dietary surveys from selected food groups and percent contribution of the selected food groups to the intake of total, free and added sugars[18]

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)																		
Sugars and confectionery	0	10	0	31	0%	20%	0	10	0	31	1%	80%	0	10	0	31	1%	82%
SSSD+SSFD	0	2	0	12	0%	3%	0	2	0	12	0%	18%	0	2	0	12	0%	25%
Fine bakery wares	0	2	0	9	0%	4%	0	2	0	9	0%	34%	0	2	0	9	0%	36%
Fruit/veg. juices	0	5	0	30	0%	9%	0	5	0	30	2%	33%	0	2	0	7	0%	23%
Fruit/veg., processed	0	16	0	75	0%	20%	0	2	0	10	0%	16%	0	2	0	10	0%	19%
Fruit/veg., fresh	2	17	24	52	3%	28%	N/A						N/A					
Cereals	0	2	0	8	0%	3%	0	1	0	11	0%	14%	0	1	0	11	0%	16%
Milk and dairy	5	37	23	114	13%	60%	0	2	0	11	0%	47%	0	2	0	11	0%	50%
Baby foods	10	45	41	104	12%	65%	0	4	0	11	0%	52%	0	4	0	11	0%	52%
Others	0	2	0	11	0%	4%	0	1	0	8	0%	17%	0	1	0	2	0%	11%
TODDLERS (≥ 12 to < 36 months)																		
Sugars and confectionery	1	13	6	51	2%	19%	1	12	6	49	6%	54%	1	12	2	36	8%	61%
SSSD+SSFD	0	18	0	83	0%	19%	0	18	0	83	0%	37%	0	16	0	77	0%	42%
Fine bakery wares	0	7	1	37	0%	10%	0	7	1	34	1%	28%	0	7	1	34	1%	34%
Fruit/veg. juices	2	19	5	72	3%	19%	2	19	5	72	10%	36%	0	4	0	17	0%	20%
Fruit/veg., processed	1	9	2	52	1%	14%	0	4	0	19	0%	13%	0	4	0	19	1%	15%
Fruit/veg., fresh	6	21	33	94	9%	30%	N/A						N/A					

[18] Data extracted from Annex D-Results of the intake assessment. Whole population.

[19] *Sugars and confectionery* includes sugar and similar, confectionery and water-based sweet desserts; *SSSD+SSFD* are sugar sweetened soft drinks and sugar sweetened fruit drinks; *Fruit/veg. juices* include nectars; *Fruit/veg. processed* excludes beverages; *Cereals* include cereal-based products and exclude fine bakery wares; *Milk and dairy* also includes dairy alternate products; Baby foods are foods for infants and young children.

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Cereals	1	4	5	17	1%	6%	0	3	0	11	0%	14%	0	3	0	11	0%	20%
Milk and dairy	10	31	56	110	17%	37%	2	15	13	45	5%	32%	2	15	13	45	7%	48%
Baby foods	1	20	2	89	1%	32%	0	4	0	12	0%	13%	0	3	0	12	0%	15%
Others	0	3	2	11	1%	4%	0	2	0	9	0%	7%	0	0	0	3	0%	2%
OTHER CHILDREN (≥ 36 months to < 10 years)																		
Sugars and confectionery	4	28	20	105	6%	24%	4	26	18	101	12%	41%	3	26	14	86	14%	62%
SSSD+SSFD	1	29	1	115	2%	24%	1	29	1	115	3%	36%	1	27	1	108	5%	39%
Fine bakery wares	0	16	0	72	0%	16%	0	15	0	65	0%	26%	0	15	0	65	0%	33%
Fruit/veg. juices	4	23	15	99	6%	20%	4	23	15	99	9%	35%	0	4	0	17	0%	11%
Fruit/veg., processed	1	13	3	57	1%	13%	0	7	1	37	1%	13%	0	7	1	37	1%	16%
Fruit/veg., fresh	9	27	39	119	12%	26%	N/A						N/A					
Cereals	2	8	5	34	2%	12%	0	6	0	25	0%	19%	0	6	0	25	0%	25%
Milk and dairy	14	37	51	139	17%	40%	3	14	21	70	8%	30%	3	14	21	70	9%	33%
Others	1	5	3	20	1%	5%	0	1	0	5	0%	2%	0	1	0	5	0%	2%
ADOLESCENTS (≥ 10 to < 14 years)																		
Sugars and confectionery	6	30	24	110	7%	24%	6	29	22	106	12%	39%	4	28	13	100	13%	56%
SSSD+SSFD	3	37	22	176	3%	27%	3	37	22	176	6%	38%	3	35	21	166	7%	41%
Fine bakery wares	0	16	0	80	0%	16%	0	15	0	75	0%	25%	0	15	0	75	0%	32%
Fruit/veg. juices	6	23	26	104	5%	19%	6	23	26	104	8%	33%	0	5	0	20	0%	12%
Fruit/veg., processed	1	11	6	56	2%	11%	1	5	1	35	1%	9%	1	5	1	35	1%	11%
Fruit/veg., fresh	9	29	40	134	8%	26%	N/A						N/A					
Cereals	2	9	7	43	2%	12%	0	6	2	32	0%	16%	0	6	2	32	1%	23%
Milk and dairy	8	36	31	143	11%	32%	1	14	3	79	3%	18%	1	14	3	79	4%	26%
Alcoholic beverages	0	1	0	8	0%	2%	0	1	0	8	0%	3%	0	1	0	0	0%	1%
Others	1	4	2	17	1%	4%	0	1	1	5	0%	2%	0	1	1	5	1%	2%
ADOLESCENTS (≥ 14 to < 18 years)																		
Sugars and confectionery	6	28	25	105	6%	24%	6	26	23	102	11%	42%	5	26	23	97	12%	59%
SSSD+SSFD	4	36	28	188	4%	28%	4	36	28	188	6%	39%	3	35	27	181	7%	44%

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Fine bakery wares	0	14	0	70	0%	14%	0	13	0	64	0%	22%	0	13	0	64	0%	30%
Fruit/veg. juices	6	34	27	167	5%	27%	6	34	27	167	8%	38%	0	3	0	19	0%	10%
Fruit/veg., processed	2	9	7	45	2%	10%	0	5	1	26	1%	8%	0	5	1	26	1%	10%
Fruit/veg., fresh	9	27	39	136	9%	25%	N/A						N/A					
Cereals	2	9	7	46	2%	11%	0	6	2	32	1%	13%	0	6	2	32	1%	16%
Milk and dairy	9	34	34	131	11%	30%	1	12	1	69	4%	16%	1	12	1	69	4%	22%
Alcoholic beverages	0	2	0	11	0%	2%	0	1	0	8	0%	2%	0	1	0	4	0%	2%
Others	1	4	3	17	1%	4%	0	1	1	5	0%	2%	0	1	1	5	1%	3%
ADULTS (≥ 18 to < 65 years)																		
Sugars and confectionery	7	28	34	95	11%	29%	7	28	32	91	18%	52%	5	26	23	90	20%	57%
SSSD+SSFD	3	19	10	119	3%	18%	3	19	10	119	7%	30%	3	19	10	115	8%	34%
Fine bakery wares	1	14	7	64	1%	14%	1	13	5	63	2%	23%	1	13	5	63	2%	30%
Fruit/veg. juices	1	24	0	124	1%	20%	1	24	0	124	2%	31%	0	2	0	21	0%	5%
Fruit/veg., processed	1	9	4	49	2%	9%	0	6	0	28	1%	12%	0	6	0	28	1%	14%
Fruit/veg., fresh	14	30	63	132	14%	39%	N/A						N/A					
Cereals	2	7	10	31	3%	8%	0	3	0	16	1%	7%	0	3	0	16	1%	9%
Milk and dairy	7	28	29	125	10%	26%	1	10	4	57	3%	14%	1	10	4	57	4%	20%
Alcoholic beverages	1	7	5	31	1%	8%	0	3	1	15	1%	5%	0	1	0	8	0%	3%
Others	1	7	3	25	2%	7%	0	2	1	6	1%	3%	0	2	1	6	1%	4%
OLDER ADULTS (≥ 65 years)																		
Sugars and confectionery	6	26	27	92	8%	27%	6	26	27	90	15%	60%	3	25	13	73	10%	66%
SSSD+SSFD	1	7	0	38	1%	7%	1	7	0	20	2%	21%	1	6	0	20	2%	22%
Fine bakery wares	2	17	4	98	1%	21%	1	16	4	84	2%	36%	1	16	4	84	2%	45%
Fruit/veg. juices	0	14	0	73	0%	13%	0	14	0	73	1%	25%	0	1	5	25	0%	3%
Fruit/veg., processed	1	13	2	62	2%	14%	0	9	0	44	2%	21%	0	9	0	44	2%	26%
Fruit/veg., fresh	17	30	74	136	19%	44%	N/A						N/A					
Cereals	2	6	8	24	3%	8%	0	2	0	9	0%	6%	0	2	0	9	0%	7%
Milk and dairy	7	24	28	123	11%	24%	0	10	0	53	2%	17%	0	10	0	53	3%	22%

Food Groups[19]	Total sugars						Free sugars						Added sugars					
	g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]		g/day[(a)]				% contrib.[(a)]	
	Mean		P95		Mean		Mean		P95		Mean		Mean		P95		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Alcoholic beverages	1	6	3	23	1%	5%	0	3	0	15	0%	9%	0	1	0	7	0%	4%
Others	1	6	4	23	2%	8%	0	2	1	10	1%	4%	0	2	1	10	1%	5%
PREGNANT WOMEN																		
Sugars and confectionery	8	16	39	67	9%	16%	7	15	36	62	17%	29%	5	14	21	54	17%	31%
SSSD+SSFD	2	10	9	55	2%	11%	2	10	9	55	4%	24%	2	10	9	55	5%	32%
Fine bakery wares	7	11	32	61	9%	11%	7	10	31	57	17%	22%	6	10	31	57	22%	29%
Fruit/veg. juices	5	10	24	54	5%	11%	5	10	24	54	10%	23%	0	2	19	23	0%	5%
Fruit/veg., processed	2	8	7	23	2%	9%	1	5	6	18	2%	9%	1	5	6	18	2%	11%
Fruit/veg., fresh	17	25	89	108	22%	30%	N/A						N/A					
Cereals	3	9	10	39	3%	9%	0	5	3	25	1%	12%	0	5	3	25	2%	16%
Milk and dairy	14	29	53	133	16%	31%	3	10	19	63	9%	22%	3	10	19	63	12%	25%
Alcoholic beverages	0	0	0	0	0%	0%	0	0	0	0	0%	0%	0	0	0	3	0%	0%
Others	2	3	10	14	3%	4%	0	1	1	4	1%	2%	0	1	1	4	1%	2%
LACTATING WOMEN																		
Sugars and confectionery	15	26	54	97	15%	23%	14	25	53	92	28%	48%	7	22	29	77	27%	52%
SSSD+SSFD	2	2	10	11	2%	2%	2	2	10	11	4%	4%	2	2	10	11	5%	8%
Fine bakery wares	6	11	26	57	5%	12%	5	11	26	53	11%	21%	5	11	26	53	13%	39%
Fruit/veg. juices	7	17	26	66	6%	17%	7	17	26	66	13%	33%	0	1	17	18	1%	1%
Fruit/veg., processed	2	9	8	44	2%	8%	1	5	7	29	2%	10%	1	5	7	29	3%	12%
Fruit/veg., fresh	18	35	92	148	19%	31%	N/A						N/A					
Cereals	4	5	16	21	4%	5%	1	2	5	6	2%	4%	1	2	5	6	2%	7%
Milk and dairy	21	21	54	82	18%	22%	4	6	12	30	7%	12%	4	6	12	30	14%	14%
Alcoholic beverages	0	0	0	2	0%	0%	0	0	0	0	0%	0%	0	0	0	0	0%	0%
Others	3	4	8	12	2%	4%	0	1	0	2	0%	1%	0	1	0	2	1%	1%

Numbers in red indicate identical estimated intake values for added and free sugars.
(a): Minimum (min) and maximum (max) means and 95th percentiles across EU surveys, for each age class.

Appendix B – Summary results_intake and percent contribution_consumers

Table B.1: Intake of free sugars across EU dietary surveys from selected food groups in consumers and percent contribution of the selected food groups to the intake of free sugars

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)										
Fine bakery wares	0	52	0	5	2	13	3	23	1%	51%
Confectionery	0	27	0	10	3	8	5	30	3%	54%
Sugar and similar	1	93	1	13	6	33	6	26	6%	82%
SSSD+SSFD	0	26	1	35	7	7	11	38	3%	100%
Fruit/veg. juices	5	52	1	14	2	23	2	32	7%	53%
TODDLERS (≥ 12 to < 36 months)										
Fine bakery wares	26	97	1	8	3	18	15	63	4%	33%
Confectionery	14	92	1	12	3	24	19	64	5%	32%
Sugar and similar	6	99	2	13	7	31	18	60	5%	53%
SSSD+SSFD	2	80	2	22	10	63	18	71	7%	41%
Fruit/veg. juices	32	89	4	24	15	47	14	66	19%	48%
OTHER CHILDREN (≥ 36 months to < 10 years)										
Fine bakery wares	1	98	1	15	5	37	32	82	1%	28%
Confectionery	36	100	7	16	17	46	35	82	14%	22%
Sugar and similar	21	100	3	15	9	39	29	82	5%	29%

[20] Data extracted from Annex E. Results of the intake assessment. Consumers.

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
SSSD+SSFD	14	97	5	31	21	72	42	86	11%	38%
Fruit/veg. juices	39	96	8	26	23	67	31	87	13%	42%
ADOLESCENTS (≥ 10 to < 14 years)										
Fine bakery wares	3	96	0	16	5	61	32	106	0%	30%
Confectionery	35	97	7	20	18	60	39	99	14%	31%
Sugar and similar	27	98	5	17	14	47	31	98	6%	28%
SSSD+SSFD	23	93	10	39	27	101	44	99	19%	47%
Fruit/veg. juices	30	93	13	26	36	71	37	105	15%	47%
ADOLESCENTS (≥ 14 to < 18 years)										
Fine bakery wares	0	88	2	19	24	54	34	101	2%	30%
Confectionery	27	94	8	21	20	59	49	111	12%	34%
Sugar and similar	32	97	6	19	21	53	34	100	9%	33%
SSSD+SSFD	20	90	12	41	40	118	46	109	16%	48%
Fruit/veg. juices	25	93	11	55	35	146	44	111	15%	49%
ADULTS (≥ 18 to < 65 years)										
Fine bakery wares	28	84	2	20	5	53	34	84	3%	31%
Confectionery	13	91	5	17	15	57	39	92	10%	30%
Sugar and similar	25	97	8	27	25	60	30	85	13%	51%
SSSD+SSFD	16	88	9	40	30	123	30	109	24%	47%
Fruit/veg. juices	15	81	1	45	5	134	30	97	3%	46%
OLDER ADULTS (≥ 65 years)										
Fine bakery wares	34	90	2	21	5	66	23	62	3%	43%
Confectionery	9	86	4	12	13	33	31	67	8%	32%
Sugar and similar	36	99	8	24	22	55	20	62	16%	59%

Free sugars										
Food groups[20]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources[(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
SSSD+SSFD	6	89	5	25	18	71	24	79	18%	48%
Fruit/veg. juices	24	78	0	30	13	94	20	71	2%	42%
PREGNANT WOMEN										
Fine bakery wares	59	76	9	15	23	43	39	55	20%	32%
Confectionery	24	39	8	18	27	46	46	62	16%	30%
Sugar and similar	33	76	7	11	23	31	38	53	15%	23%
SSSD+SSFD	15	40	13	30	33	85	42	64	22%	46%
Fruit/veg. juices	37	70	8	17	28	53	36	58	22%	35%
LACTATING WOMEN										
Fine bakery wares	55	86	10	12	27	27	52	59	17%	24%
Confectionery	46	54	7	13	35	35	55	60	12%	22%
Sugar and similar	74	93	15	19	49	49	54	56	27%	36%
SSSD+SSFD	16	37	6	13	42	42	50	69	12%	19%
Fruit/veg. juices	46	86	15	19	46	46	51	63	23%	37%

Confectionery includes water-based desserts; SSSD+SSFD are sugar sweetened soft drinks and sugar sweetened fruit drinks.
(a): Minimum (min) and maximum (max) means (and 95th percentiles when calculated) across EU surveys, for each age class.

Table B.2: Intake of added sugars across EU dietary surveys from selected food groups in consumers and percent contribution of the selected food groups to the intake of free sugars

Food groups[21]	Added sugars									
	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
INFANTS (≥ 4 to < 12 months)										
Fine bakery wares	0	52	0	5	2	13	3	19	1%	53%
Confectionery	0	27	0	10	3	8	5	27	3%	54%
Sugar and similar	1	93	1	13	5	33	2	22	6%	82%
SSSD+SSFD	0	26	1	31	6	6	10	31	4%	100%
Fruit/veg. juices	5	52	0	8	0	7	2	25	0%	32%
TODDLERS (≥ 12 to < 36 months)										
Fine bakery wares	26	97	1	8	3	18	11	43	5%	41%
Confectionery	14	92	1	12	3	24	17	47	6%	36%
Sugar and similar	6	99	0	12	3	29	11	40	3%	61%
SSSD+SSFD	2	80	2	21	9	59	16	62	8%	46%
Fruit/veg. juices	32	89	0	8	0	18	9	41	0%	32%
OTHER CHILDREN (≥ 36 months to < 10 years)										
Fine bakery wares	1	98	1	15	5	37	25	71	3%	37%
Confectionery	36	100	7	16	17	46	27	72	17%	29%
Sugar and similar	21	100	1	13	5	37	20	70	3%	38%
SSSD+SSFD	14	97	5	29	20	67	32	73	14%	41%
Fruit/veg. juices	39	96	0	10	0	21	23	68	0%	16%

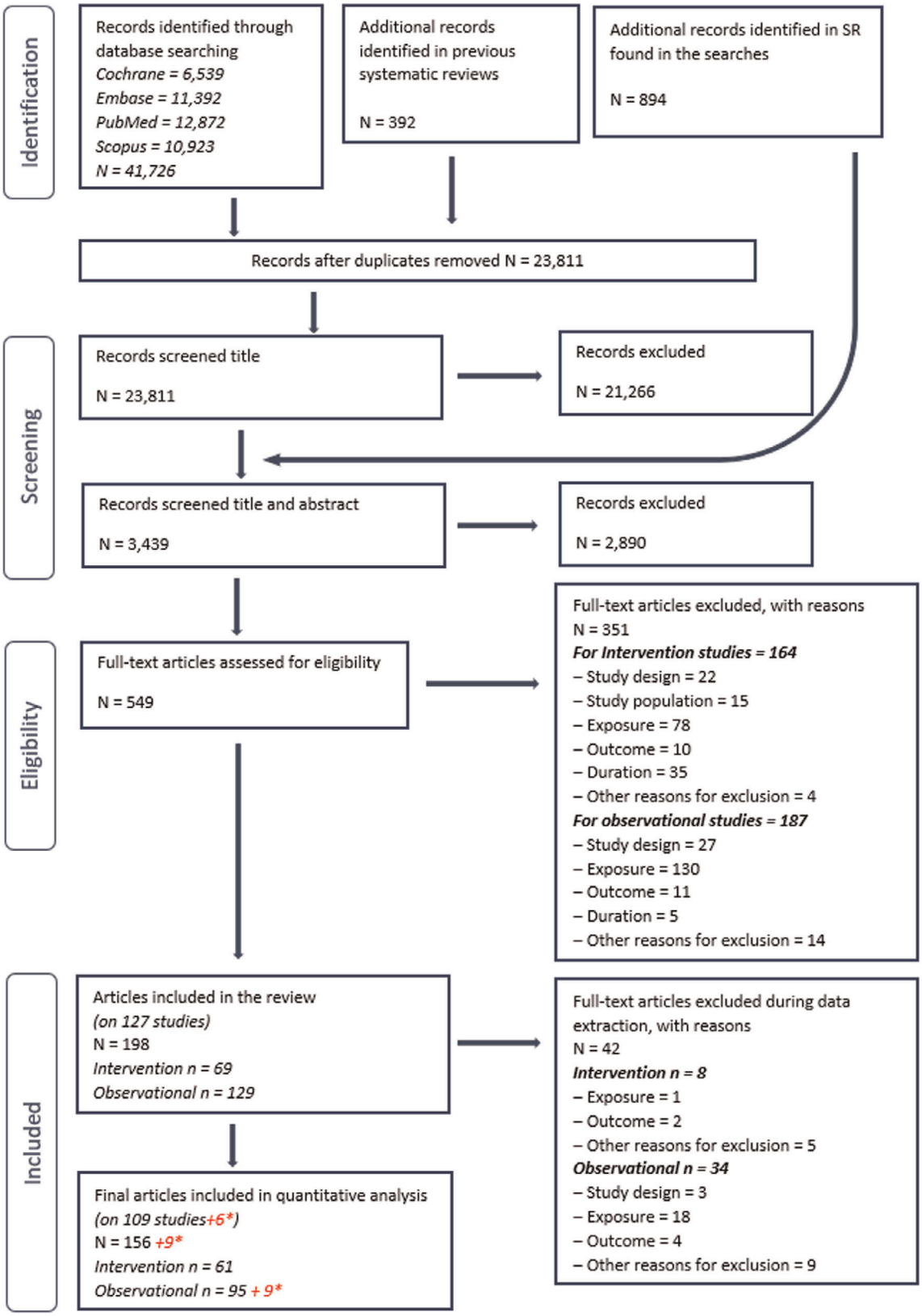
[21] Data extracted from Annex E. Results of the intake assessment. Consumers.

Added sugars										
Food groups[21]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
ADOLESCENTS (≥ 10 to < 14 years)										
Fine bakery wares	3	96	0	16	5	61	26	87	1%	36%
Confectionery	35	97	7	20	18	60	34	89	16%	38%
Sugar and similar	27	98	1	16	13	47	22	85	3%	31%
SSSD+SSFD	23	93	10	37	26	97	37	88	21%	56%
Fruit/veg. juices	30	93	0	10	0	25	25	83	0%	26%
ADOLESCENTS (≥ 14 to < 18 years)										
Fine bakery wares	0	88	2	19	24	54	29	83	3%	38%
Confectionery	27	94	8	21	20	59	39	89	14%	39%
Sugar and similar	32	97	3	18	12	53	28	88	7%	37%
SSSD+SSFD	20	90	12	40	40	118	41	88	24%	59%
Fruit/veg. juices	25	93	0	12	0	26	33	81	0%	21%
ADULTS (≥ 18 to < 65 years)										
Fine bakery wares	28	84	2	20	5	53	27	61	3%	39%
Confectionery	13	91	5	17	15	57	33	71	11%	36%
Sugar and similar	25	97	4	25	19	59	23	62	9%	55%
SSSD+SSFD	16	88	9	40	29	123	28	83	26%	51%
Fruit/veg. juices	15	81	0	10	0	23	21	58	0%	17%
OLDER ADULTS (≥ 65 years)										
Fine bakery wares	34	90	2	21	5	66	19	48	4%	52%
Confectionery	9	86	4	12	13	33	25	54	9%	39%
Sugar and similar	36	99	2	22	15	53	15	47	7%	65%
SSSD+SSFD	6	89	5	25	18	71	22	64	20%	53%
Fruit/veg. juices	24	78	0	2	0	12	15	49	0%	9%

Added sugars										
Food groups[21]	Percentage of consumers of the food group in the surveys		Consumers							
			From food group[(a)] (g/day)				From all sources [(a)] (g/day)		% contrib.[(a)]	
			Mean		P95		Mean		Mean	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
PREGNANT WOMEN										
Fine bakery wares	59	76	9	15	23	43	31	49	26%	40%
Confectionery	24	39	8	18	27	46	36	56	17%	34%
Sugar and similar	33	76	2	9	7	30	27	47	5%	25%
SSSD+SSFD	15	40	13	30	33	85	33	57	24%	55%
Fruit/veg. juices	37	70	0	4	0	13	26	42	0%	11%
LACTATING WOMEN										
Fine bakery wares	55	86	10	12	27	27	29	49	20%	42%
Confectionery	46	54	7	13	35	35	33	51	20%	26%
Sugar and similar	74	93	6	16	48	48	30	44	20%	37%
SSSD+SSFD	16	37	6	13	42	42	32	61	18%	22%
Fruit/veg. juices	46	86	0	1	8	8	26	47	1%	2%

Confectionery includes water-based desserts; *SSSD+SSFD* are sugar sweetened soft drinks and sugar sweetened fruit drinks.
(a): Minimum (min) and maximum (max) means (and 95th percentiles when calculated) across EU surveys, for each age class.

Appendix C – Flow chart for the selection of human studies



*: Articles identified through the update of the literature search that were incorporated into the assessment (see Annex A).

Figure C.1: Flow chart for the selection of studies on metabolic diseases

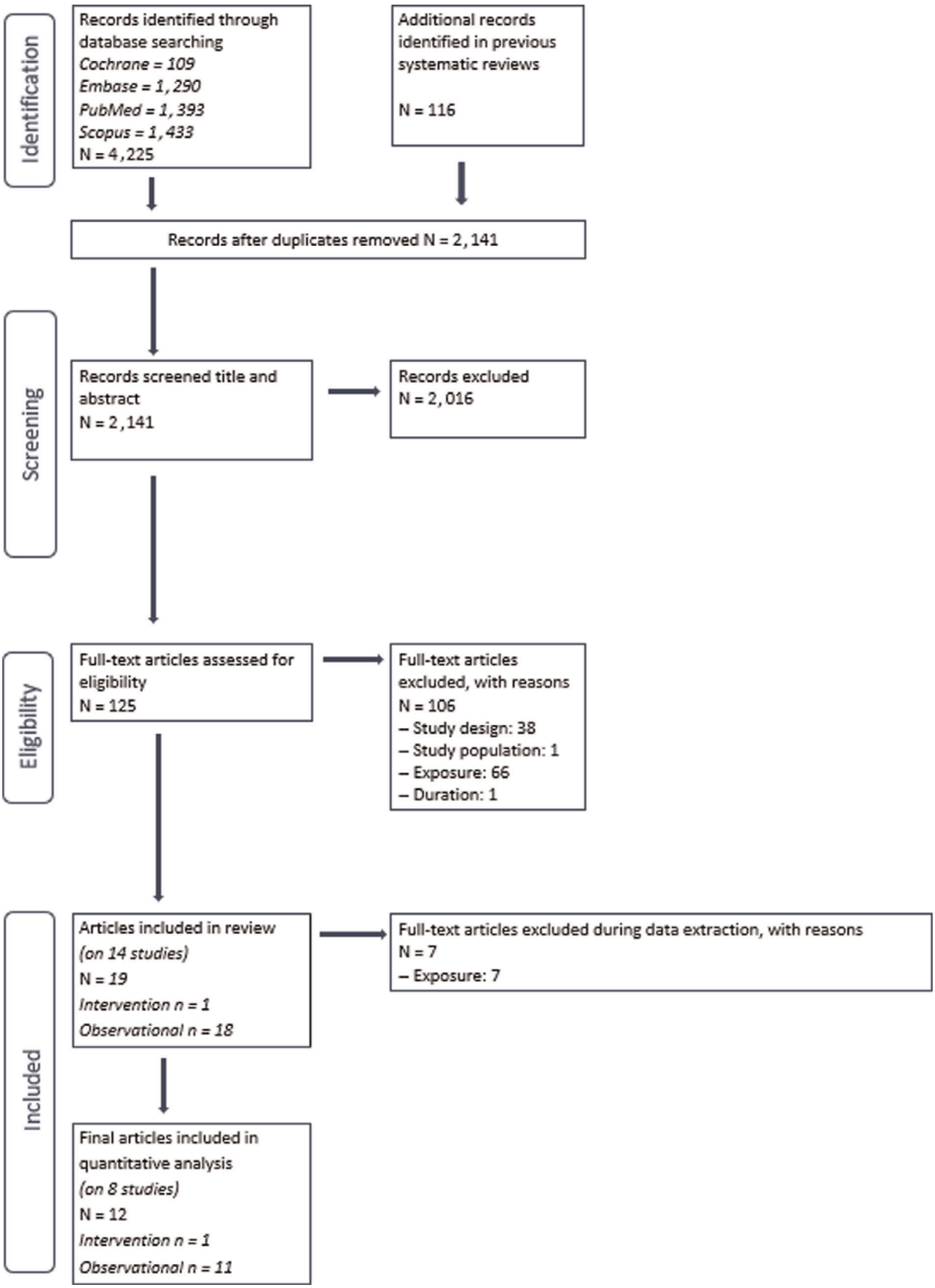


Figure C.2: Flow chart for the selection of studies on caries

Appendix D – Intervention studies on metabolic diseases reported in multiple references

Several randomised controlled trials that were eligible for this assessment were reported in multiple references. To facilitate the identification of the individual studies when reporting the results in forest plots, a main reference was identified for each of them. In some cases, data on different endpoints were extracted from linked references, and not from the main reference indicated in the forest plots or the text. In other cases, linked references did not provide additional data for this assessment with respect to the main reference and were excluded at data extraction (e.g. report on reanalysis of data already presented in the main reference or other linked references). Main references for studies with data extracted from linked references appear in forest plots with an asterisk (e.g. Angelopoulos et al., 2015*).

Main reference and endpoints extracted	Linked references and endpoints extracted	Linked references excluded at data extraction
Angelopoulos et al. (2015)* Uric acid, SBP, DBP	Angelopoulos et al. (2016) Triglycerides, total cholesterol, HDL-c, LDL-c, fasting glucose, body weight, BMI, WC	
Hallfrisch et al. (1983a)* Glucose at 120′ during an OGTT, insulin at 120′ during an OGTT, fasting insulin, fasting glucose	Hallfrisch et al. (1983b) Triglycerides, total cholesterol, HDL-c, LDL-c, SBP, DBP	
Israel et al. (1983)* Uric acid, SBP, DBP	Reiser et al. (1981a) Triglycerides, total cholesterol, HDL-c, LDL-c	
	Reiser et al. (1981b) fasting glucose, fasting insulin, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT	
Ebbeling et al. (2012) Body weight, BMI		Ebbeling et al. (2006)
Ruyter et al. (2014) Body weight, WC		Katan et al. (2016)
Lowndes et al. (2014b)* WC, BF, fasting glucose, SBP, DBP, total cholesterol, triglycerides, HDL-c, LDL-c, uric acid	Bravo et al. (2013) Liver fat	Yu et al. (2013)
Maersk et al. (2012)* VAT, Liver fat	Engel et al. (2018) Body weight, BF, triglycerides, total-c, HDL-c, LDL-c, fasting insulin, fasting glucose, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT, Matsuda index, SBP, DBP	
	Bruun et al. (2015) Uric acid	
Raben et al. (2002)* Body weight, BMI, BF, SBP, DBP,	Raben et al. (2011) Triglycerides, total cholesterol, HDL-c, fasting glucose, fasting insulin, HOMA-IR, HOMA-β	

Main reference and endpoints extracted	Linked references and endpoints extracted	Linked references excluded at data extraction
Reiser et al. (1979a)* Total cholesterol, triglycerides	Reiser et al. (1979b) Glucose at 120′ during an OGTT, insulin at 120′ during an OGTT	
	Solyst et al. (1980) Uric acid	
Reiser et al. (1989a) Triglycerides, total cholesterol, HDL-c, LDL-c, uric acid		Reiser et al. (1989b)
Saris et al. (2000) Body weight, fasting glucose, fasting insulin, triglycerides, total cholesterol, HDL-c, LDL-c		Poppitt et al. (2002)
Stanhope et al. (2009)* WC, VAT, SBP, DBP, triglycerides, total cholesterol, HDL-c, LDL-c, fasting glucose, fasting insulin, glucose at 120′ during an OGTT, insulin at 120′ during an OGTT		Stanhope et al. (2011)
	Cox et al. (2012) Uric acid	
	Rezvani et al. (2013) Body weight, BF	

BF, body fat; BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model of assessment; IR, insulin resistance; LDL-c, low density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; VAT, visceral adipose tissue; WC, waist circumference.

Appendix E – Main characteristics of intervention studies on metabolic diseases

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Isocaloric with neutral energy balance[5]														
Bantle et al. (2000)	US	Public	CX, 6	Fructose Glucose	14 14	24/12 F BMI ≤ 32 kg/m^2	Range: 18–80 12/6F[3] 40 12/6F < 40	CHO: 55 Protein: 15 Fat: 30 Fibre: 23 P/S: 0.947	Mixed diet	BL	–	I:14 Fr R:14 G	–	–
Black et al. (2006)	UK	Private	CX, 6	Sucrose Sucrose	10 25	13 M BMI < 35 kg/m^2	33.3 ± 3	CHO: 55 Protein: 12 Fat: 33 Fibre: 18	Mixed diet	GH, BP, BL	I: 25 R: 10	–	–	–
Despland et al. (2017)	CH	Public	CX, 8d	Starch Honey Glucose/ Fructose	0 25 25	8 M GP	NR	CHO: 55 Protein: 15 Fat: 30	Mixed diet	GH	I: 25 Gl/Fr R:0	–	–	–
Gostner et al. (2005)	DE	NR	CX, 4	Isomalt Sucrose (30 g/ day)	0 6	19 /12F GP	Median: 30.5	CHO: 46 Protein: 14 Fat: 40 Fibre: 14	Foods	GH, BL	I:6 R:0	–	–	–
Groen et al. (1966)	US	Mixed	CX, 5	Starch Sucrose (140 g/ day)	0 30	8/6F 7/4F GP	40.2 ± 3.16	*Starch/sucrose* CHO: 62.1/66.4 Protein: 18.4/14.6 Fat: 19.3/18.9		BL	I:30 R:0	–	–	–
Hallfrisch et al. (1983a)*	US	NR	CX, 5	Starch Fructose Fructose	0 7.5 15	12 M N-I 12 M H-I	39.8 ± 2.4 39.5 ± 2.1	CHO: 45 Protein: 15 Fat: 40 Fibre: 5 P/S: 0.4	Foods	GH, BP, BL	I:15 R:0	–	–	–
Israel et al. (1983)*	US	NR	CX, 6	Sucrose Sucrose Sucrose	2 15 30	24/12F H-I	Mean: 36.8 Range: 21–51	CHO: 44 Protein: 14 Fat: 42 Fibre: 4 P/S: 0.29	Foods	GH, BP, BL, UA	I:30 R:2	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Johnston et al. (2013)	US	Mixed	P, 2	Fructose Glucose	25 25	32 M, AO	35 ± 11 33 ± 9	CHO: 55 Protein: 15 Fat: 30	Beverages	EFD, GH, BL, UA	–	I:25 Fr R:25 Gl	–	–
Kelsay et al. (1974)	US	NR	CX, 4	Glucose Sucrose	42.5 42.5	7F GP	Range: 18–23	CHO: 50 Protein: 12 Fat: 38 P/S: 0.23	Foods	GH	–	–	–	–
Koh et al. (1988)	US	NR	CX, 4	Fructose Glucose	15 15	9/6F NGT 9/6F IGT	50 ± 5 54.6 ± 6	CHO: 51 Protein: 17 Fat: 32 Fibre: 22.5 P/S: 0.9	Mixed diet	GH, BP, BL	–	I:15 Fr R:15 Gl	–	–
Lewis et al. (2013)	IE	Private	CX, 6	Sucrose Sucrose	5 15	13/4F, OW/OB	46.1 ± 1.9	*5E% / 15 E%:* CHO: 54.8/55 Protein: 12.3 /12.1 Fat: 32.9/32.8 Fibre: 18.3/17.9 P/S: 0.35/0.31	Mixed diet	GH, BP, BL	I:15 R:5	–	–	–
Lowndes et al. (2014a)	US	Private	P, 10	Sucrose HFCS Sucrose HFCS	10 10 20 20	18/6F 17/8F 13/ 8F 17/9F OW/OB	39.82 ± 11.6 39.33 ± 10.94 41.15 ± 12.24 36.48 ± 12.5	NR	Beverages	BF, BP, BL	I:20 Suc R:10 Suc	–		–
Lowndes et al. (2014b)*	US	Private	P, 10	Sucrose HFCS Sucrose HFCS Sucrose HFCS	8 8 18 18 30 30	58/26F 69/42F 64/38F 60/30F 53/26F 51/28F BMI < 35	38.62 ± 12.33 38.93 ± 11.65 41.3 ± 11.1 40.43 ± 11.33 38.85 ± 11.56 43.41 ± 11.33	NR	Beverages	BF, EFD, GH, BP, BL, UA	I: 30 Suc R: 8 Suc	–		–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Lowndes et al. (2015)	US	Private	P, 10	Control milk Fructose Glucose Sucrose HFCS	0 9 9 18 18	31/21F 30/14F 34/17F 33/18F 31/21F BMI < 35	35.3 ± 12.5 35.6 ± 10.4 37 ± 11.7 34.1 ± 11 36.5 ± 11.3	NR	Beverages	GH	I: 18 Suc R: 0	I:9 Fr R:9 Gl		
Moser et al. (1986)	US	NR	CX, 4	Starch Sucrose	0 43	6F non-OC users 6F OC users	Range: 19–25	CHO: 51 Protein: 13 Fat: 36	Foods	GH, BL	I:43 R:0	–	–	–
Reiser et al. (1979a)*	US	NR	CX, 6	Starch Sucrose	0 30	19/9F GP	Mean: 42 Range: 35–55	CHO: 43 Protein: 15 Fat: 42 Fibre: 4.2 P/S: 0.26	Foods	GH, BL, UA	I:30 R:0	–	–	–
Reiser et al. (1989a)*	US	NR	CX, 5	Starch Fructose	0 20	11 M N-I 10 M H-I	Mean: 38 Range: 23–64 Mean: 47 Range: 23–64	*Starch / fructose:* CHO: 51 / 51 Protein: 13 / 13 Fat: 36 / 36 Fibre: 12.1 / 11 P/S: 0.33 / 0.33	Foods	BL, UA	I:20 R:0	–	–	–
Schwarz et al. (2015)	US	Public	CX, 9d	Starch Fructose	0 20	8 M Non-OB	42 ± 3	*Starch / fructose:* CHO: 50 / 50 Protein: 15 / 15 Fat: 35 / 35 Fibre: 28 / 17	Beverages	GH	I:20 R:0	–	–	–
Sunehag et al. (2008)	US	Mixed	CX, 1	Fructose Fructose	6 24	6/3F OB	15.2 ± 0.5	CHO: 60 E% Protein: 15 E% Fat: 25 E%	Mixed diet	GH	I:24 Fru R:6 Fru	–	–	–
Swanson et al. (1992)	US	Mixed	CX, 4	Starch Fructose	0 16.6	14/7F GP	Mean: 34 Range: 19–60	*Starch / fructose:* CHO: 55 / 55 Protein: 15 / 15 Fat: 30 /30 Fibre: 27 /26 P/S: 1 / 1	Mixed diet	GH, BL	I:16.6 R:0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Szanto and Yudkin (1969)	UK	Public	CX,2	Starch Sucrose (438 g/day)	0 54	19 M GP	Mean: 28 Range: 22–44	NR	Mixed diet	GH	I:54 R:0	–	–	–
Thompson et al. (1978)	US	Mixed	CX, 10d	Corn syrup Sucrose Corn syrup Sucrose	45 45 65 65	8 M GP	Range: 19–24	*45E% / 65E%:* CHO: 45 / 65 Protein: 15 /15 Fat: 40 / 20 P/S: 0.7 /0.7	Beverages	GH	I:65 Suc R:45 Suc	–	–	–
Umpleby et al. (2017)	UK	Public	CX, 12	NMES NMES	6 26	14 M OW/no NAFLD 11 M OW/NAFLD	Mean: 54 Range: 41–65 Mean: 59 Range: 49–64	NR	Mixed diet	EFD, GH, BL	I:6 R:26	–	–	–
Isocaloric with positive energy balance[6]														
Beck-Nielsen et al. (1978)	DK	Mixed	P, 2	Fat (250 g/day) Sucrose (250 g/day)	0 32	6 NR 6 NR GP	Range: 23–33	NR	Mixed diet	GH	I:32 R:0	–	–	–
Beck-Nielsen et al. (1980)	DK	NR	P, 1	Fructose (250 g/day) Glucose (250 g/day)	33 33	8NR 7NR GP	Range: 21–35	CHO: 44 Protein: 18 Fat: 35	Beverages	GH	–	I:36 Fr R:36 Gl	–	–
Johnston et al. (2013)	UK	Private	P, 2	Fructose Glucose	25 25	32 M, AO	35 ± 11 33 ± 9	NR	Beverages	EFD, GH	–	I:25 Fr R:25 Gl	–	–
Silbernagel et al. (2011)	DE	Mixed	P, 4	Fructose (150 g/day) Glucose (150 g/day)	22 22	10/3F 10/5F BMI < 35	30.5 ± 2	CHO: 50 Protein: 15 Fat: 35	Beverages	EFD, GH, BP, BL, UA	–	I:22 Fr R:22 Gl	–	–
Hypercaloric [7]														
Le et al. (2009)	US	NR	CX, 1	No sugars Fructose	0 35	8 M non-OffT2DM 16 M OffT2DM	24.0 ± 1.0 24.7 ± 1.3	CHO: 55 Protein: 15 Fat: 30	Beverages	GH	I:35 R:0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Ad libitum														
Aeberli et al. (2013)	CH	Mixed	CX, 3	Fructose (40 g/day) Fructose (80 g/day) Glucose (80 g/day) Sucrose (80 g/day)	8 16 16 16	9 M NW	22.8 ± 1.7	No target	Beverages	GH	I:16 Fr R:8 Fr	I:16 Fr R:16 Gl	–	–
Angelopoulos et al. (2015)*	US	NR	P, 10	Fructose Glucose Sucrose HFCS	9 9 18 18	65NR 77NR 64NR 61NR BMI < 35 kg/m^2	38.65 ± 12.19 36.1 ± 12.06 39.83 ± 12.19 36.32 ± 10.72	No target	Beverages	BF, GH, BP, BL, UA	–	I:9 Fr R:9 Gl	–	–
Campos et al. (2015)	CH	Mixed	P, 12	ASSD SSSD	0 18	14/6F 13/7F OW/OB	NR	No target	Beverages	BF, EFD, GH, BP, BL, UA	I: 18 R: 0	–	–	–
Ruyter et al. (2014)	NL	Public	P, 72	ASSD SSSD (26 g/day)	0 5	319/147F 322/151F GP	8.2 ± 1.8 8.2 ± 1.8	No target	Beverages	BF	I: 5 R: 0	–	–	–
Ebbeling et al. (2012)	US	Public	P, 52	ASSD+water SSSD+SSFD+TFJ	0 17	110/48F 114/52F OW/OB	15.3 ± 0.7 15.2 ± 0.7	No target	Beverages	BF	I: 17 R: 0	–	–	–
Hayashi et al. (2014)	JP	Public	P, 12	HFCS (28 g/day; 26 g sugar) RSS (30 g/day; 23 g sugar)	– –	17/8F 17/9F OB	42.4 ± 2.6 41.7 ± 2.8	No target	Beverages	BF, GH, BP, BL, UA	–	–	–	–
Hernandez-Cordero et al. (2014)	MX	Private	P, 36	Water SSBs	0 20	120F 120F OW/OB	33.5 ± 6.7 33.3 ± 6.7	No target	Beverages	BF, GH, BP, BL	I: 20 R: 0	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms[1]	Sugars dose (E%)[2]	Participants	Age, years (mean ± SEM)	Background diet[3]	Food form	Outcome clusters[4]	Q1	Q2	Q3	Q4
Hollis et al. (2009)	US	Private	P, 12	No beverage Grape juice (82 g/day) Grape drink (82 g/day)	0 18 18	25NR 25NR 26NR OW	28 ± 10 22 ± 4 26 ± 9	No target	Beverages	BF, GH, BL	I: 18 GD R: 0	–	–	–
Houchins et al. (2012)	US	NR	CX, 8	Fruits/ vegetables (20E %) Fruit Juice (20E %)	– –	34NR GP	23 ± 1	No target	Beverages	BF	–	–	–	–
Huttunen et al. (1976)	FI	NR	P, 72	Xylitol Fructose (70 g/ day) Sucrose (73.5 g/ day)	0 14 16	48NR 35NR 33NR GP	Range: 13–55	No target	Mixed diet	GH, BL, UA	I: 16 Suc R: 0	I: 15 Fr R:15 Gl	–	–
Jin et al. (2014)	US	Mixed	P, 4	Fructose (99 g/ day) Glucose (99 g/ day)	20 20	9/6F 12/4F NAFLD	14.2 ± 0.88* 13.0 ± 0.71*	No target	Beverages	BF, EFD, GH, BL	–	I: 20 Fr R:20 Gl	–	–
Maersk et al. (2012)*	DK	Mixed	P, 24	Semi-skim milk Water ASSD SSSD (106 g/ day)	– 0 0 18	15/11F 16/11F 15/12F 14/6F OW/OB	37.7 ± 9.1 39 ± 7.3 39 ± 7.6 37.8 ± 8	No target	Beverages	BF, EFD, GH, BP, BL, UA	I:18 R:0 ASSD	–	–	–
Majid et al. (2013)	PK	Public	P, 4	No beverage Honey (46 g/ day)	0 8	31 M 32 M GP	20 ± 0.15 20.13 ± 0.14	No target	Beverages	GH, BL	I:8 R:0	–	–	–
Mark et al. (2014)	DK	Public	P, 4	Fructose (60 g/ day) Glucose (66 g/ day)	14 16	35F 38F OW/OB	Range: 20–50	No target	Beverages	BF, GH	–	I: 15 Fr R:15 Gl	–	–
Markey et al. (2016)	UK	Private	CX, 8	NMES (29 g/ day) NMES (75 g/ day)	6 16	50/34F Non-OB	31.6 ± 9.5	No target	Mixed diet	BF, GH, BP, BL	I:6 R:16	–	–	–

Author, year*	Country	Funding	Design, duration (wks)	Arms(1)	Sugars dose (E%)(2)	Participants	Age, years (mean ± SEM)	Background diet(3)	Food form	Outcome clusters(4)	Q1	Q2	Q3	Q4
Raben et al. (2002)*	DK	NR	P, 10	Artificial sweeteners Sucrose	0 23	21NR 21NR OW	37.1 ± 2.2 33.3 ± 2.0	No target	Mixed diet	BF, GH, BP, BL	I:23 R:0	–	–	–
Rasad et al. (2018)	IR	Public	P, 6	Honey (70 g/day) Sucrose (70 g/day)	– –	30 M 30 M GP	21.53 ± 1.63 24.23 ± 1.88	No target	Beverages	BP, BL	–	–	–	–
Saris et al. (2000)*	EU	Mixed	P, 24	High complex CHO Control High simple CHO	19 22 38	83/40F 77/40F 76/40F OW/OB	38 ± 9 38 ± 9 41 ± 9	No target	Mixed diet	BF, GH, BL	I:38 R:19	–	–	–
Smith et al. (1996)	NZ	Public	P, 24	Sugar-free diet Sucrose (66 g/day)	0 12	22NR 10NR HTG	53 ± 9 50 ± 11	No target	Mixed diet	BF, BL	I: 12 Sucr R: 0	–	–	–
Stanhope et al. (2009)*	US	Public	P, 8	Fructose Glucose	25 25	17/8F 15/8F OW/OB	Range: 40–72	No target	Beverages	BF, EFD, GH, BP, BL, UA	–	I:25 Fr R:25 Gl	–	–
Werner et al. (1984)	UK	Mixed	CX, 6	Artificial sweeteners Sucrose (100 g/day)	0 24	12/8F gallstones	Mean: 48 Range: 26–69	No target	Mixed diet	BF, GH, BL	I:24 R:0	–	–	–
Yaghoobi et al. (2008)	IR	Private	P, 4	Honey (70 g/day) Sucrose (70 g/day)	– –	38NR 17NR OW/OB	39.6 ± 10.6 42.4 ± 8.7	No target	Beverages	GH, BL	–	–	–	

AO = abdominal obesity; ASSD = artificially sweetened soft drinks; BF = body fatness; BL = blood lipids; BP = blood pressure; UA = uric acid; CHO = carbohydrates; CX = cross-over; EFD = ectopic fat deposition; F = females; Fr = fructose; GD = grape drink; GH = glucose homeostasis; GP = general population; HFCS = high fructose corn syrup; HGP = healthy general population; H-I = hyperinsulinaemia; HTG = hypertriglyceridaemia; I: intervention group; IGT = impaired glucose tolerance; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose tolerance; N-I = normo-insulinaemia; NMES = non-milk extrinsic sugars; NR = not reported; NW = normal weight; OB = obese; OC = oral contraceptives; OffT2DM = Offspring's from parents with type 2 diabetes mellitus; OW = overweight; P = parallel; R = reference group; RSS = rare sugars syrup; S = sucrose; SSFD = sugar-sweetened fruit drinks; SSSD = sugar-sweetened soft drinks; TFJ = total fruit juices. Columns Q1 and Q2 identify the arms that were selected from each study to answer questions 1 and 2, respectively. Columns Q3 and Q4 identify the studies that address questions 3 and 4, respectively.

*: Identifies whether the study has been reported in other publications from which one or more outcome variables could have been extracted (see **Appendix D**).

(1): In parenthesis, amount of sugars in g/day, either provided in the publication or calculated from the amount consumed from a given source (e.g. honey, sugar-sweetened beverages).

(2): Refers to the sugars contribution of the dietary fraction manipulated in the study to total energy intake.

(3): Carbohydrates (CHO), protein and fat are expressed as % of total energy (E%); fibre is given in g/day; P/S is the ratio of polyunsaturated to saturated fatty acids.

(4): Identifies the outcome variables that have been assessed in a study (by cluster) which are eligible for this assessment considering the duration of the intervention, as described in the protocol. Measures of body fatness (BF) include one or more of the following: body weight, BMI, body fat, waist circumference, lean body mass. For studies conducted in isocaloric conditions, changes in body weight and BMI have only been considered as explanatory variables, and not as outcome variables. Measures of ectopic fat deposition (EFD) include one or more of the following: visceral adipose tissue, liver fat, skeletal muscle fat. Measures of glucose homeostasis (GH) include either static measurements (fasting glucose, insulin and derived indices, such as HOMA-IR), dynamic measurements (measures of glucose and insulin and derived indices during an OGTT or an euglycaemic–hyperinsulinaemic clamp) or both.
(5): All arms in neutral energy balance.
(6): All arms in positive energy balance.
(7): Only sugars arm in positive energy balance (vs. a control on neutral energy balance).

Appendix F – Results of intervention studies on metabolic diseases

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Isocaloric with neutral energy balance[2]												
Bantle et al. (2000)	24/12F BMI ≤ 32 kg/m^2	CX, 6	i: Fructose c: Glucose	14 14	Mixed Diet	**NSD:** *Bw*		**Note:** glucose and insulin reported only 90 min after breakfast and AUC 24-h not eligible x this outcome		↑TG (men only) **NSD**: T-c, LDL-c, HDL-c		High fructose intake increased fasting triglycerides only in men as compared to glucose
Black et al. (2006)	13 M BMI < 35 kg/m^2	CX, 6	c: Sucrose i: Sucrose	10 25	Mixed Diet	**NSD:** *Bw*		**NSD:** WB-IS and Hep IS (clamp); FG and FI	**NSD**	↑ T-c, LDL-c **NSD:** HDL-c, TG		High sucrose intake had no effect on insulin sensitivity or BP but increased total and LDL-cholesterol
Despland et al. (2017)	8 M GP	CX, 8d	c: Starch i1: Honey i2: Glu/Fr	0 25 25	Mixed Diet	***NSD:*** *Bw*		**NDS:** glucose and insulin responses on OGTT				Fructose (pure or from honey) did not affect insulin sensitivity when consumed with glucose
Gostner et al. (2005)	19/12F GP	CX, 4	i: Isomalt c: Sucrose	0 6	Foods	***NSD:*** *Bw*		**NSD:** fructosamine		↓ Apo A-1 **NSD:** T-c, LDL-c, HDL-c, LDL-c:HDL-c ratio, TG, Apo B_{100}		No effect of isomalt on blood lipids or fructosamine
Groen et al. (1966)	8/6F 7/4F GP	CX, 5	i: Starch c: Sucrose	0 30		***NSD:*** *Bw*				↑ T-c		High sucrose intake increased total cholesterol
Hallfrisch et al. (1983a)*	12 M H-I 12 M N-I	CX, 5	c: Starch i1: Fructose i2: Fructose	0 7.5 15	Foods			↑ FG (data given for H-I and N-I combined) ↑ glucose and insulin responses (AUC) on OGTT (i2)	↓ SBP **NSD:** DBP	↑ T-c ↑ TG (i2 > i1, H-I only) ↑ LDL-c **NSD:** HDL-c, VLDL-c		Fructose increased glucose and insulin responses but reduced SBP; it also **increased TG (dose-response)** in men with hyperinsulinaemia

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Israel et al. (1983)*	24/12F H-I	CX, 6	c: Sucrose i1: Sucrose i2: Sucrose	2 15 30	Foods	***NSD:*** *Bw*		↑ FG ↑ FI (i2 > i1) ↑ glucose response (AUC) on OGTT[3] ↑ insulin response (AUC) on OGTT (i2 > i1)	↑ DBP (i2) **NSD:** SBP	↑ TG (i2 > i1, men only) ↑ T-c, LDL-c, HDL-c, VLDL-c ↓ HDL-c:T-c ratio[22] (i2, men only)	↑ FUA ↑ UA response (i1 in men only, i2)	High sucrose intakes **increased** fasting glucose and **insulin (dose-response)**, **TG (men only, dose-response),** DBP, blood lipids and uric acid in subjects with hyperinsulinaemia
Johnston et al. (2013)	15 M 17 M AO	P, 2	i: Fructose c: Glucose	25 25	Beverages	***NSD:*** *Bw*	**NSD:** liver fat, Skm fat	**NSD:** W-B IS and Hep IS (clamp; 12 subjects only, not powered for these outcomes as reported by the authors)				High fructose intake had no effect on glucose homeostasis or ectopic fat deposition as compared to glucose
Koh et al. (1988)	9/6F IGT 9/6F NGT	CX, 4	i: Fructose c: Glucose	15 15	Mixed diet	***NSD:*** *Bw*		↓ FG (IGT only) ↓ FI ↓ glucose and insulin responses (iAUC) on OGTT[4]	↓ SBP (IGT only) ↓ DBP (IGT only)	↓ TG (IGT only) ↓ T-c **NSD:** VLDL-c, LDL-c, HDL-c		Moderate intake of fructose lead to lower fasting glucose and insulin, lower BP and lower cholesterol and triglycerides compared to glucose in subjects with impaired glucose tolerance
Lewis et al. (2013)	9/4F, OW/OB	CX, 6	c: Sucrose i: Sucrose	5 15	Mixed diet	***NSD:*** *Bw*		↑ FG, FI, insulin response (iAUC) on OGTT **NSD:** glucose response (iAUC) on OGTT; W-B IS and Hep IS (clamp)	**NSD**	**NSD:** T-c, LDL-c, HDL-c, TG		A low sucrose diet reduced fasting glucose and the incremental insulin area under the curve during an OGTT with no effect on insulin sensitivity, blood pressure or blood lipids

[22] Calculated as HLD-cholesterol/(total cholesterol-HDL-cholesterol).

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Lowndes et al. (2014a)	18/6F 17/8F 13/ 8F 17/9F OW/OB	P,10	i1: Sucrose i2: HFCS i3: Sucrose i4: HFCS	10 10 20 20	Beverages	↑ Bw, BF (pooled cohort) **NSD:** Bw, WC, BF, LBM (for sugars dose or sugars type)			**NSD** (all arms combined) BP per study arm at the end of the intervention: NR	↓ HDL-c (pooled cohort) ↓ T-c, LDL-c, ApoB (i3 vs. i4) ↑ T-c/HDL-c ratio (pooled cohort) **NSD:** TG; HDL-c for sugars dose or type		Sugar consumption increased body fatness and decreased HDL-c but no effect of sugars dose or source
Lowndes et al. (2014b)*	58/26F 69/42F 64/38F 60/30F 53/26F 51/28F BMI < 35	P, 10	i1: Sucrose i2: HFCS i3: Sucrose i4: HFCS i5: Sucrose i6: HFCS	8 8 18 18 30 30	Beverages	↑ Bw, *BMI* and BF *(significant time x sugar dose interaction)* ↑ BW, BMI, WC, BF, LBM (pooled cohort) **NSD** for time x sugar dose x sugar type interaction	**NSD:** liver fat, Skm fat (data available for 64 subjects)	**NSD:** FG, FI (data available for 138 subjects)	↓ SBP (i1) **NDS:** DBP	↑ TG (pooled cohort) ↓ HDL-c (pooled cohort) **NSD:** TG, HDL-c for sugars dose or type **NSD**: T-c, LDL-c	**NSD**	**Dose-response** increase in measures of body fatness. No effect of sugar source. Changes in the lipid profile compatible with changes in body weight, unaffected by sugars dose or source
Lowndes et al. (2015)	31/21F 30/14F 34/17F 33/18F 28/17F BMI < 35 kg/m^2	P, 10	c1: Milk i1: Fructose c2: Glucose i2: Sucrose i3: HFCS	0 9 9 18 18	Beverages	↑ Bw (pooled cohort) **NSD** for sugars dose or sugars type interaction		↑ insulin response (AUC) and hepatic insulin response on OGTT (i1) (data available for 93 subjects) **NSD:** glucose response (AUC) and ISI on OGTT; FG, FI and HOMA-IR				Fructose increased the insulin response and hepatic insulin resistance during an OGTT. Effect not observed when consumed together with glucose.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Moser et al. (1986)	6F non-OC 6F OC	CX, 4	c: Starch i: Sucrose	0 43	Foods	***NSD:*** *Bw*		↓ insulin response (AUC) on OGTT[5] **NSD:** glucose response (AUC) on OGTT		↑ TG (OC vs. non-OC) **NSD:** T-c		Sucrose decreased insulin responses compared to starch with no effect on blood lipids
Reiser et al. (1979a)*	19/9F GP	CX, 6	Starch Sucrose	0 30	Foods	***NSD:*** *Bw*		**NSD:** insulin and glucose response on OGTT[3] (insulin ↑ only at 1 h)		↑ T-c, TG	↑ FUA ↑ UA response	Sucrose consumption increased total cholesterol, fasting triglycerides and uric acid. Glucose and insulin response to the sucrose load was not influenced by the nature of the carbohydrate fed (insulin response was significantly greater in those consuming sucrose only at 1 h during the OGTT).
Reiser et al. (1989a)*	10 M H-I 11 M N-I	CX, 5	c: Starch i: Fructose	0 20	Foods					↑ TG, T-c (H-I and N-I) ↑ VLDL-c, B-100 (H-I only) ↑ LDL-c (N-I only) **NSD:** HDL-c	↑ FUA (pooled H-I and N-I)	Fructose worsened the blood lipid profile and increased uric acid (background diet high in saturated fat)
Schwarz et al. (2015)	8 M Non-OB	CX, 9d	c: Starch i: Fructose	0 20	Beverages	***NSD:*** *Bw*	↑ *Liver fat*	↓ Hep-IS (clamp) **NSD:** WB-IS (clamp)				Fructose blunted suppression of endogenous glucose production
Sunehag et al. (2008)	6/3F OB Tanner 5	CX, 1	c: Fructose i: Fructose	6 24	Mixed diet			**NSD:** WB-IS (SLIVGTT), indices of insulin secretion				Fructose had no effect on insulin sensitivity in obese adolescents

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Swanson et al. (1992)	14/7F GP	CX, 4	c: Starch i: Fructose	0 16.6	Mixed diet	***NSD:*** *Bw*		**NSD:** FG, glycosylated albumin		↑ T-c, LDL-c **NSD:** TG, HDL-c, HDL-c/LDL-c ratio		Fructose increased total and LDL-c compared to starch
Szanto and Yudkin (1969)	19 M GP	CX, 2	c: Starch i: Sucrose	0 52	Mixed diet	↑ *Bw*		↑ insulin response on OGTT **NSD:** glucose response on OGTT				Sucrose increased body weight and insulin response on OGTT compared to starch. Changes driven by a subgroup of six responders
Thompson et al. (1978)	8 M GP	CX, 10d	i1:Corn syr i2:Sucrose i3:Corn syr i4:Sucrose	45 45 65 65	Beverages			↓ glucose response (AUC) on OGTT (i4 vs. i1) **NSD:** insulin response on OGTT				No clear effect of high intakes of sucrose or corn syrup on glucose homeostasis
Umpleby et al. (2017)	11 M NAFLD 14 M no NAFLD OW	CX, 12	c: NMES i: NMES	6 26	Mixed diet	↑ Bw Statistical analyses for other variables adjusted for changes in Bw	↑ Liver fat (NAFLD and no-NAFLD) **NSD:** VAT (all in 17 subjects with available data)	**NSD:** FI, FG, HOMA-IR		↑ TG, VLDL-c (NAFLD only) **NSD:** LDL-c, HDL-c, T-c		High sugars intakes increased liver fat. High liver fat lead to a differential increase in blood lipids in response to high or low intake of free sugars
Isocaloric with positive energy balance[6]												
Beck-Nielsen et al. (1978)	6 NR 6 NR GP	P, 2	c: Fat i: Sucrose	0 32	Mixed diet	***NSD:*** *Bw*		↓ WB-IS (IVITT)				High sucrose intake (and not fat) reduced insulin sensitivity
Beck-Nielsen et al. (1980)	8NR 7NR GP	P, 1	i: Fructose c: Glucose	33 33	Beverages	***NSD:*** *Bw*		↓ WB-IS (IVITT)				High fructose (and not glucose) intake reduced insulin sensitivity

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Johnston et al. (2013)	15 M 17 M AO	P, 2	i: Fructose c: Glucose	25 25	Beverages	↑ Bw *(vs neutral energy balance)*	↑ liver fat, Skm fat (vs neutral energy balance)	**NSD:** W-B IS and Hep IS (clamp; 12 subjects only, not powered for these outcomes as reported by the authors)				Increases in liver and muscle fat correlated with the increase in body weight in both groups
Silbernagel et al. (2011)	10/3F 10/5F BMI < 35kg/m^2	P, 4	i: Fructose c: Glucose	22 22	Beverages	***NSD:*** *Bw*	**NSD:** liver fat, SKm fat, VAT	**NSD:** FG, FI, HOMA-IR; ISI (Matsuda) index on OGTT (ISI ↓ in both groups)	**NSD**	↑ TG **NSD:** T-c, LDL-c, HDL-c	**NSD**	Fructose increased triglycerides vs. glucose with no effect on other metabolic variables
Hypercaloric[7]												
Le et al. (2009)	8 M no-offT2DM 16 M offT2DM	CX, 1	No sugars Fructose	0 35	Beverages	↑ *Bw (vs neutral energy balance)*		↑ Hep-IS (clamp) **NSD:** WB-IS (clamp)				A hypercaloric diet with high intake of fructose had no effect on WB-IS but decreased hepatic insulin sensitivity
Ad libitum												
Aeberli et al. (2013)	9 M, NW	CX, 3	i1: Fructose i2: Fructose c: Glucose i3: Sucrose	8 16 16 16	Beverages	↓ *Bw (i1, i2)*		↓ Hep-IS (clamp, i2) **NSD:** WB-IS (clamp)				High fructose intake reduced hepatic insulin sensitivity
Angelo-poulos et al. (2015)*	65NR 77NR 64NR 61NR BMI < 35 kg/m^2	P, 10	i1: Fructose c: Glucose i2: Sucrose i3: HFCS	9 9 18 18	Beverages	↑ Bw, BMI, WC (pooled cohort) **NSD:** Bw, BMI, WC for sugars dose or sugars type interaction		**NSD:** FG	↓ SBP, DBP (pooled cohort) **NSD** for sugars type interaction	↑ TG (pooled cohort, men only) ↑ TG (i3, men only) **NSD:** T-c, LDL-c, HDL-c	**NSD**	Moderate fructose intakes had no effect on fasting glucose or uric acid. Increased energy intake leads to an increase in body weight in the whole cohort, while blood pressure decreased. Triglycerides increased only in men.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Campos et al. (2015)	14/6F 13/7F OW/OB	P, 12	i: ASB c: SSB	0 18	Beverages	**NSD:** Bw, BMI, BF, LBM	↓ Liver fat **NSD:** VAT	**NSD:** FG, FI, HOMA-IR	**NSD**	**NSD:** T-c, HDL-c, TG	**NSD**	Replacing SSBs in high consumers with ASBs decreases liver fat
Ruyter et al. (2014)	319/147F 322/151F GP	P, 72	i: ASSD c: SSSD	0 5	Beverages	↓ BMI z score, Bw, WC						Consumption of ASSDs reduced weight gain in children as compared to SSSDs
Ebbeling et al. (2012)	110/48F 114/52F OW/OB	P, 52	i: ASSD +water c: SSSD+SSFD +TFJ	0 17	Beverages	↓ Bw, BMI (greatest in Hispanics)						Increase in BMI and body weight were smaller in the experimental group
Hernandez-Cordero et al. (2014)	120F 120F OW/OB	P, 36	i: Water c: SSBs	0 20	Beverages	**NSD:** Bw, BMI, BF, WC		**NSD:** HbA1c, FG	**NSD**	↓ TG (obese only) **NSD:** T-c, LDL-c, HDL-c, TG		Replacing SSBs in high consumers with water did not affect body fatness or metabolic variables, except for a decrease in triglycerides in the obese (secondary analysis)
Hollis et al. (2009)	25NR 25NR 26NR OW	P, 12	c2: No drink i: GJ c1: GD	0 18 18	Beverages	**NSD:** Bw, BMI, WC		↑ glucose and insulin responses (AUC) on OGTT (vs c1 and c2)		**NSD:** T-c, LDL-c, HDL-c, TG		Grape juice increased glucose and insulin responses vs. grape sugar drink or no intervention
Huttunen et al. (1976)	48NR 35NR 33NR GP	P, 72	i1:Xylitol i2:Fructose i3:Sucrose	0 14 16	Mixed diet			**NSD:** FG, FI, glucose and insulin response on OGTT[8]		↓ T-c (i2 only) **NSD:** TG	**NSD**	Total cholesterol was lower in the fructose group. The change was driven by hypercholesterolaemic participants.
Jin et al. (2014)	9/6F 12/4F OW NAFLD	P, 4	c: Fructose i: Glucose	20 20	Beverages	***NSD:*** *Bw*	**NSD:** Liver fat	↓ Adipose tissue IR index[9] **NSD:** FG, FI, HOMA-IR		↓ VLDL **NSD:** TG		Sugar type had no effect on body weight, liver fat or triglycerides. Adipose tissue IR and VLDL decreased with glucose vs. fructose

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)[1]	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Maersk et al. (2012)*	15/11F 16/11F 15/12F 14/6F OW/Obese	P, 24	c1: SK milk c2: Water c3: ASSD i: SSSD	0 0 0 18	Beverages	**NSD:** Bw, BMI, BF, LBM	↑ Liver fat ↑ VAT ↑ SKm fat (data available for 47 subjects)	**NSD:** FG, FI, HOMA-IR; glucose and insulin responses (AUC) and derived indices of IR on OGTT	↑ SBP (c1, c3) **NSD:** DBP	↑ T-c (vs c3) ↑ TG (vs c2 and c3) **NSD:** LDL-c, HDL-c, T-c/HDL-c ratio	↑ FUA (data available for 47 subjects)	Consumption of SSSD increased triglycerides, uric acid and ectopic fat deposition with no effect on body weight, total body fat or glucose homeostasis
Majid et al. (2013)	31 M 32 M GP	P, 4	c: No drink i: Honey	0 8	Beverages			↓ FG		↓ T-c, LDL-c, TG ↑ HDL-c		Honey consumption limited the rise in blood glucose and improved the blood lipid profile. Background diet and changes in body weight were not assessed.
Mark et al. (2014)	35F 38F OW/OB	P, 4	i: Fructose[10] c: Glucose[10]	15 15	Beverages	**NSD:** BW, BMI, WC		**NSD:** FG, FI, HOMA-IR; glucose and insulin responses and ISI on OGTT		**NSD:** T-c, LDL-c, HDL-c, TG		The type of sugar had no effect on glucose homeostasis, blood lipids or body weight.
Markey et al. (2016)	50/34F Non-OB	CX, 8	i: NMES c: NMES	6 16	Mixed diet	**NSD:** Bw		**NSD:** FG, FI	**NSD**	**NSD:** T-c, LDL-c, HDL-c, TG, T-c/HDL-c ratio		Reduction of free sugars intake did not affect body weight, fasting glucose or insulin, or blood lipids.
Raben et al. (2002)*	20NR 21NR OW	P, 10	i1: AS i2: Sucrose	0 23	Mixed diet	↑ Bw, BMI, BF (all i2) **NSD:** Sagittal height, LBM		↑ FI (i2) **NSD:** FG, HOMA-IR, HOMA-β (data available for 23 subjects)	↑ SBP, DBP (i2)	↑ TG (i2) **NSD:** T-c, HDL-c (data available for 23 subjects)		High intakes of sucrose increased body weight, fat mass and blood pressure. Sucrose increased fasting insulin and triglycerides.
Saris et al. (2000)*	83/40F 77/40F 76/40F OW/OB	P, 24	i1: LF/LS c: Control i2: LF/HS	19 22 38	Mixed diet	↓ Bw (i1, i2) **NSD:** Bw (i1 vs. i2)		**NSD:** FG, FI		**NSD:** T-c, zLDL-c, HDL-c, TG, HDL-c/LDL-c ratio		The type of carbohydrates in low fat diets did not affect body weight, the blood lipid profile, or fasting glucose or insulin.

Study, Year	Subjects	D/D weeks	Arms	Sugars dose (E%)(1)	Food form	Body fatness	Ectopic fat	Glucose homeostasis	Blood pressure	Blood lipids	Uric acid	Comments
Smith et al. (1996)	22 NR 10 NR HTG	P, 24	i: Sugar-free c: Sucrose	0 12	Mixed diet	↓ Bw				↓ TG **NSD:** T-c, HDL-c		Lower sucrose intake reduced triglycerides accounting for changes in body weight in subjects with hypertriglyceridaemia.
Stanhope et al. (2009)*	17/8F 15/8F OW/OB	P, 8	i: Fructose c: Glucose	25 25	Beverages	↑ Bw, WC, BF (both groups)	↑ VAT (men)	↑ FG; insulin response on OGTT ↑ ISI on OGTT ↑ Glucose response on OGTT (both groups) **NSD:** FI, fructosamine	**NSD**	↑ T-c, LDL-c, ApoB, ApoB/ApoA1 ratio **NSD:** TG, HDL-c	↑ FUA	Fructose decreased insulin sensitivity, increased insulin excursions, visceral adiposity and uric acid and promoted dyslipidaemia vs. glucose.
Werner et al. (1984)	12/8F Gallstones	CX, 6	c: AS i: Sucrose	0 24	Mixed diet	↑ Bw		**NSD:** FG (data not shown in the paper)		↓ HDL-c ↑ TG **NSD:** T-c, LDL-c		High sucrose intake increased body weight and triglycerides while decreasing HDL-c concentrations.

Results presented in *italics* were not eligible as the studies did not meet the duration criteria outlined in the opinion protocol.
AO = abdominal obesity; AS = artificial sweeteners; ASB = artificially sweetened beverages; ASSD = artificially sweetened soft drinks; AUC = area under the curve; BF = body fat; BMI = Body mass index; Bw = Body weight; C = control; CX = Crossover; DBP = diastolic blood pressure; D/D = study design and duration (in weeks); F = females; FG = fasting glucose; FI = fasting insulin; FUA = fasting uric acid; GD = grape drink; GJ = grape juice; GR = glucose response; GP = General Population; HbA1c = Glycated haemoglobin; HDL-c = High density lipoprotein cholesterol; Hep-IS = hepatic insulin sensitivity; HFCS = high fructose corn syrup; H-I = hyperinsulinaemia; HOMA-IR = homeostatic model assessment IR; HTG = hypertriglyceridaemia; I = intervention; IGT= impaired glucose tolerance; IR = insulin resistance; IS = insulin sensitivity; ISI = insulin sensitivity (Matsuda) index; IVITT= intravenous insulin tolerance test; LBM = Lean body mass; LDL-c= Low density lipoprotein cholesterol; LF/HS = low fat diet high in sugars; LF/LS = low fat diet low in sugars; OB = Obese; OC = oral contraceptives; offT2DM = offspring from parents with type 2 diabetes mellitus; OGTT = Oral glucose tolerance test; OW = Overweight; NAFLD = non-alcoholic fatty liver disease; NGT = normal glucose tolerance; N-I = normoinsulinaemia; NMES = non-milk extrinsic sugars; NR = not reported; NSD = no significant difference; NW = normal weight; M = males; P = Parallel; Skm = skeletal muscle; SBP = systolic blood pressure; SLIVGTT = stable labelled intravenous glucose tolerance test; SSFD = sugar sweetened fruit drink; SSSD = sugar sweetened soft drinks; T-c = total cholesterol; TG = Triglycerides; TFJ = total fruit juice; UA = uric acid; VAT = Visceral adipose tissue; VLDL = Very low density lipoprotein; WB-IS = whole body insulin sensitivity; WC = waist circumference.
*: Only within-group comparisons tested in the study.
(1): Refers to the sugars contribution of the dietary fraction manipulated in the study to total energy intake.
(2): All arms in neutral energy balance.
(3): OGTT with sucrose load of 2 g/kg body weight over 3 h.
(4): OGTT with 100 g dextrose solution over 3 h.
(5): OGTT with glucose load of 1 g/kg body weight over 3 h.
(6): All arms in positive energy balance.
(7): Only sugar arm in positive energy balance (vs a control on neutral energy balance).

(8): OGTT with glucose load of 1 g/kg body weight.
(9): Adipose tissue IR index was calculated as fasting FFA (mEq/L) × insulin (mU/L).
(10): These intervention arms were in combination with either high or low advanced glycation end product diets.