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Tolerable upper intake level for dietary sugars

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Abstract

Following a request from five European Nordic countries, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was tasked to provide scientific advice on a tolerable upper intake level (UL) or a safe level of intake for dietary (total/added/free) sugars based on available data on chronic metabolic diseases, pregnancy-related endpoints and dental caries. Specific sugar types (fructose) and sources of sugars were also addressed. The intake of dietary sugars is a well-established hazard in relation to dental caries in humans. Based on a systematic review of the literature, prospective cohort studies do not support a positive relationship between the intake of dietary sugars, in isocaloric exchange with other macronutrients, and any of the chronic metabolic diseases or pregnancy-related endpoints assessed. Based on randomised control trials on surrogate disease endpoints, there is evidence for a positive and causal relationship between the intake of added/free sugars and risk of some chronic metabolic diseases: The level of certainty is moderate for obesity and dyslipidaemia (> 50–75% probability), low for non-alcoholic fatty liver disease and type 2 diabetes (> 15–50% probability) and very low for hypertension (0–15% probability). Health effects of added vs. free sugars could not be compared. A level of sugars intake at which the risk of dental caries/chronic metabolic diseases is not increased could not be identified over the range of observed intakes, and thus, a UL or a safe level of intake could not be set. Based on available data and related uncertainties, 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. This opinion can assist EU Member States in setting national goals/recommendations.

Keywords: added sugars, free sugars, chronic metabolic diseases, pregnancy-related endpoints, dental caries, Tolerable upper intake level, safe level of intake

Requestor: European Commission

Question number: EFSA-Q-2016-00414

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Amendment: An editorial error in relation to the conclusions on fruit juices was corrected. Information describing the process of the public consultation on the draft opinion was added. An editorial correction was carried out that does not materially affect the contents or outcome of this scientific output. To avoid confusion, the original version of the output has been removed from the EFSA Journal, but is available on request.

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Summary

Following a request from the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden), the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver a Scientific Opinion on the tolerable upper intake level (UL) for dietary sugars on the basis of available data on chronic metabolic diseases, pregnancy-related endpoints and dental caries.

The UL is the maximum level of chronic daily intake of (total/added/free) sugars from all dietary 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. The underlying assumption of the UL concept 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, then assessing a safe level of intake could be considered. This requires the identification of a level of sugars intake up to which no adverse health effects are observed. Advice on quantitative intakes of a particular type of sugar (e.g. fructose, glucose, sucrose), and/or on one or more sources of sugars, could also be provided to assist EU Member States when developing food-based dietary guidelines (FBDGs).

The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose). Among these, glucose and fructose as monosaccharides, and sucrose and lactose as disaccharides, are the most abundant sugars in mixed diets. Added sugars are defined as 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. Free sugars are defined as added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.

This assessment follows the principles and processes illustrated in the EFSA PROMETHEUS project. A draft protocol was developed, opened for public consultation and amended in view of the comments received. According to EFSA's principles for deriving UL for nutrients, a four-step approach was applied: hazard identification, hazard characterisation, intake assessment and risk characterisation. Systematic reviews of the literature on dietary sugars and their sources and chronic metabolic diseases (obesity, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension (HTN), cardiovascular diseases (CVDs) and gout), pregnancy-related endpoints (gestational diabetes mellitus, birthweight-related endpoints) and dental caries were conducted to inform the hazard identification and hazard characterisation. The Office of Health Assessment and Translation (OHAT) of the US National Toxicology Program Approach for Systematic Review and Evidence Integration was used as reference and modified to appraise the internal validity of eligible studies and to formulate conclusions on hazard identification, accounting for the uncertainties identified in the eligible body of evidence (BoE). Dose-response analyses were conducted where data allowed. Background information on digestion, absorption and metabolism of sugars from different sources in humans and the mode(s) of action underlying the potential adverse effects were addressed through a narrative review. Intakes of dietary sugars in European populations were calculated by developing food composition databases for total, added and free sugars using harmonised food composition data (EFSA Nutrient Composition Database), linked to data from the EFSA Comprehensive Food Consumption Database.

Body of evidence

Eligible studies were randomised controlled trials (RCTs) and non-randomised comparative studies of interventions, and prospective (cohort and case-cohort) studies (PCs) in humans on the exposures and endpoints of interest.

Dental caries

One publication reporting on an intervention study and 11 publications reporting on seven PCs met the inclusion criteria. Five PCs report on total sugars (of which two also report on sugar-sweetened beverages (SSBs) and one on fruit juices (FJs)) and two PCs report on sucrose. Cohorts were very heterogeneous regarding the outcome of interest consistent with the demographic characteristics of their participants, which included children, adolescents, adults and older adults.

Chronic metabolic diseases including pregnancy-related endpoints

A total of 49 RCTs reported in 61 publications were included. These allowed investigating the effect of the amount of added sugars, free sugars and SSBs when consumed ad libitum and in isocaloric exchange with other macronutrients (mostly starch), as well as the effect of fructose compared to glucose.

A total of 104 publications reporting on 66 different cohorts were included. PCs assessed total sugars, added sugars, sucrose, free sugars, fructose, SSBs and FJs. Dietary sugars (total, added and free sugars; glucose and fructose) were investigated mostly keeping total energy intake (TEI) constant in the analysis (i.e. in isocaloric exchange with other macronutrients). In contrast, most PCs on SSBs and FJs have explored whether these could be associated with the endpoint not keeping TEI constant in the analysis when the exposure was analysed as a categorical variable (e.g. for dichotomous disease endpoints).

Dietary sugars

Studies investigating added sugars, sucrose (as a proxy for added sugars) and free sugars were combined to draw conclusions in relation to the endpoints of interest, owing to the low number of studies available per each exposure and endpoint and the fact that intakes of added and free sugars widely overlap. Therefore, the health effects of added vs. free sugars could not be compared.

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 and between the intake of sucrose and risk of dental caries in primary dentition in individual PCs across a wide range of total sugars and sucrose intakes. Dose-response relationships could not be explored across the BoE owing to the high heterogeneity of the exposures and endpoints assessed. Therefore, the available data do 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 sugar intake at which the risk of dental caries is not increased.

The mechanisms by which the intake of dietary sugars increases the risk of developing dental caries are well established. Dietary sugars are metabolised by plaque microorganisms to organic acids which demineralise enamel and dentine, subsequently causing caries. Sucrose is also known to contribute to the formation of dental plaque.

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' sugar intake on surrogate disease endpoints, i.e. body weight, liver fat, fasting glucose, fasting triglycerides and systolic blood pressure. 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 ≥ 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).

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 Panel concludes that the available data do not allow the setting of a UL or a safe level of intake for either total, added or free sugars.

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.

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), followed by beverages (SSBs, FJs) and fine bakery wares, with high variability across countries. The main difference between the intake of added and free sugars was accounted for by FJs. 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 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.

Sugar types

Fructose

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

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. 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%) is used to replace sucrose in foods and beverages.

Sources of dietary sugars

Sugar-sweetened beverages

There is evidence for a positive and causal relationship between the intake of SSBs and risk of some chronic metabolic diseases. 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), based on data from RCTs and PCs. When dose-response relationships between the intake of these beverages and incidence of disease (T2DM, HTN and CVDs) could be investigated using data from PCs, these were positive and linear. It is unclear, however, whether the risk of HTN and CVDs associated with the consumption of these beverages could be attributed to their sugar content because the relationship between the consumption of artificially sweetened (sugar-free) beverages and incidence of HTN and CVDs was similar to, or stronger than, for SSBs in these studies. 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 gestational diabetes mellitus (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 small for gestational age.

In PCs, SSBs were mostly assessed not keeping TEI constant in the analysis, thus allowing for the contribution of energy to the associations.

The proportion of consumers of SSBs (sugar-sweetened soft drinks and sugar-sweetened fruit drinks) in Europe varied widely across population groups and countries, ranging from 0% to 97% of the dietary survey's sample. In consumers, the contribution of added and free sugars in SSBs to total energy intake ranged from 1 to 8 E%, depending on the survey. With few exceptions, the contribution of SSBs to the intake of added and free sugars ranged from 15% to about 50%.

Fruit juices

There is evidence for a positive and causal relationship between the intake of FJs and risk of some chronic metabolic diseases. 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), based on data from PCs. The dose-response relationship between the intake of FJs and incidence of T2DM was positive and linear. Fruit juices were mostly assessed not keeping TEI constant in the analysis, thus allowing for the contribution of energy to the associations. As for SSBs, the external validity of the findings in relation to the risk of gout for European populations is unclear.

The proportion of consumers of fruit juices in Europe varied widely across population groups and countries, ranging from 15% to 96% of the sample. 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. With few exceptions, the contribution of fruit juices to the intake of free sugars ranged from 15% to about 50%.

Other sources of dietary sugars

Data from PCs on other sources of dietary sugars were not extracted because: (a) reliable estimates of sugars intake from these sources were not feasible, (b) foods for which sugar intakes could have been calculated were either small contributors to the intake of sugars or were investigated in relation to metabolic disease endpoints for other reasons than their sugar content and/or (c) the few studies quantifying sugars intake from other sources were heterogeneous regarding the exposure of interest and the endpoint assessed, so that only one study was available for each specific exposure–endpoint relationship. However, all major contributors to the intake of added and free sugars should be considered by Member States when setting FBDGs.

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Background as provided by the requestor

In June 2016, the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden) sent a request to the European Food Safety Authority (EFSA) in order to provide a dietary reference value (DRV) for sugars, with particular attention to added sugars, on the basis of most recent scientific evidence. After discussing the mandate at its plenary meeting on 22–23 September 2016, the NDA Panel asked for some clarifications to the requestors, particularly regarding the type of DRV to be established, the exposure of interest, the target population and the health endpoints to be considered. In February 2017, the requestors clarified that they were interested in a science-based cut-off value for a daily exposure to added sugars from all sources (i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing) which is not associated with adverse health effects. The target population for the assessment was defined as the general healthy population, including children, adolescents, adults and elderly. The requestors also clarified that the request relates to an update of the EFSA's Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010a) in relation to the effects of added sugars on nutrient density, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

In the EFSA NDA Panel (2010a) opinion, the term 'added sugars' referred to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing.

With regard to the effects of added sugars intake, the NDA Panel reached the following conclusions on the endpoints assessed:

- Micronutrient density of the diet: observed negative associations between added sugars intake and micronutrient density of the diet are mainly related to patterns of intake of the foods from which added sugars in the diet are derived rather than to the intake of added sugars per se. The available data are not sufficient to set an upper limit for (added) sugars intake.
- Glucose and insulin response: there are limited, and mainly short-term, data on the effects of high intakes of sugars on glucose and insulin response. Most studies do not find any adverse effects at intakes of predominantly added sugars up to 20–25% of total energy (E%), provided that body weight is maintained.
- Serum lipids: although there is some evidence that high intakes (> 20 E%) of sugars may increase serum triglycerides and cholesterol concentrations, the available data are not sufficient to set an upper limit for (added) sugars intake.
- Body weight: the evidence relating high intake of sugars (mainly as added sugars), compared to high intakes of starch, to weight gain is inconsistent for solid foods. However, there is some evidence that high intakes of sugars in the form of sugar-sweetened beverages (SSBs) might contribute to weight gain. The available evidence is insufficient to set an upper limit for sugars based on their effects on body weight.
- Type 2 diabetes: controversial findings on the association between total sugars and/or specific types of sugars and diabetes risk were reported in large prospective cohort studies. However positive associations were found between SSBs and increased type 2 diabetes risk. The available evidence was found insufficient to set a Tolerable Upper Level of Intake (UL) for sugars based on their effects on type 2 diabetes risk.
- Dental caries: available data do not allow the setting of a UL for (added) sugars on the basis of a risk reduction for dental caries, as caries development related to consumption of sucrose and other cariogenic carbohydrates does not depend only on the amount of sugars consumed, but it is also influenced by oral hygiene, exposure to fluoride, frequency of consumption and various other factors.

The NDA Panel concluded that the available data did not allow the setting of a UL for total or added sugars, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However, evidence on the relationship between patterns of consumption of sugar-containing foods and dental caries, weight gain and micronutrient intake should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDGs).

Terms of Reference as provided by the requestor

The request is for scientific assistance in line with Regulation (EC) No 178/2002 in assessing a DRV for added sugars, which would benefit risk managers and substantially support their work with dietary guidelines and nutrient recommendations if they could base their advices on an up-to-date assessment by EFSA. To this end, EFSA has been requested to update its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre published in 2010 (EFSA NDA Panel, 2010a), on the basis of the most recent scientific evidence, in order to derive a science-based cut-off value for a daily exposure to added sugars which is not associated with adverse health effects. The mandate requestor clarified that the intake of interest is added sugars from all sources, i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing. The health endpoints of interest are those already addressed in the EFSA NDA Panel (2010a) opinion, i.e. micronutrient density of the diet, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

Interpretation of the Terms of Reference

The interpretation of the terms of reference can be found in Section 5 of the Protocol for the scientific opinion on the tolerable upper intake level (UL) of dietary sugars (EFSA NDA Panel, 2018), which was subject to public consultation from 9 January to 4 March 2018. A technical meeting with stakeholders was held in Brussels on 13 February 2018, during the consultation period. After consultation with stakeholders and the mandate requestors, EFSA interprets this mandate as a request to provide scientific advice on a UL for (total/added/free) sugars, i.e. the maximum level of total chronic daily intake of sugars (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route. The health endpoints of interest relate to the development of chronic metabolic diseases, pregnancy-related endpoints and dental caries.

If there are no, or insufficient, data on which to base the establishment of a UL, an indication should 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). If there are no, or insufficient, data on which to base the establishment of a UL or a cut-off value for (total/added/free) sugars from all sources because the evidence available relates to one or few sources only, or to a particular type of sugar (e.g. fructose, glucose, sucrose), and the extrapolation of the results to (total/added/free) sugars from all sources is found to be unjustified, scientific advice could be provided on quantitative intakes in relation to one or few sources of sugars only, and/or in relation to one type of sugar only (e.g. fructose, glucose, sucrose) (**Figure 1**). The Panel wishes to clarify that a UL is not a recommended level of intake.

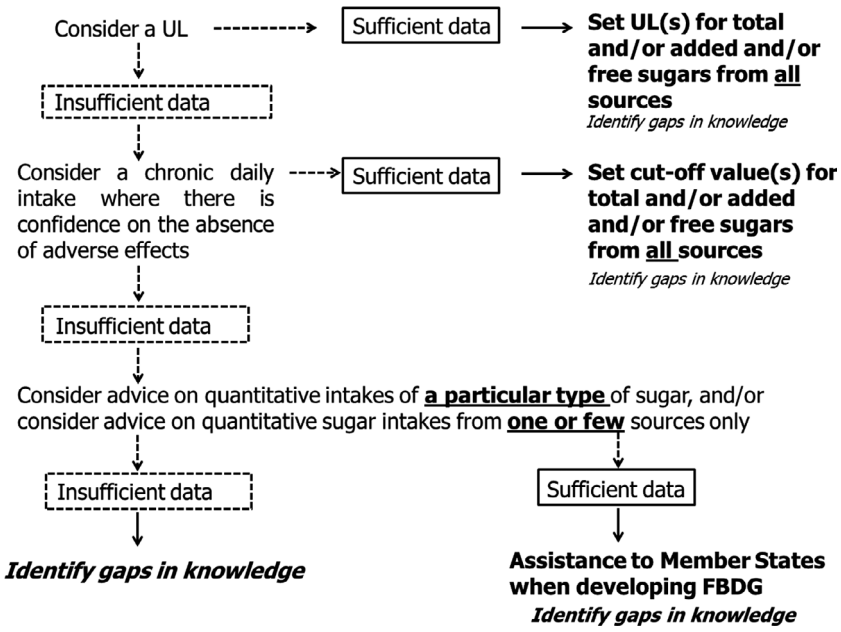


Figure 1: Stepwise process to provide scientific advice on total/added/free sugars

Dietary goals for populations or recommendations for individuals for a nutrient, and for food sources of the nutrient (e.g. FBDGs), are based on considerations of health effects associated with its consumption. DRVs, including ULs, provide the scientific bases for such considerations. However, other factors are also considered, such as 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 dietary goals and recommendations are developed. Establishing dietary goals or recommendations for dietary sugars (e.g. a limit of intake) and FBDGs on sugar-containing foods is part of national nutrition policies and thus in the remit of individual EU Member States, not under EFSA's remit.

Additional information

To address this mandate EFSA was requested to consider, as background information and sources of data, published reports from national and international authorities/bodies addressing the health effects of sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

Data and methodologies

This assessment follows the principles for the application of risk assessment to nutrients in general, and for deriving ULs in particular, which have been described elsewhere (SCF and EFSA NDA Panel, 2006; EFSA NDA Panel, 2010b).

The assessment has been developed following the principles and process illustrated in the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments) (EFSA, 2015). In this context, a draft protocol was developed with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data (i.e. which data to use for the assessment and how to identify and select them), appraising the relevant evidence and analysing and integrating the evidence in order to draw conclusions that will form the basis for the Scientific Opinion. The draft protocol was open for public consultation from 9 January to 4 March 2018. The public consultation included a technical meeting with stakeholders held in Brussels on 13 February 2018. The draft protocol was amended in view of the comments received. All comments received were addressed and published in a technical report (EFSA NDA Panel, 2018), and a final version of the protocol was published (EFSA NDA Panel, 2018).

The six assessment subquestions defined in the Protocol (EFSA NDA Panel, 2018) for this Scientific Opinion on the UL of dietary sugars, the methods used and the sections of the opinion in which they are addressed, are as follows:

No.	Subquestion	Method	Sections
1	What are the levels of (total/added/free) sugars in foods and beverages in Europe?	Food composition data (EFSA Nutrient Composition Database, Mintel's Global New Products Database)	4.1, 4.2, 4.3, 4.4, 4.5
2	What is the distribution of intakes of (total/added/free) sugars from all dietary sources (and by food source) by population group?	Food composition data Food consumption data (EFSA Comprehensive Food Consumption Database)	4.6, 4.7, 4.8
3	What are the digestion, absorption and metabolism of different types of sugars from different sources in humans?	Narrative review	3.1, 3.2, 3.3, 3.4, 3.5
4	What is the relationship between the intake of (total/added/free) sugars and metabolic diseases (disease endpoints and other endpoints) in the target population?	Systematic review	8, 9, 11
5	What is the relationship between the intake of (total/added/free) sugars and dental caries in the target population?	Systematic review	10, 11
6	Which could be the potential mode(s) of action underlying the adverse effects (if any) of (total/added/free) sugars intake?	Narrative review	3.6

The Handbook for Conducting a Literature-Based Health Assessment Using the Office of Health Assessment and Translation (OHAT) from the US National Toxicology Program Approach for Systematic Review and Evidence Integration (NTP, 2019) has been used as reference to conduct the systematic reviews on metabolic diseases and dental caries. The OHAT/NTP tool has been adapted to appraise the internal validity of human intervention and observational studies (Section 7.4). The OHAT approach has also been modified to draw conclusions on hazard identification for metabolic diseases including pregnancy endpoints. The principles for evidence integration and uncertainty analysis, including the adaptations introduced to the OHAT approach to fit this scientific assessment, can be found in Section 8.1.3.

A draft opinion was endorsed by the NDA Panel on 6 July 2021 and was open for public consultation from 22 July to 30 September 2021. The public consultation included a technical meeting with stakeholders held online on 21 September 2021. The draft opinion has been amended in view of the comments received, which have all been addressed and are published in a technical report (**Annex O**).

Protocol amendments

Two amendments have been introduced to the published protocol:

Version of the EFSA Comprehensive Food Consumption Database used in the assessment. The intake assessment of dietary sugars is based on the latest version of the EFSA Comprehensive Food Consumption Database published on 7 February 2020, rather than the one available on 31 December 2018, as written in the protocol. The reason for this amendment is that, having the deadline for the mandate extended by one year (from February 2020 to March 2021), it was feasible to consider most recent European data, collected under the EU Menu project, in the assessment. This includes data from nine new food consumption surveys collected in six European countries. The protocol amendment was endorsed by the NDA Panel on 25 February 2020.

Update of the literature searches for systematic reviews. The literature searches were conducted earlier than planned owing to the high number of hits retrieved in scoping searches to allow incorporation of the new data into the scientific opinion (i.e. they were performed 10 months before the planned endorsement of the scientific opinion instead of the 3 months foreseen in the protocol). The protocol foresees the incorporation of the new studies meeting the inclusion criteria into the opinion by a weight of evidence approach (narratively). Instead, as agreed with the mandate

requestor, only new studies meeting certain criteria have been considered to draw conclusions on hazard identification, but these studies have also been fully incorporated into the opinion, also in meta-analyses and dose-response analyses where appropriate (see Section 7.1 and **Annex A**). The NDA Panel was informed on 21 January 2021.

Questionnaire to National Competent Authorities of European countries

A total of 37 European countries were asked to supply information on current national recommendations for dietary sugars through the EFSA focal points[1] and the EFSA Food Consumption Network[2] using a questionnaire developed for that purpose (**Annex F**). The questionnaire was also designed to gather sugars intake data from national surveys and national food composition data on added and free sugars.

Assessment

1. Introduction

Digestible carbohydrates are the main source of energy in most human diets. Dietary sugars belong to this category of non-essential nutrients. In 2010, a reference intake range for carbohydrates of 45–60 E% was established by EFSA for adults and children older than 1 year of age (EFSA NDA Panel, 2010a). The available data were not sufficient to set an upper limit for (added) sugars intake.

2. Definition/category

2.1. Chemistry

Dietary sugars are a class of carbohydrates with a degree of polymerisation of one (monosaccharides) or two (disaccharides), which are digestible in the small intestine, with the exception of lactose in individuals with low intestinal lactase activity (EFSA NDA Panel, 2010a) (**Table 1**).

Table 1: Main types of dietary sugars

Subgroup	Components	Monomers
Monosaccharides	Glucose	
	Galactose	
	Fructose	
Disaccharides	Sucrose	Glucose, fructose
	Lactose	Glucose, galactose
	Trehalose	Glucose
	Maltose	Glucose

Maltose and trehalose, with two molecules of glucose each, only differ in the configuration of the glycosidic bond.

This assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route only. Among these, glucose and fructose as monosaccharides, and sucrose and lactose as disaccharides, are the most abundant sugars in mixed diets. The energy conversion factor used for labelling purposes for dietary carbohydrates including sugars is 4 kcal/g (17 kJ/g).

According to European legislation (Regulation 1169/2011[3]), sugar alcohols (polyols) such as sorbitol, xylitol, mannitol and lactitol, which are low-calorie sugar replacers that can be used in foods also for purposes other than sweetening, are 'carbohydrates' not included under the term 'sugars' and

[1] https://www.efsa.europa.eu/en/people/fpmembers
[2] https://www.efsa.europa.eu/sites/default/files/dcmfoodconsnetworklist.pdf
[3] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.

will not be considered in this opinion. Alongside polyols, other substances used as sugar replacers and other mono- or disaccharides present in the diet in marginal amounts are not included in the term 'sugars' for the purpose of this assessment (e.g. isomaltulose, D-tagatose).

Mono- and disaccharides have very similar chemical structures. Most disaccharides are isomers, with the same molecular weight, almost the same functional groups and only small structural differences which are responsible for differences in sweetness, solubility and chemical reactivity (Pokrzywnicka and Koncki, 2018). Several methods are available for the analysis of sugars in food and beverages (Hadjikinova et al., 2017; Schievano et al., 2017; Pokrzywnicka and Koncki, 2018; Vennard et al., 2019). High-pressure liquid chromatography (HPLC) is mostly used for routine analyses. It allows a simple, rapid and simultaneous determination of several sugars also at quantitative level (Hadjikinova et al., 2017; Pokrzywnicka and Koncki, 2018; Vennard et al., 2019). HPLC is used in connection with several columns and different detectors. Recently, high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) has been endorsed by the AOAC[4] as the official method for sugar profiling in foods and dietary supplements and it is becoming the primary choice for nutrition labelling (BeMiller, 2017; Vennard et al., 2019).

2.2. Definition of the exposure

This scientific assessment addresses total, added and free sugars, as defined in the protocol (EFSA NDA Panel, 2018). Namely, total sugars are all mono- and disaccharides, as defined in Section 2.1, found in mixed diets; added sugars include 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; free sugars include added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates (**Figure 2**).

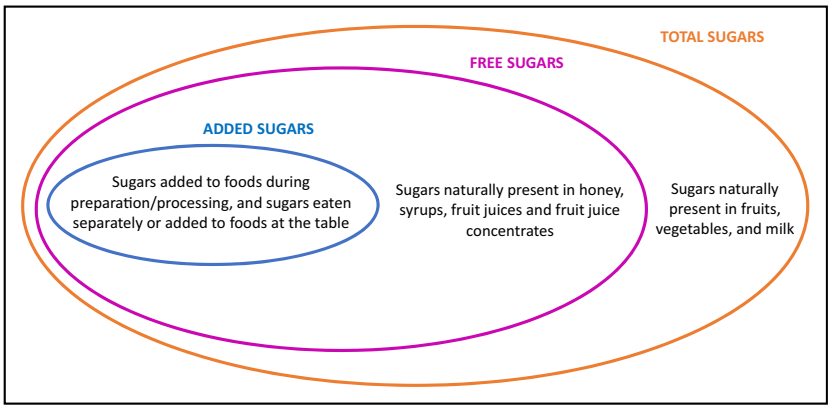


Figure 2: Classification of dietary sugars

3. Physiology and metabolism

3.1. Digestion

Digestion of food functions on two levels, mechanical and chemical. Starting in the mouth, food is mechanically broken down during the process of chewing while salivary amylase, secreted during mastication, initiates the chemical breakdown of starch. In addition to digestive properties, saliva aids in hydrating and lubricating the food to allow for easier swallowing. The partially broken down food, or bolus, travels through the oesophagus which propels it to the stomach. In the stomach, at the mechanical level, peristaltic contractions churn the bolus which allows it to mix with gastric acids, released by parietal cells in the stomach epithelium, resulting in chyme. Food may remain in the stomach from a few minutes up to several hours depending on the amount of food eaten, the physical characteristics and the nutrient composition. As the chyme leaves the stomach, it enters the duodenum, the first segment of the small bowel, where most of the chemical digestion occurs. Already within minutes after swallowing, some of the food enters the duodenum. The pancreas, liver and gall bladder are stimulated to release several enzymes (and bile) that help in digestion.

[4] Available online https://www.eoma.aoac.org/methods/info.asp?ID=52134

Digestible dietary carbohydrates are mainly starch (a polymer of glucose molecules linked by alpha 1-4 and alpha 1-6 glycosidic bonds), disaccharides (sucrose, lactose) and monosaccharides (glucose, fructose). Pancreatic amylase is the primary starch digestive enzyme that cleaves the α 1-4 (but not the α 1-6) glycosidic bonds. End products are maltose, maltotriose and α-limit dextrins, which are small glucose polymers containing α 1-6 glycosidic bonds. Alpha-limit dextrins, maltotrioses and disaccharides are digested into monosaccharides by digestive enzymes present in the brush border membrane of the small bowel: sucrase-isomaltase is involved in the digestion of α-limit dextrins and maltotriose into glucose, and in the digestion of sucrose into glucose and fructose (Boron and Boulpaep, 2016), maltase-glucoamylase in that of maltose into two molecules of glucose, lactase in that of lactose into glucose and galactose and trehalase in that of trehaloseinto two molecules of glucose (Amiri and Naim, 2017). Congenital disaccharidase deficiencies are extremely rare, but lactase expression in the gut decreases drastically during childhood in approximately two-thirds of the world population, leading to adult lactose maldigestion (Storhaug et al., 2017).

Digestion of dietary sugars and starch results in the release of the monosaccharides glucose, galactose and fructose at the surface of small bowel enterocytes.

3.2. Absorption

Sugars (and starch, after digestion to glucose) are absorbed in the blood as monosaccharides. Disaccharides are not absorbed as such, except for traces.

Glucose and galactose are transferred from the gut lumen to the enterocyte by a Sodium-Glucose-coTransporter, SGLT1. This process is driven by the extra-intracellular sodium gradient maintained by the energy-dependent Na^+/K^+ ATPase and results in the complete absorption of glucose and galactose. Fructose is absorbed by facilitated diffusion through a GLUT5 transporter. This absorption depends on the presence of a gut lumen-intracellular fructose gradient and it is not complete. Symptoms of fructose malabsorption frequently occur in individuals with very low fructose intakes but tend to decrease over time upon chronic exposure to fructose due to an increased expression of GLUT5. Co-ingestion of glucose with fructose potentiates fructose absorption, thus decreasing symptoms of fructose malabsorption. Intracellular glucose, galactose and fructose are transported by facilitated diffusion from the enterocyte into the hepatic portal circulation through the same transporter, GLUT2 (Wright et al., 2003).

3.3. Metabolism

Monosaccharides (glucose, fructose, galactose) reaching the hepatic portal circulation are delivered to the liver and eventually entirely metabolised to CO_2 and H_2O.

Glucose can be metabolised in all cells of the human organism. Its metabolism involves a transport from the interstitial fluid to the cell, which is operated by a variety of non-insulin-dependent (mainly GLUT1-3), insulin-responsive (GLUT4) and sodium-glucose (SGLT1-2) membrane transporters. Intracellular glucose is initially metabolised by a member of the hexokinase enzyme family to glucose-6-phopshate (glucose-6-P) (Wilson, 2003). According to the cell type and energy status, glucose-6-P is further metabolised to pyruvate and lactate in the glycolytic pathway, to glucose-1-P and glycogen for storage or metabolised in the pentose monophosphate pathway.

Ingested glucose is already metabolised in part in the gut and liver. Hepatocytes transport glucose through non-insulin-dependent GLUT2 transporters and synthesise glucose-6-P by the enzyme hexokinase IV (also called glucokinase), whose activity is mainly dependent on glucose concentration (Iynedjian, 1993). Glycolysis in the hepatocytes is tightly regulated at the level of the enzyme phosphofructokinase, which is potently inhibited by high intracellular ATP and citrate concentrations. As a consequence, only a portion (usually 10–25%) of absorbed glucose is metabolised in hepatocytes, and the rest escapes hepatic uptake to reach the systemic circulation, where it will increase systemic glycaemia, elicit insulin secretion and stimulate insulin-dependent and non-insulin-dependent glucose disposal in the various organs and tissues (Petersen and Shulman, 2018).

The amount of glucose escaping splanchnic metabolism, thus reaching the systemic circulation and arterial blood can transiently increase blood glucose levels from ca. 5 mmol/L (fasting) to 8–10 mmol/L (postprandial). This increase elicits a marked stimulation of insulin secretion, and arterial glucose will be taken up by peripheral organs, either independently of insulin (brain) or under the control of insulin (skeletal muscle, adipose tissue) (Gerich, 1993).

Different from glucose, fructose cannot be readily phosphorylated by hexokinases and its initial metabolic steps rely on the presence of specific (GLUT5) or non-specific (GLUT2) membrane

transporters (Thorens and Mueckler, 2010) and of specific fructolytic enzymes: ketohexokinase C or fructokinase, which catalyses the conversion of fructose into fructose-1-phosphate (F-1-P); aldolase B, which splits F-1-P into dihydroxyacetone-phosphate and glyceraldehyde, and triokinase, which phosphorylates dihydroxyacetone-phosphate and glyceraldehyde to glyceraldehyde-3-phosphate. Dihydroxyacetone-P and glyceraldehyde-P (triose phosphates) then join the normal glycolytic pathways.

Fructolytic enzymes are expressed in small bowel enterocytes, hepatocytes and kidney proximal tubules, which are the organs primarily involved in fructose metabolism. Part of ingested fructose is already metabolised to glucose (gluconeogenesis), lactate, glyceric acid and fatty acids in small bowel enterocytes. Any fructose escaping gut metabolism reaches the liver through the hepatic portal circulation. In hepatocytes, fructolysis, unlike glycolysis, is not inhibited by intracellular mediators such as ATP or citrate, and almost all fructose transported in liver cells is converted into triose phosphates. An excess of intracellular triose phosphates triggers the synthesis of lactate, glucose, glycogen, glycerol and fatty acids (Ter Horst and Serlie, 2017).

Very little fructose escapes gut and liver metabolism. Fructose concentrations in blood increase transiently up to about 0.5 mmol/L after ingestion of fructose-containing sugars. The fate of this systemic fructose remains unknown. Experiments with intravenous administration of fructose suggest that systemic fructose is mainly metabolised in the kidney (Mayes, 1993), gut and liver, although a portion may also be metabolised in non-fructolytic tissues using alternative metabolic pathways (Helsley et al., 2020). Fructose does not increase blood glucose and insulin concentration to any great extent.

Galactose is almost completely converted into glucose in the liver by way of the Leloir pathway. The enzymes galactose mutarotase, galactokinase, galactose-1-phosphate uridyltransferase and UDP-galactose 4-epimerase are sequentially involved. Defects in the genes encoding for galactokinase, uridylyltransferase or epimerase can lead to galactosaemia, an extremely rare but potentially severe condition (Holden et al., 2003; Sørensen et al., 2011).

Like for fructose, ingestion of a pure galactose load does not increase blood glucose and insulin concentration to any great extent. The concentration of galactose in peripheral arterial blood hardly increases, indicating that the near totality is extracted by splanchnic organs. Tracer experiments with ^{13}C-labelled galactose indicate that ca. 10 g was released into the blood stream as glucose over the 8 h following ingestion of a 50-g galactose load (Gannon et al., 2001).

3.4. Rate of appearance in blood

Glycaemic responses following the intake of carbohydrate-containing foods depend primarily on the amount and type of carbohydrates consumed. Other factors, such as composition (e.g. content of dietary fibre, fat, protein, organic acids and their salts, etc.) and physical properties of the food (e.g. state [liquid, semisolid, solid], cooking methods, processing), which have an impact on gastric emptying, the rate of intraluminal digestion of starches in the gut and the rate of appearance of the mono- and disaccharides at the gut brush border, are also important.

Carbohydrate-containing foods have been classified with respect to their relative impact on blood glucose concentrations by using the glycaemic index (GI), a unitless number between 0 and 100 (Atkinson et al., 2008). Pure glucose is used as reference, while tests are usually standardised to 50 g of digestible carbohydrates.[5] The GIs of pure glucose (100), maltose (~ 105), sucrose (~ 65), lactose (~ 48) and fructose (~ 15), and the GI of different types of honey and syrups diluted in water, mostly reflect their sugars composition. The GI of starchy foods varies widely, from ~ 75 for white wheat bread to ~ 50 for pasta, depending on the rate of digestion of starch among other factors. The glycaemic impact of foods is calculated through the glycaemic load (GL), which accounts for both the GI and the total amount of carbohydrates consumed and is expressed as glucose equivalents.

3.5. Excretion

Trace amounts of disaccharides that reach the systemic circulation are excreted in the urine as such. Glucose reabsorption occurring in the kidneys is almost complete under normal conditions but depends on glycaemia. When blood glucose levels exceed about 10 mmol/L (180 mg/dL), as in uncontrolled diabetes, glucose is lost in urine. The small amounts of galactose and fructose remaining in the systemic circulation after splanchnic extraction and metabolism are filtered in primary urine and

[5] International Organization for Standardization. Food products – Determination of the glycaemic index (GI) and recommendation for food classification: ISO 26642. 1-10-2010.

almost entirely reabsorbed by kidney tubule cells through the SGLT-1 transporter. In normal conditions, only traces of galactose and fructose appear in the urine (Gammeltoft and Kjerulf-Jensen, 1943). When a threshold level of filtered hexoses is reached, as in inherited fructokinase deficiency (essential fructosuria), fructose absorbed in the blood after ingestion is excreted as such in the urine (Tran, 2017).

3.6. Mode(s) of action underlying potential adverse health effects of dietary sugars

3.6.1. Metabolic diseases

Excessive consumption of dietary sugars, and particularly of added sugars, has been proposed to be involved in the development of diet-related chronic diseases (i.e. obesity, diabetes mellitus, dyslipidaemias, hypertension and other cardiovascular diseases) through several mechanisms which are briefly described below.

3.6.1.1. Positive energy balance

A positive energy balance (i.e. energy intake > energy expenditure) is invariably present during the phase of development of obesity. Sugars have been proposed to favour a positive energy balance due to their hedonic properties, leading to an increase in the consumption of energy dense sweet foods and beverages so that energy intake is increased not only due to energy coming from sugars but also from other macronutrients (Freeman et al., 2018; Olszewski et al., 2019).

The mere thought, sight, smell or taste of food starts the cephalic phase of digestion, in which the stomach and gut respond to such stimulus. Nutrient sensing through taste receptors that are located along the entire gastrointestinal tract contributes to the regulation of digestion and impacts on satiety and satiation. Chewing increases the sensory experience of food and contributes to sensory-specific satiation, limiting intake. This sensory experience of (digestion of) food is an important determinant of feeding behaviour and has an impact on deciding what to eat. Sugars stimulate specific taste receptors in the mouth, providing sweet taste and induce nutrient-specific satiation. Nutrient sensing, however, may differ depending on the food source. It has been proposed (although not univocally demonstrated) that sugars in beverages may specifically increase energy intake because liquid foods pass rapidly through the gut limiting sensory detection, such that nutrient sensing impacts less on satiation (de Graaf, 2011; Pan and Hu, 2011).

In addition, stimulation of energy intake may be related to the fact that the fructose component of sugars fails to elicit the release of satiating hormones such as insulin, leptin, PYY or GLP-1 and to inhibit the release of the orexigenic hormone ghrelin (Teff et al., 2004). Compared to glucose, fructose dissolved in water has a lower ability to suppress cerebral blood flow in the hypothalamic nuclei which contribute to the control human feeding behaviour and therefore has been hypothesised to impact less on satiation (Page et al., 2013).

3.6.1.2. Adiposity, ectopic fat deposition, inflammation and insulin resistance

The body stores energy coming from food mainly as fat, primarily in subcutaneous adipose tissue (SAT). Several organs are surrounded by a certain amount of adipose tissue, but these locations are not usually associated with fat storage. Adipose tissue is known to release a large number of adipokines (e.g. hormones, cytokines, extracellular matrix proteins and growth and vasoactive factors) that serve several physiological functions.

Chronic excess energy intake may exceed the storage capacity of SAT, resulting in excessive flow of lipids to other organs. Fat storage shifts then to ectopic sites, including the viscera, liver, muscle, pancreas, kidney, heart and the vascular tree. This phenomenon is collectively described as ectopic fat deposition. Ectopic fat accumulation is associated with adipose tissue dysfunctionality, low-grade local and systemic inflammation, insulin resistance (IR) and end-organ damage (Landecho et al., 2019). It has been postulated that different fat depots may determine different metabolic consequences.

Under conditions of excessive lipid storage, visceral adipose tissue (VAT) contributes to systemic inflammation (through macrophage infiltration and upregulation of the secretion of adipokines). Systemic inflammation and ectopic fat in the liver and skeletal muscle are associated with organ-specific IR, which in turn fosters ectopic fat deposition and inflammation, creating a vicious circle.

Insulin has a central role in glucose and lipid metabolism. Both hepatic and skeletal muscle IR, which can coexist in the same individual to different degrees, induce compensatory hyperinsulinaemia

and increase the risk of developing T2DM. The metabolic response to the intake of dietary sugars (e.g. their effect on glycaemia, insulinaemia, blood lipids), however, can vary widely depending on the metabolic profile of the individual.

The mechanisms by which ectopic fat accumulates and how this affects (and is affected by) IR appear to be tissue specific. In skeletal muscle, altered lipid uptake, impaired capacity to oxidise lipids and accumulation of lipotoxic compounds interfere with insulin signalling and glucose uptake. In the liver, the mechanisms linking lipid metabolism and IR are less well understood. Increased uptake of fatty acids, insulin-induced *de novo* lipogenesis (DNL) and impaired lipid oxidation enhance liver fat accumulation (hepatic steatosis), the main characteristic of non-alcoholic fatty liver disease (NAFLD) (Ipsen et al., 2018). NAFLD can progress to hepatic inflammation and fibrosis (non-alcoholic steatohepatitis, NASH). The prevalence of NAFLD and its progression to NASH is about double in patients with T2DM than in non-diabetic individuals (Cernea and Raz, 2020).

Fructose has been shown to stimulate hepatic DNL to a larger extent than glucose (Hirahatake et al., 2011), and hence has been suspected to be more closely associated with the development of NAFLD (Ter Horst and Serlie, 2017). However, diets supplemented with free fructose or free glucose were shown to have similar effects on intrahepatic fat in short-term experiments in overweight humans. Both free glucose and free fructose increased intrahepatic fat to the same extent when administered in excess of energy needs for weight maintenance but had no effect when administered as part of a weight maintenance diet (Johnston et al., 2013). Ingestion of a hypercaloric high fat diet also increased intrahepatic fat to the same extent as free glucose or free fructose, indicating that energy balance may be a primary determinant of intrahepatic fat concentration (Sobrecases et al., 2010).

Excess VAT, intrahepatic and intramuscular fat are thus strongly associated with systemic metabolic alterations in glucose and lipid metabolism. However, whether ectopic fat in these locations is causally related to the development of systemic metabolic diseases, as well as the relative role of each fat depot, needs to be confirmed (Britton and Fox, 2011). Conversely, ectopic fat depots surrounding the kidney (sinus), the heart and blood vessels and myocardial fat appear to have primarily local effects, inducing organ-specific dysfunction and damage (Britton and Fox, 2011). For example, excess perivascular adipose tissue deposition induces inflammation, oxidative stress, decreased production of vasoprotective adipocyte-derived relaxing factors and increased production of paracrine factors such as resistin, leptin, cytokines (IL-6 and TNF-α) and chemokines. These adipocyte-derived factors initiate and orchestrate inflammatory cell infiltration, including primarily T cells, macrophages, dendritic cells, B cells and NK cells (Nosalski and Guzik, 2017), which negatively impact on the function of the cardiovascular system (Lovren et al., 2015).

It is of note that the preferential storage of fat in non-ectopic vs. ectopic sites depends on several factors, including age, sex, ethnicity, genetic factors, hormonal status, diet and physical activity among others, leading to high inter-individual variability (Trouwborst et al., 2018). For the same age and BMI, VAT, intrahepatic and intramyocellular lipids are higher in men than in women, leading to higher cardiometabolic risk (Schorr et al., 2018).

Short-term intervention studies (3–4 weeks duration) in non-diabetic normal weight and obese individuals have shown that fructose at doses > 80 g/day in isocaloric exchange with other carbohydrates (mainly glucose) increases fasting glucose production and impairs insulin-mediated suppression of hepatic glucose output, indicating hepatic IR. A stimulation of gluconeogenesis may be involved in this process. In hypercaloric conditions, fructose in addition increased fasting serum insulin concentrations. Fructose-induced hepatic IR was, however, not associated with the development of fasting hyperglycaemia in normal weight subjects, or with peripheral (skeletal muscle) IR (Ter Horst et al., 2016). Of interest, consumption of a high fructose but not a high glucose diet for 6 weeks significantly impaired glucose tolerance in overweight subjects (Stanhope et al., 2009). Since impaired suppression of hepatic glucose production is instrumental in the development of impaired glucose tolerance (Mitrakou et al., 1990), this suggests that fructose may specifically be responsible for the development of hepatic insulin resistance. No data are available regarding the effects of a high galactose diet on hepatic insulin resistance.

3.6.1.3. *De novo* lipogenesis

High intakes of sucrose have been shown to increase fasting and postprandial blood triglyceride (TG) concentrations in animal models (Bizeau and Pagliassotti, 2005) and in humans (Stanhope, 2012), most likely due to its fructose component. In humans, fasting and postprandial blood TG concentrations increase at intakes of fructose above 100 g/day and 50 g/day, respectively (Livesey and Taylor, 2008). A higher hepatic DNL, an increased secretion of TG-rich lipoprotein particles (TRL) (VLDL

and chylomicrons) and a lower postprandial clearance of TRL are involved in this process (Chong et al., 2007). Rodent (Federico et al., 2006) and human studies (Theytaz et al., 2014) indicate that intestinal DNL may contribute to this hypersecretion of TRL. Increased TRL concentrations are in turn often associated with increased concentrations of chylomicron remnants, increased concentrations of small, dense LDL particles and low HDL-cholesterol, which may be directly involved in the development of atherosclerotic lesions.

Fructose has also been shown to increase intrahepatic TG concentrations in healthy, normal weight subjects and in overweight subjects within a few days. However, this has been observed only with high amounts of fructose (≥ 30% E) and under hypercaloric conditions (Lecoultre et al., 2013; Yki-Järvinen, 2015).

3.6.1.4. Hyperuricaemia

It has been known for a long time that both ingestion of an acute fructose load and the chronic consumption of a high fructose diet can increase blood uric acid concentrations. Several mechanisms can account for this. After administration of large iv or oral fructose loads, hepatic fructose uptake and phosphorylation to fructose-1-P are markedly increased while the degradation of fructose-1-P to trioses phosphate is slightly delayed. This results in a transient depletion of intrahepatic ATP stores, leading to the formation of AMP and to the degradation of purines (Kedar and Simkin, 2012). In addition, fructose may impair renal uric acid clearance and fractional excretion, as observed in rats (Hu et al., 2009).

Hyperuricaemia is an established risk factor for gout (Shiozawa et al., 2017). The association between high uric acid levels and hypertension, renal disease, cardiovascular diseases (CVD) and T2DM has also been known for some time (Feig et al., 2008a), although it is only recently that the causality of the relationship between serum uric acid levels and the pathogenesis of these diseases has been systematically investigated.

Uric acid levels, even within the normal range, have been proposed as an independent risk factor for the development of primary hypertension, particularly in young individuals. An increase in oxidative stress during uric acid synthesis leading to local and systemic inflammation, reduced availability of nitric oxide and endothelial dysfunction, proliferation of vascular smooth muscle cells and vasoconstriction have been involved in the progression of atherosclerosis. Renal vasoconstriction activates the renin–angiotensin system, increasing blood pressure (Feig et al., 2008a). Uric acid has also been shown to impair insulin-mediated glucose disposal by inducing endothelial dysfunction and by inhibiting insulin-mediated muscle vasodilation (Nakagawa et al., 2005).

Recent meta-analysis of prospective cohort studies has reported dose-response relationships between uric acid levels and risk of both stroke and CHD in both sexes, and the relationship appears to be stronger in women. It is still unclear, however, whether high uric acid levels are independent risk factors for the development of CVD, once traditional risk factors are accounted for (Kuwabara, 2016; Ndrepepa, 2018). The measurement of uric acid in the management of primary hypertension and in the primary prevention of CVD is acknowledged in current European professional guidelines (Williams et al., 2018; Visseren et al., 2021).

3.6.1.5. Other proposed mechanisms

Evidence is mounting that the composition and function of the gut microbiota could play a role in the development of obesity and associated metabolic disorders. The gut microbiome of obese individuals has been shown to be lower in bacterial diversity and gene richness and more capable to harvest energy from the diet than that of normal weight individuals, whereas some bacterial metabolites appear to correlate with metabolic biomarkers of disease (Turnbaugh et al., 2006; Le Chatelier et al., 2013; Vallianou et al., 2019). In addition, dietary factors, including the intake of added sugars, may act as external triggers inducing profound changes in the gut microbiome that have been related to obesity and metabolic disorders (Vallianou et al., 2019). However, the current lack of standards for defining what is considered to be a baseline healthy/stable microbiome precludes linking a particular metabolic disease state with a specific microbiome profile and furthermore establishing any causal relationships.

3.6.2. Pregnancy endpoints

Gestational diabetes mellitus (GDM) is defined as the development of impaired glucose tolerance during pregnancy in a non-diabetic woman. The mechanisms underlying this condition are the existence of a low insulin sensitivity, of a low insulin secretion or both simultaneously in the context of

a diabetogenic stress elicited by the neuroendocrine alterations associated with pregnancy. Obesity and a family history of type 2 diabetes mellitus or GDM are two of many risk factors for the development of GDM. Of note, the occurrence of GDM is itself a risk factor for the development of type 2 diabetes mellitus later in life (Feig et al., 2008b). High intakes of dietary sugars and fats during pregnancy have been associated with increased body weight gain during pregnancy in epidemiological studies. However, evidence is limited to few studies and the role of dietary sugars *per se* on weight gain during pregnancy has not been systematically investigated (Casas et al., 2020).

High birthweight, or macrosomia, is the major complication of diabetes during pregnancy to fetal metabolism. It is secondary to hyperglycaemia-driven fetal hyperinsulinaemia, which stimulates anabolism and the growth of fetal adipose tissue (Kc et al., 2015). High birthweight is widely recognised as a risk factor for later childhood obesity and type 2 diabetes (Wang et al., 2021).

Low birthweight and more specifically a small weight related to gestational age (SGA) occurs because of intrauterine growth retardation (IUGR). It results from chronic fetal undernutrition during gestation, which is most often due to placental insufficiency secondary to decreased uteroplacental blood flow, or to maternal protein/energy undernutrition (Krishna and Bhalerao, 2011). The unfavourable uterine environment causing growth restriction results in programming that predisposes IUGR infants to long-term health issues such as poor physical growth, metabolic syndrome, cardiovascular disease, neurodevelopmental impairment and endocrine abnormalities, warranting careful monitoring (Kesavan and Devaskar, 2019). Accelerated weight gain secondary to catch-up growth is also associated in SGA infants with a higher risk for overweight and obesity later in life (Nordman et al., 2020).

Protein/energy undernutrition during pregnancy is rare in European countries nowadays, and the majority of cases of European intrauterine growth retardation develop as a consequence of pre-eclampsia, a condition of unknown aetiology characterised by increased vascular resistance in placental blood vessels leading to placental hypoperfusion (Huppertz, 2008; Maršál, 2017). Both type 1 and type 2 diabetes increase the risk of pre-eclampsia. Few epidemiological studies have reported a correlation between the intake of dietary sugars and increased risk of pre-eclampsia during pregnancy (Casas et al., 2020). Excess energy intake may also directly contribute to the development of placental insufficiency, as reported in pregnant mice fed a high fat, high sucrose diet (Musial et al., 2017). This may be related to fructose-induced alterations of placental metabolism, including increased uric acid production, lipid accumulation and oxidative stress (Asghar et al., 2016).

3.6.3. Dental caries

Dental caries is the localised loss of dental hard tissues as a result of acids produced by bacterial fermentation of sugars in the mouth. The tooth is composed of three mineralised tissues – enamel, dentine and cementum. Dentine forms the bulk of the tooth including the roots and is covered by a thin layer of cementum. Enamel forms the hard, outer crown of the tooth and comprises hydroxyapatite crystals, composed of calcium and phosphate in a dispersed organic matrix.

The oral cavity contains a diverse microbiota, with a complex biogeography that differs across different areas, but whose dynamic equilibrium appears to be crucial to avoid the onset of specific diseases such as periodontitis and dental caries. Such microbiota, when developed along a tooth surface, constitutes what is clinically known as dental plaque (Kilian et al., 2016; Sanz et al., 2017; Zhang et al., 2018). An essential factor in the aetiology of dental caries is the dental plaque biofilm, which is made up of a pellicle, plaque microbiota and an extracellular matrix. The pellicle, comprised of adsorbed salivary proteins, is the first layer to form onto the enamel surface. Microorganisms then become attached to the pellicle and multiply, forming a continuous layer increasing in depth. The microorganisms make up 70% of plaque. Dental plaque contains over 500 different types of bacteria, yet the majority do not have a direct role in dental caries development but influence the properties of the plaque. Thirty per cent of plaque consists of the plaque matrix which is largely composed of glucans derived from dietary sucrose by the action of glucosyltransferases from plaque bacteria. Mutans streptococci and Lactobacillus acidophilus are major bacteria associated with dental caries playing a key role in the initiation and progression of dental caries; however, many other types of bacteria in the oral biofilm can metabolise sugars to acid (Roberts, 2015). Mutans streptococci produce acids from dietary sugars, synthesise glucan from sucrose and create ideal conditions for other cariogenic bacteria such as lactobacilli, bifidobacteria and some non-mutans streptococci.

Dietary sugars diffuse into the dental plaque where they are metabolised by plaque microorganisms to organic acids (mostly lactic acid) which diffuse into the enamel causing subsurface demineralisation and initiating the caries process (Pitts et al., 2017). Enamel hydroxyapatite usually begins to

demineralise at around pH 5.5, which is sometimes referred to as the 'critical pH'. Saliva contains several buffer systems that increase plaque pH, thus promoting remineralisation in porous areas where demineralisation has occurred. A demineralised lesion may therefore be remineralised in the early stages. However, if acid conditions and resulting demineralisation dominate, the enamel becomes more porous until finally the surface gives way and a cavity forms. The rate of demineralisation is affected by the concentration of hydrogen ions (i.e. pH at the tooth surface) and the duration for which the plaque pH falls below the critical pH. Another factor is the amount of calcium, phosphate and fluoride available in plaque, because high levels of these minerals in plaque will help resist demineralisation. There is some evidence to suggest that sucrose is more cariogenic compared with other mono- and disaccharides partly due to it being the sole substrate for glycan synthesis (Zero, 2004). However, there is not enough evidence to rank the cariogenic potential of sugars and likely no benefit of substituting one for another (Koulourides et al., 1976). In theory, the form of the sugars containing food and its oral retentiveness (stickiness) could impact the cariogenic potential by extending the length of exposure of the acidogenic bacteria to sugars substrate in the mouth. However, epidemiological evidence to support this is lacking.

Dental caries requires sugars and acidogenic bacteria to occur, but is influenced by the composition of the tooth, the quantity and composition of saliva and the time sugars are available for fermentation. Furthermore, behavioural factors, e.g. toothbrushing, interdental cleaning, the use of plaque revealing solutions or fluoride use, can further affect caries incidence, by altering the oral microenvironment, i.e. reducing the amount of plaque on tooth surfaces, making oral hygiene easier or modifying the mineral composition of tooth surfaces and possibly bacterial activity.

4. Dietary sources and intake data

4.1. Dietary sources

Glucose and fructose are found naturally in fruits, berries, some vegetables and honey. Sucrose is naturally present in sugar cane and sugar beet, in honey and in many vegetables, berries and fruits. However, the most prevalent dietary source consists of sucrose added at the table and to processed foods, as a sweetener to improve palatability, as a food preserver and to confer functional characteristics to foods. Galactose is found in fermented and lactase-hydrolysed milks but is rare. Lactose is naturally found exclusively in milk and dairy products (Cummings and Stephen, 2007; EFSA NDA Panel, 2010a).

Maltose and trehalose are naturally present in small amounts in some foods. Maltose is found naturally in e.g. barley, wheat, germinating grain, maltodextrins and glucose syrups, while trehalose is found in yeast products, mushrooms and crustaceans. Trehalose can be used to replace sucrose in foods to reduce the sweet taste while keeping similar technological properties (Cummings and Stephen, 2007; EFSA NDA Panel, 2010a).

Glucose–fructose (or fructose–glucose) syrups[6] are increasingly used as a substitute for sucrose in processed foods and beverages due to their technological characteristics such as longer shelf-life, higher stability in solutions and lower price. These syrups are derived from the hydrolysation of starch into individual glucose units, about half of which are then enzymatically converted to fructose. In the United States, such syrups are known as 'high fructose corn syrups' (HFCS) as they are produced from corn, and to differentiate them from corn syrups, which contain 100% glucose. In the EU, where glucose–fructose syrups are consumed three times less frequently than in the United States (kg/capita), they are not necessarily produced from corn, and are referred to as 'isoglucose'[7]. The percentage of fructose contained in the syrups varies across countries and no defined composition is available. Typically, most syrups contain either 42% fructose, as those used in processed foods, or 55% fructose, as those used in SSBs. Compared to sucrose (50% glucose and 50% fructose), the proportion of the two monosaccharides is fairly similar, but in HFCS and isoglucose, they are not bound together (free monosaccharides). Following the abolition of the EU sugar quota system in 2017, which had controlled the sugar market since 1968, sugar production and exports are no longer limited. It has been estimated that, by 2026 (i.e. within 10 years from the sugar quota abolition), the internal production of isoglucose will more than double, reaching 10% of the EU sweetener market. Consumption of free fructose in Europe is likely to increase in parallel (Sanders and Lupton, 2012;

[6] Council Directive 2001/111/EC of 20 December 2001 relating to certain sugars intended for human consumption.
[7] Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (Single CMO Regulation) – Part II.

European Commission, 2017,2018). Free fructose is generally perceived as sweeter than sucrose in foods and beverages on a weight basis (Hobbs, 2009).

4.2. Methodological considerations

Estimates of intake of total, added and free sugars from all dietary sources were obtained using data from the EFSA Comprehensive Food Consumption Database in combination with the food composition databases for total, added and free sugars as described in the protocol and illustrated in **Figure 3**. The methodology used is fully described in **Annex B**.

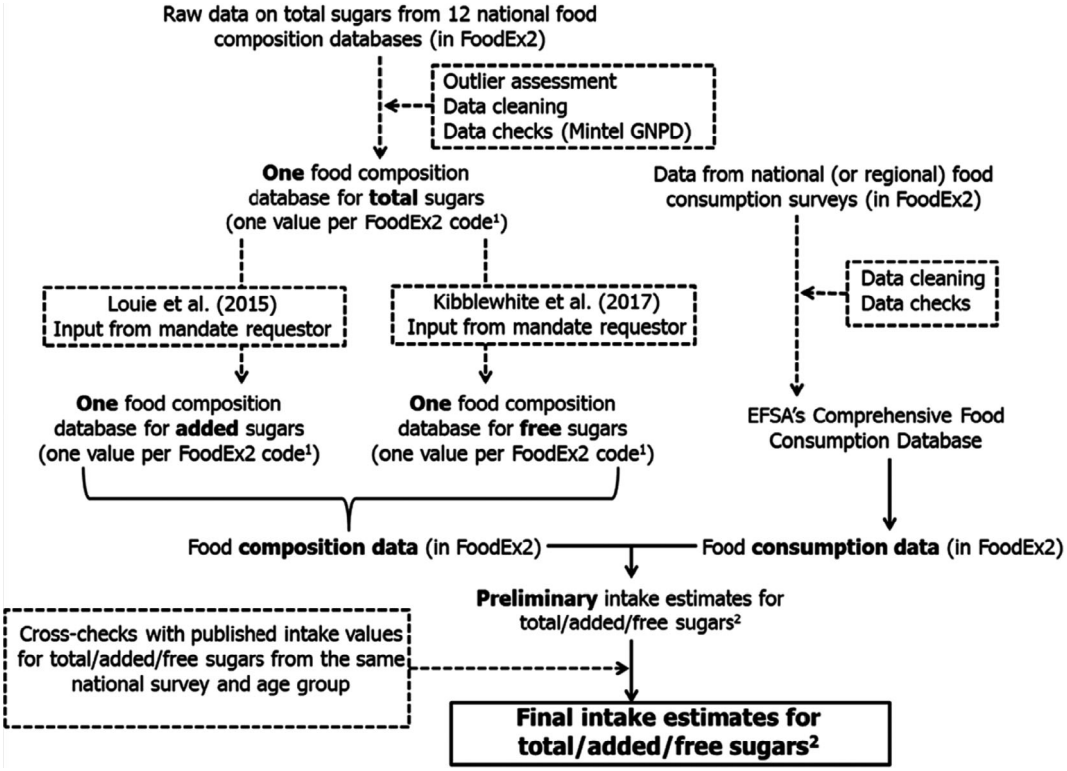


Figure 3: Methodology used to estimate intakes of total, free and added sugars in European countries

Solely for the purpose of developing the food composition databases for added and free sugars, the definitions of added and free sugars were modified as illustrated in **Figure 4**. This is because the exact product consumed was not specified at national level (e.g. cookies, with no specification of the type or brand), so that the ingredient used for sweetening purposes (e.g. sucrose, fructose, syrups, honey, fruit juice concentrates, other) was not specified, and thus, the amount of added and free sugars originating from the different ingredients could not be assigned.

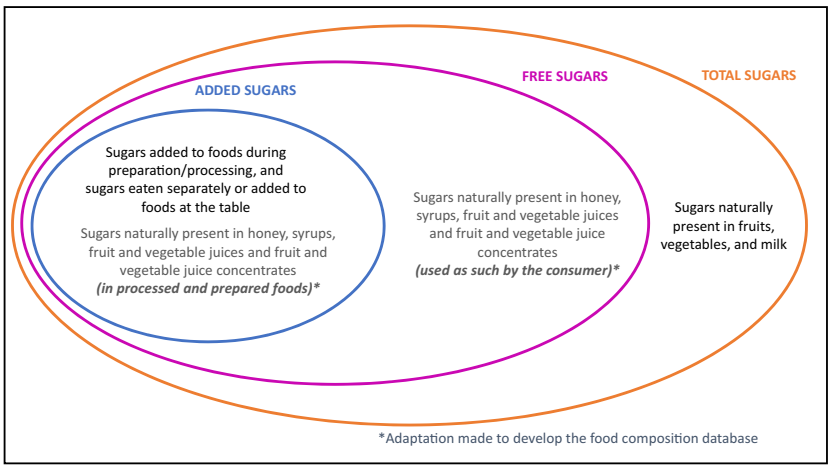


Figure 4: Adaptation of the definitions of added and free sugars for the development of the food composition database

The procedure by Wanselius et al. (2019) developed from previous methods for estimation of added sugars content in foods by Louie et al. (2015) and for estimation of free sugars content by Kibblewhite et al. (2017) was systematically used as the basis for the estimation of added and free sugars.

The food composition databases on total, added and free sugars and details on the characteristics of the food consumption surveys included in the EFSA Comprehensive European Food Consumption Database that was used to estimate intakes of dietary sugars (name, population group covered, number of subjects, number of consumption days recorded and dietary method used) can be found in **Annex C. Annex C** also includes information on the FoodEx2 levels and corresponding categories used to link food composition and food consumption data (i.e. linking categories). Intake estimates of total, added and free sugars in the whole population and in consumers of selected food groups are in **Annex D** and **Annex E**, respectively. Data are provided by age group, consumption survey and country.

Data on the content of single mono- and disaccharides in foods in the EFSA Nutrient Composition Database are scarce and not adequate to provide estimates of intake for individual types of sugars. This paucity of data was confirmed in the questionnaires completed by the National Competent Authorities of European Countries (**Annex F**).

The latest version of the EFSA Comprehensive Food Consumption Database, updated in 2020, contains results from a total of 69 different dietary surveys carried out in 25 different European countries covering 134,929 individuals. Consumption data were collected using repeated 24-hour dietary recalls or dietary records covering from 2 to 9 days per subject. Because of the differences in the methods used for data collection, direct country-to-country comparisons are not always possible. In addition, data on total energy intake reported by data providers were used to calculate intakes of dietary sugars as E%. Since different methodologies, assumptions and national food composition databases may have been used to calculate energy intakes for each survey, between-country comparisons for sugars intakes expressed as E% should be read with caution.

Food groups contributing to the intake of dietary sugars have been constructed by clustering the linking categories in different ways (**Table 2**). For the whole population, the purpose was to identify major sources of dietary sugars and calculate intakes of sugars coming from both core food groups (i.e. food groups supplying most macro- and micronutrients in the diet as recommended in FBDGs) and non-core food groups (i.e. food groups that could be removed from the diet without substantially affecting its nutritional quality and for which FBDGs generally advise to limit consumption). Non-core food groups being major contributors to the intake of added and free sugars have been broken down further to identify consumer groups of interest (consumers). The Panel acknowledges that the above-mentioned classification is functional to this opinion, and that the contribution of specific foods to nutrient intakes may differ across population groups and countries depending on dietary patterns and traditions.

Table 2: Food groups contributing to the intake of dietary sugars in the whole population and food groups used to define consumer groups[(a)]

Food groups (whole population)		Food groups (consumers)	
Short name	**Description**	**Short name**	**Description**
SUGARS AND CONFECTIONERY	Sugar and similar (i.e. table sugar, honey and syrups), confectionery and water-based sweet desserts	SUGAR AND SIMILAR	Table sugar, honey and syrups
		CONFECTIONERY	Confectionery and water-based sweet desserts
SSSD+SSFD	Soft and fruit drinks sweetened with sugar	SSSD+SSFD	Soft and fruit drinks sweetened with sugar
FINE BAKERY WARES	e.g. cakes, biscuits, pastries	FINE BAKERY WARES	e.g. cakes, biscuits, pastries
FRUIT/VEG JUICES	Fruit/vegetable juices and nectars	FRUIT/VEG JUICES	Fruit/vegetable juices and nectars
FRUIT/VEG_processed	Processed fruits and vegetables excluding beverages		
FRUIT/VEG_fresh	Fresh fruits, vegetables		
CEREALS	Cereal and cereal-based products including bread but excluding fine bakery wares		
MILK AND DAIRY	Milk and dairy products including dairy alternatives		
BABY FOODS	Foods for infants and young children		
ALCOHOLIC BEV	Alcoholic beverages		
OTHERS	Others		

(a): Detailed composition of each food group could be found in **Annex D (Tables 6, 7 and 8)**.

The intake of 'fruit and vegetable juices' was estimated together. In about 88% of the consumption occasions, these were coded by data providers as fruit juices, which in FoodEx2 are 100% fruit juices, with no added sugars. The remaining consumption occasions were coded as fruit nectars (25–99% fruit, with added sugars; 3%), vegetable juices (2%), mixtures of fruit and vegetable juices (0.5%), or by using FoodEx2 codes at higher levels that made it impossible to identify whether the juices consumed were with added sugars or not (e.g. 'fruit juices and nectars', 7%). Therefore, consumption of 'fruit and vegetable juices' mostly refers to fruit juice with no added sugars (100% fruit juice). It is important to highlight that participants in the food consumption surveys might not have the knowledge or information to differentiate between fruit juices with no added sugars and fruit nectars with added sugars, and/or the question in the food consumption survey may have not been specific enough to retrieve that information. The Panel notes that consumption of fruit nectars is likely to have been underestimated using the EFSA Comprehensive Database and the consumption of 100% fruit juices overestimated leading to underestimation of the intake of added sugars from 'fruit and vegetable juices', whereas the intake of free sugars is not affected by this uncertainty.

4.3. Estimates of intake of total, free and added sugars from all dietary sources

Intakes of total, free and added sugars by European country and population group in grams per day, as E%, and as non-alcohol E%, both from all sources and from specific food groups, as well as the percent contribution of these food groups to the total intakes, are shown in **Annex D**.

Intakes of added and free sugars by country and population group in grams per day, as E%, and as non-alcohol E% are also provided for consumers in relation to five food groups which have been identified as major contributors to the intake of added and free sugars. Consumers were defined as subjects who had consumed at least one food product within the food group at least once within the survey period. The percent contribution of each food group to the intake of free and added sugars from all sources in consumers of the food category only is provided in **Annex E**.

A summary of the intake of total, added and free sugars from all sources in g/day across European surveys by population group and sex is given in **Tables 3** and **4**, and as percent of total energy (E%) for both sexes combined in **Table 5**.

Table 3: Daily intakes of total, free and added sugars across European dietary surveys by population group – females

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 month to < 12 month (n = 13)	39	87	78	103	1	18	5	44	1	14	4	35
Toddlers, ≥ 12 month to < 36 months (n = 16)	58	100	93	141	11	54	31	104	8	39	21	89
Other children, ≥ 3 to < 10 years (n = 19)	61	116	97	179	29	79	61	135	22	67	49	120
Adolescents, ≥ 10 to < 14 years (n = 19)	69	126	107	214	31	89	74	156	25	77	59	145
Adolescents, ≥ 14 to < 18 years (n = 17)	56	118	96	210	25	78	65	177	21	68	58	145
Adults, ≥ 18 years to < 65 (n = 22)	59	119	101	215	24	67	61	166	19	51	50	125
Older adults, ≥ 65 years (n = 21)	54	109	96	185	17	53	52	122	13	43	43	95
Pregnant women (n = 5)	71	97	117	163	32	50	76	113	25	44	66	92
Lactating women (n = 2)	95	112	144	190	50	52	90	118	27	43	60	98

(a): The 95th percentile estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

Table 4: Daily intakes of total, free and added sugars across European dietary surveys by population group – males

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 month to < 12 month (n = 13)	43	81	81	132	2	19	9	41	1	14	8	35
Toddlers, ≥ 12 month to < 36 month (n = 16)	62	105	96	154	14	68	37	105	10	45	27	92

Population group, age range (n surveys)	Total sugars (g/day)				Free sugars (g/day)				Added sugars (g/day)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Other children, ≥ 3 to < 10 years (n = 19)	67	134	101	220	31	86	62	156	23	74	46	139
Adolescents, ≥ 10 to < 14 years (n = 19)	67	142	130	258	27	104	85	178	22	92	72	178
Adolescents, ≥ 14 to < 18 years (n = 17)	78	148	146	284	36	109	95	252	30	96	77	174
Adults, ≥ 18 to < 65 years (n = 22)	68	131	132	270	29	86	72	219	24	67	70	163
Older adults, ≥ 65 years (n = 21)	59	117	105	206	17	63	51	142	11	51	43	131

(a): The P95 estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

Table 5: Daily intakes of total, free and added sugars across European dietary surveys by population group – males and females combined[a]

Population group, age range (n surveys)	Total sugars (E%)				Free sugars (E%)				Added sugars (E%)			
	Mean		P95[a]		Mean		P95[a]		Mean		P95[a]	
	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥ 4 to < 12 month (n = 13)	24	44	36	94	1	11	4	31	1	11	3	30
Toddlers, ≥ 12 months to < 36 month (n = 15)	20	32	30	50	4	18	10	36	3	13	8	29
Other children, ≥ 3 to < 10 year (n = 16)	16	31	23	43	8	20	14	33	6	17	11	28
Adolescents, ≥ 10 to < 14 years (n = 15)	15	26	23	41	8	18	15	30	5	16	12	28
Adolescents, ≥ 14 to < 18 year (n = 13)	14	26	23	45	8	18	15	38	6	15	13	27
Adults, ≥ 18 to < 65 year (n = 17)	12	25	23	42	6	15	13	33	5	10	12	23
Older adults, ≥ 65 year (n = 17)	13	23	25	36	4	11	11	24	3	9	9	18
Pregnant women; 5 (n = 4)	14	21	23	32	6	10	14	22	5	9	10	20
Lactating women (n = 2)	19	23	30	34	10	10	19	21	6	8	11	18

(a): The P95 estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently were not considered in this table.
(b): Minimum (min) and maximum (max) means and 95th percentiles across European surveys, for each age class.

The population group 'elderly adults' defined in the protocol encompasses the age categories 'elderly' and 'very elderly' described in the EFSA Comprehensive database (EFSA, 2011). Individuals aged 65 years and older will be referred to as older adults in this opinion.

A summary of the intake of total, added and free sugars from specific food groups across European surveys by population group can be found in **Appendix A**. A summary of the intake of added and free sugars from the five food groups contributing the most to the intake of added and free sugars in consumers across European surveys by population group is depicted in **Appendix B**.

4.3.1. Adults and older adults

4.3.1.1. Whole population

In adults, mean intakes of total, added and free sugars in absolute amounts were higher in males than in females within each survey, as expected from the higher body size and energy intake, whereas mean intakes of total sugars as E% were systematically higher in females than in males.

For **total sugars**, mean intakes ranged from 12 E% in Croatian males to 25 E% in German females. The P95 ranged from 23 to 42 E%. Overall, the major contributor to total sugars intake was fresh fruits and vegetables (from 14% in the Netherlands to 39% in Romania), followed by sugars and confectionery (from 11% in Slovenia and Sweden to 29% in Hungary) and milk and dairy products (from 10% in Latvia and Romania to 26% in Finland). The contribution of cereals, processed fruits and vegetables and alcoholic beverages to the intake of total sugars was low (≤ 9% each), as well as the variability across countries. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy and cereals) to the intake of total sugars ranged between 31% in Germany and 54% in Spain, whereas the contribution of beverages (i.e. SSSD, SSFD, fruit and vegetable juices) ranged from 8% in Italy to 29% in Germany **(Annex D)**.

Mean intakes of **added and free sugars** ranged from 4 E% in Cypriot females to 10 E% in Dutch males and females, and from 5 E% in Croatian males to 15 E% in German females, respectively. The P95 ranged from 12 to 23 E% and from 13 to 33 E%, respectively. By definition, the food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% to 5 E% (P95 from 1 E% to 24 E%). The major contributor to the intake of added sugars in virtually all countries was sugar and confectionery (from 20% in Austria to 57% in Italy), followed by SSSD+SSFD (from 8% in Latvia and Italy to 34% in Belgium) and fine bakery wares (from 2% in Denmark to 30% in Austria), with high variability across countries. The contribution of cereals (≤ 9%), fruit and vegetable juices (≤ 5%) and alcoholic beverages (≤ 3%) to mean intakes of added sugars was low, with low variability across countries. The contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) to the intake of added sugars ranged between 8% in Latvia and 35% in Croatia, whereas their contribution to the intake of free sugars ranged from 16% in Italy and Latvia to 46% in Germany **(Annex D)**.

In the older adults, mean and P95 intakes of total, added and free sugars as E% were comparable to those in adults, but generally lower. Beverages combined contributed less to **total** sugars intake (between 4% in Italy and 15% in Germany), particularly SSSD+SSFD, while core food groups combined contributed more (from 37% in Austria up to 66% in Greece). Sugars and confectionery contributed more to **added** sugars intake (between 10% in Austria and 66% in Italy), as well as fine bakery wares and processed fruits and vegetables (from 2% in Denmark to 45% in Austria and from 2% in Portugal to 26% in Sweden, respectively), while the contribution of beverages combined was lower (from 3% in Finland to 22% in Cyprus and Romania).

4.3.1.2. Consumers of selected food groups

In adults, intakes of added and free sugars from all sources and from food groups identified as the major contributors to the intake of added and free sugars in the whole population have also been calculated for the population of consumers of each food group **(Appendix B, Annex E)**. In virtually all countries, mean intakes of added and free sugars from all sources (g/day) were higher in adult consumers of SSSD+SSFD than in consumers of any other food group. Exceptions were Czech Republic, Hungary, Romania and the United Kingdom, where the highest intakes of added and free sugars were among consumers of confectionery, and the Netherlands, where the highest intakes of free sugars were among consumers of fruit and vegetable juices. Intakes of added sugars were higher from SSSD+SSFD than from any other food group in consumers in all countries (mean intakes up to 40 g/day, P95 up to 123 g/day). Likewise, intakes of free sugars were higher from SSSD+SSFD than from any other food group in consumers in most countries, except for Finland and Germany. In these

countries, intakes of free sugars were higher from fruit and vegetables juices than from any other food group in consumers, with mean intakes of 27 g/day (P95 76 g/day) and 45 g/day (P95 134 g/day) in Finland and Germany, respectively. The contribution of SSSD+SSFD to added sugars and of fruit and vegetables juices to free sugars was up to 51% and up to 46%, respectively, in consumers of these beverages.

As for adults, **older adults** consumers of SSSD+SSFD had generally the highest mean intakes of added and free sugars from all sources (g/day). Intakes of added sugars from SSSD+SSFD and of free sugars from fruit and vegetable juices were higher than from any other food group in consumers in most countries, but lower than in adults (up to 25 g/day, P95 up to 71 g/day and up to 30 g/day, P95 up to 94 g/day, respectively). SSSD+SSFD contributed slightly more to added sugars intake (up to 53%) and fruit and vegetable juices slightly less to free sugars intake (from 2% to 42%) in consumers of these beverages in the older adults compared to adults **(Appendix B, Annex E)**.

4.3.2. Infants

4.3.2.1. Whole population

In infants aged from ≥ 4 to < 12 months, mean intakes of total, free and added sugars in absolute amounts were generally higher in males than in females, but comparable between sexes when expressed as E% (differences up to ±1 E% in most countries), with few exceptions.

Mean **total sugar** intake as E% ranged from 24 E% in Italian females and Danish males, to 44 E% in German males and females. The P95 ranged between 36 E% and 94 E%. The major contributors to total sugar intake where baby foods (from 12% in Latvia to 65% in France), milk and dairy (from 13% in Finland to 60% in Estonia), followed by fresh fruits and vegetables (above 10% in all countries but France and Estonia, where it was only 3% and 8%, respectively, and up to 28% in Slovenia). The contribution of SSSD+SSFD (≤ 3%), cereals (≤ 3%) and fine bakery wares (≤ 4%) to the mean intake of total sugars was low. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy, cereals and baby foods) to the intake of total sugars ranged between 66% in Bulgaria and 97% in Portugal and Estonia, whereas the contribution of SSSD+SSFD and fruit and vegetable juices combined was ≤ 9% in all countries **(Annex D)**.

Mean intakes of **added and free sugars** in infants ranged from ≅ 0 E% in Cypriot females to 11 E% in Finnish males, and from 1 E% in Cypriot and Estonian males and females and Spanish females to 11 E% in Finnish males, respectively. The P95 for added sugars ranged between 3 E% and 30 E% and for free sugars from 4 E% to 31 E%, respectively. The food groups contributing the most to the difference between the intake of added and free sugars were sugars and confectionery (intake from ≅ 0E% to 9 E%, P95 from ≅ 0 E% to 22 E%), owing to the contribution of honey and syrups to the intake of free (but not added) sugars, and fruit and vegetable juices (intake from ≅ 0 E% to 2 E%, P95 from ≅ 0 E% to 14 E%). The contribution to mean added sugars intake of fruit and vegetable juices, processed fruits and vegetables, SSSD+SSFD and cereals was low in most countries (≤ 6%, ≤ 9%, ≤ 9% and ≤ 10%, respectively), with exceptions for fruit and vegetable juices (up to 23% in Italy), processed fruits and vegetables and cereals (up to 19% and 16% in Estonia, respectively), and for SSSD+SSFD (up to 25% in Germany). The contribution of baby foods to the mean intake of added sugars was very variable across countries, owing to the high heterogeneity of the individual foods grouped under this category and to differences in food choices among countries (e.g. selection of regular foodstuffs vs. foods specially formulated for infants and young children). It ranged from ≅ 0 E% in Bulgaria, Denmark, Latvia, Portugal, Finland and Spain, where only consumption of baby foods with no added or free sugars was reported, to 52% in France **(Annex D)**.

Major contributors to the intake of **added** sugars, with high variability across countries, were milk and dairy (from 3% in Bulgaria and Italy to 58% in Spain), sugars and confectionery (from 1% in Spain and Portugal to 72% in Bulgaria) and fine bakery wares (from 0% in Italy to 36% in Portugal). In Finland, foods were disaggregated into their main components by the data providers **(Annex B)**, and consequently, the contribution from sugars and confectionery to added sugar intake was 82%, whereas the contribution from fine bakery wares and milk and dairy was 0%. In most countries, consumption of SSSD+SSFD in infants was negligible (≤ 1%). Among countries reporting any significant consumption of these beverages, the contribution of SSSD+SSFD and fruit and vegetable juices combined to the intake of added sugars ranged from 1% in Denmark and Estonia to 25% in Germany. The contribution of these beverages combined to the intake of free sugars ranged from 2% in Finland to 37% in Germany **(Annex D)**.

4.3.2.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) in infants were higher in consumers of SSSD+SSFD than in consumers of any other food group in all countries with a significant consumption of these beverages. The exceptions were the United Kingdom and Slovenia, where confectionery was the highest contributor to the intake of free sugars from all sources. Mean intakes of added and free sugars were, in most countries, higher from SSSD+SSFD (added sugars: intake up to 31 g/day, P95 up to 6 g/day and free sugars: up to 35 g/day, P95 up to 7 g/day) than from any other food group in consumers. The contribution of SSSD+SSFD to added sugar intake and free sugar intake in consumers was up to 100% (Portugal) **(Appendix B, Annex E)**.

4.3.3. Toddlers and children

4.3.3.1. Whole population

In toddlers (12 to < 36 months) and in other children (≥ 36 months to < 10 years, from now on children), mean intakes of total, free and added sugars in absolute amounts were generally higher in males than in females, but comparable between sexes when expressed as E% (differences up to ±1 E% in most countries), with few exceptions.

In **toddlers**, mean **total sugar** intakes as E% ranged between 19 E% in Italian females and 33 E% in German males. The P95 ranged between 30 E% and 50 E%. The major contributor to total sugar intake was milk and dairy in almost all countries (from 17% in Cyprus to 37% in Portugal), followed by fresh fruits and vegetables (from 9% in France to 30% in Slovenia) and baby foods (from 1% in Denmark to 32% in Cyprus) with high variability across countries. The contribution of cereals and fine bakery wares to total sugar intake was low, with low variability across countries (≤ 6% and ≤ 10%), followed by processed fruits and vegetables (≤ 14%). The contribution of SSSD+SSFD to the intake of total sugars was ≤ 8% in all countries but Germany and the Netherlands (16% and 19%, respectively). Fruit and vegetable juices contributed generally more to total sugar intake (from 3% in the United Kingdom (DNSIYC 2011) and Portugal to 19% in Belgium and Bulgaria) than SSSD+SSFD, with high variability across countries. Collectively, the contribution of core food groups (i.e. fresh fruits and vegetables, milk and dairy, cereals and baby foods) ranged between 45% in Bulgaria and 84E% in Portugal, whereas the contribution of beverages (i.e. SSSD, SSFD, fruit and vegetable juices) ranged between 4% in Finland and 29% in Germany **(Annex D)**.

Mean intakes of **added and free sugars** in toddlers ranged from 2 E% in Cypriot females to 13 E% in German males and females and Dutch females, and from 3 E% in Cypriot females to 18 E% in German males, respectively. The P95 ranged between 8 E% and 29 E% for added sugars and between 10 E% and 36 E% for free sugars. The food groups contributing the most to the difference between the intake of added and free sugars were fruit and vegetable juices (mean intake of free sugars from 0 E% to 4 E%, P95 from 2 E% to 24 E%). The major contributors to added sugars intake were sugars and confectionery (< 10% only in Spain and Cyprus, and up to 49% in Denmark), milk and dairy (< 10% only in Bulgaria, and up to 48% in Spain) and fine bakery wares (≥ 10% in all countries but Denmark, Estonia and Finland, and up to 34% in Cyprus), with high variability across countries. The contribution to mean added sugars intake of fruit and vegetable juices, processed fruits and vegetables, baby foods and cereals was low in most countries (≤ 5%, ≤ 7%, ≤ 8% and ≤ 8%, respectively), with exceptions for fruit and vegetable juices and baby foods (up to 20% and 15%, respectively, in Italy), processed fruits and vegetables (up to 15% on Latvia) and for cereals (up to 20% in Cyprus). In Finland, where foods were disaggregated by the data providers (Section 5.2), the contribution from sugars and confectionery to added sugars intakes was 61%, whereas the contribution from baby foods and fine bakery wares was negligible. The contribution of SSSD+SSFD to added sugar intakes was < 10% in half the countries and ranged from 0% in Finland to 42% in the Netherlands, with high variability across the countries. The contribution of beverages combined to added and free sugar intakes ranged from 0% in Finland to 44% in the Netherlands, and from 13% in Finland to 53% in Germany, respectively **(Annex D)**.

In children, despite a generally lower intake of total sugars as E%, mean intakes of added and free sugars were generally higher than in toddlers. Compared to toddlers, beverages combined contributed more (up to 32% in Germany (VLS)) to total sugars intake, whereas the contribution of core food groups combined (i.e. fresh fruits and vegetables, milk and dairy, cereals) was lower (from 37% in Germany (ESKIMO) to 65% in Cyprus). Baby foods, barely consumed by this population group, were combined with other minor contributors to the intake of total sugars in the miscellaneous group 'others'. As in toddlers, milk and dairy contributed the most to the intake of total sugars (up to 40%),

but its contribution was lower in children than in toddlers in most countries, with few exceptions. The contribution of SSSD+SSFD to added sugar intakes in children (up to 39% in the Netherlands) was generally higher compared to toddlers in almost all countries. The food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% in Portugal to 5 E% in Germany (ESKIMO) and Finland (P95 from 6 E% to 22 E%). There was a general trend towards a higher contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) to added and free sugar intakes in children compared to toddlers in most countries (up to 24% higher in Denmark and up to 26% higher in Finland, respectively). Notable exceptions in children were two countries where the very high contribution of beverages to added and to free sugars intakes reported in toddlers dropped slightly (up to 40% in the Netherlands and up to 44% in Germany (ESKIMO), respectively) **(Annex D)**.

4.3.3.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) **in toddlers** were higher in consumers of SSSD+SSFD and in consumers of confectionery than in consumers of any other food group in almost all countries **(Appendix B, Annex E)**. Exceptions were Finland, where the highest mean intakes of added sugars were among consumers of fine bakery wares, and Estonia and the United Kingdom (NDNS 1–3),[8] where the highest intakes of free sugars were among consumers of fruit and vegetable juices. Mean intakes of added and free sugars were, respectively, higher from SSSD +SSFD (up to 21 g/day, P95 up to 59 g/day) and fruit and vegetable juices (up to 24 g/day, P95 up to 47 g/day) than from any other food group in consumers, with a few exceptions. The contribution of SSSD+SSFD to added sugar intake and of fruit and vegetable juices to free sugar intake in these consumer groups was, respectively, up to 46% and up to 48%.

Mean intakes of added sugars from all sources (g/day) **in children** were mainly higher in consumers of SSSD+SSFD than in consumers of any other food group, while mean intakes of free sugars were highest in consumers of SSSD+SSFD or fruit and vegetable juices, with few exceptions. Intakes of added and free sugars in children were higher from SSSD+SSFD (mean intakes up to 29 g/day, P95 up to 67 g/day and up to 31 g/day, P95 up to 72 g/day, respectively) than from any other food group in consumers in most countries. The contribution of SSSD+SSFD to the mean added and free sugars intakes in these consumer groups was up to 41% and up to 38%, respectively **(Appendix B, Annex E)**.

4.3.4. Adolescents

4.3.4.1. Whole population

In adolescents aged ≥ 10 to < 14 years (younger adolescents), mean intakes of total, added and free sugars in absolute amounts (g/day) were the same or higher in males than in females in most countries, while in adolescents aged ≥ 14 to < 18 years (older adolescents), as in adults, they were higher in males than in females in all countries. Mean intakes of total sugars as E% were the same or higher in females than in males (up to +5 E%) in older and younger adolescents, with few exceptions in younger adolescents only.

In **younger adolescents**, mean intakes of **total sugars** ranged from 15 E% in Cypriot and Italian males and females to 27 E% in Estonian males and females and Finnish males. The P95 ranged from 23 to 41 E%. The major contributors to mean total sugar intake were milk and dairy (from 11% in Austria to 32% in Finland), fresh fruits and vegetables (from 8% in Sweden to 26% in Estonia[9]), sugars and confectionery (from 7% in Spain to 24% in Germany) and SSSD+SSFD (from 3% in Latvia to 27% in the Netherlands). The contributions from alcoholic beverages (≤ 2%), processed fruits and vegetables (≤ 11%) and cereals (≤ 12%) were low, with low variability across countries. Collectively, the contribution from core food groups (i.e. fresh fruits and vegetables, milk and dairy and cereals) was between 33% in Belgium and 58% in Greece. The contribution from SSSD+SSFD and fruit and vegetable juices combined to total sugars intake ranged from 14% in Latvia to 34% in the United Kingdom and the Netherlands **(Annex D)**.

Mean intakes of **added and free sugars** in younger adolescents ranged from 5 E% in Cypriot males to 16 E% in Dutch males, and from 8 E% in Cypriot and Italian males and females to 19 E% in Dutch males, respectively. The P95 ranged from 12 to 28 E% for added sugars and from 15 to 30 E%

[8] NDNS ROLLING PROGRAMME YEARS 1-3.
[9] DIET-2014-EST-C.

for free sugars. The food group contributing the most to the difference between the intake of added and free sugars was fruit and vegetable juices, the intake of which ranged from 1 E% in the Czech Republic to 5 E% in Germany (P95 from 5 to 22 E%). The major contributors to mean added sugars intake were sugars and confectionery (from 13% in Portugal to 56% in Finland) and SSSD+SSFD (from 7% in Latvia to 41% in the Netherlands), followed by fine bakery wares (≥ 10% in most countries and up to 32% in Greece) and milk and dairy (≥ 10% in most countries and up to 26% in Spain). The lowest contributions to mean added sugar intakes were from alcoholic beverages (≤ 1%), cereals (≤ 11% in all countries but Cyprus, where it was 23%), processed fruits and vegetables (≤ 11%) and fruit and vegetable juices (≤ 12%). The contribution from beverages to added and free sugar intakes ranged between 10% in Cyprus and 42% in the Netherlands, and between 24% in Latvia and 49% in the United Kingdom, respectively **(Annex D)**.

In older adolescents, mean intakes of total, added and free sugars as E% were comparable to those of younger adolescents in all countries. Only in Germany, the P95 for total and free sugars were notably higher (up to 46 E% and 39 E% in females, respectively). The contribution from beverages combined to the intake of total and free sugars was similar in younger and older adolescents in all countries but Germany, where for older adolescents it was as high as 43% and 59%, respectively **(Annex D)**.

4.3.4.2. Consumers of selected food groups

In younger adolescents, no consistent pattern was found when calculating the highest mean intake of added and free sugars from all sources (g/day) for the consumers of different food groups, by country. For example, in Finland, the highest mean intake of added and free sugars from all sources was reported for consumers of fine bakery wares, whereas in Spain, the highest mean intake of added and free sugars from all sources was reported for consumers of confectionery and in Germany for consumers of SSSD+SSFD **(Appendix B, Annex E)**. Intakes of added sugars from SSSD+SSFD in consumers were higher than intakes from any other food group (mean intakes up to 37 g/day, P95 up to 97 g/day), whereas intakes of free sugars from either SSSD+SSFD (up to 39 g/day, P95 101 g/day) or fruits and vegetable juices (up to 26 g/day, P95 71 g/day) were higher than from any other food group in consumers in most countries. The contribution of SSSD+SSFD to added and free sugars intake was up to 56% and up to 47% in this consumer group, respectively.

In older adolescents, mean intakes of added and free sugars from all sources (g/day) were higher in consumers of SSSD+SSFD than in consumers of any other food group in most countries. Mean intakes of added sugars were higher from SSSD+SSFD than from any other food group in consumers (up to 40 g/day, P95 up to 118 g/day) whereas the highest intakes of free sugars were from either SSSD+SSFD (up to 41 g/day, P95 up to 118 g/day) or fruits and vegetable juices (up to 55 g/day, P95 146 g/day), with a few exceptions. These intakes were generally higher compared to younger adolescents. The contribution of SSSD+SSFD to added and free sugars intake was also higher than in younger adolescents (up to 59% and up to 48% in this consumer group, respectively) **(Appendix B, Annex E)**.

4.3.5. Pregnant and lactating women

4.3.5.1. Whole population

In the only five surveys available on **pregnant women** (Austria, Cyprus, Latvia, Portugal and Spain), the mean intake of **total sugars** ranged from 14 E% in Cyprus to 21 E% in Austria, with the P95 ranging from 23 to 32 E%, respectively. Mean intakes of total sugars in pregnant women compared to non-pregnant women from the same countries were generally higher in absolute amounts but similar when expressed as E%. Major contributors to total sugar intake were fresh fruit and vegetables (from 22% in Spain to 30% in Cyprus), milk and dairy products (from 16% in Austria to 31% in Portugal) and sugars and confectionery (from 9% in Austria to 16% in Latvia). The contribution from processed fruit and vegetables and cereals was low (≤ 9% for both). Core food groups collectively, i.e. fresh fruits and vegetables, cereals and milk and dairy, contributed between 52% in Spain and 60% in Cyprus, whereas the contribution from beverages (i.e. SSSD, SSFD, fruit and vegetable juices) was between 8% in Latvia and 22% in Austria **(Annex D)**.

Mean **intakes** of **added and free sugars** ranged from 5 E% in Cyprus to 9 E% in Latvia and from 6 E% to 10 E% in the same countries, respectively. The P95 ranged from 10 to 20 E% and from 14 to 22 E%, respectively. As for total sugars, mean absolute intakes of added and free sugars were generally higher in pregnant women than in non-pregnant women from the same countries, but similar

when expressed as E%. As for other population groups, fruit and vegetable juices contributed the most to the difference between the intake of added and free sugars, although the intake of these was very low in pregnant women (mean intakes between 1 E% and 2 E%; P95 from 4 to 13 E%). The major contributors to added sugars intake were fine bakery wares (from 22% in Spain to 29% in Cyprus), sugar and confectionery (from 17% in Austria to 31% in Latvia) and SSSD+SSFD (from 5% in Latvia to 32% in Austria). The contribution from processed fruit and vegetables (≤ 6% for all but Latvia which was 11%) and from fruits and vegetable juices (≤ 5%) was very low or null in most countries. The contribution from beverages combined to added and free sugar intakes ranged from 5% in Latvia to 32% in Austria, and from 15% to 46% in the same countries, respectively **(Annex D)**.

In the only two surveys available for **lactating women** (from Estonia and Greece), mean and P95 intakes of total, added and free sugar as E% were similar to pregnant women. Likewise, compared to non-lactating women from the same country, mean intakes in absolute amounts were higher in lactating women but similar when expressed as E%. Compared to pregnant women, core food groups collectively contributed less to total sugar intake (46% in Greece and 53% in Estonia) and SSSD+SSFD contributed less to the intake of added sugar (≤ 8%). The contribution of fine bakery wares (13% in Estonia and 39% in Greece) and sugars and confectionery (52% in Estonia and 27% in Greece) to the intake of added sugars was highly variable **(Annex D)**.

4.3.5.2. Consumers of selected food groups

Mean intakes of added and free sugars from all sources (g/day) in **pregnant women** were higher in consumers of SSSD+SSFD than in consumers of any other food group in all countries except Cyprus, where consumers of confectionery had the highest intakes. Intakes of added and free sugars were higher from SSSD+SSFD than from any other food group in consumers (mean intakes up to 30 g/day, P95 up to 85 g/day for both). SSSD+SSFD contributed up to 55% and up to 46% to the intake of added and free sugars, respectively, in consumers of these beverages **(Appendix B, Annex E)**.

In Estonia, **lactating women** consumers of SSSD+SSFD had the highest mean intake of added and free sugars from all sources (61 and 69 g/day, respectively), and intakes of added and free sugars from sugars and similar were the highest of all food groups in consumers (16 g/day, P95 48 g/day, and 19 g/day, P95 49 g/day, respectively). The mean intakes of added and free sugars from SSSD +SSFD were substantially lower in lactating women consumers than pregnant women consumers. The contribution of sugars and similar to the mean added and free sugars intakes in these consumer groups was, respectively, 37% and 36%. In Greece, the highest mean intake of added and free sugars from all sources (g/day) was in lactating women consumers of confectionery and in consumers of sugars and similar, respectively. Intakes of added sugars from fine bakery wares were the highest of all food groups (12 g/day),[10] while the highest intakes of free sugars were from fruits and vegetable juices (19 g/day)[10] in consumers. The contribution of fine bakery wares to the mean added sugars intake was 42% and the contribution of fruit and vegetable juices to free sugars intake was 37% in consumers of these food groups, respectively.

4.4. Overview of published data on intake of total, added and free sugars collected by Member States

EFSA requested Member States to provide intake data on dietary sugars from national dietary surveys, as estimated using national food composition databases. The aim was to compare such data with sugar intake estimates obtained for the same national surveys and population groups calculated by EFSA using the EFSA food composition databases for total, added and free sugars.

National (aggregated) sugars intake data were received from 18 countries, for a total of 27 national surveys. Of these, only 14 surveys were in the EFSA Comprehensive Database **(Annex C)**. For some surveys, however, a comparison between national sugars intake data and data calculated by EFSA was not possible due to major differences in the exposure assessed and/or in the age ranges for which intakes were calculated. For the remaining surveys, an exact comparison between identical age ranges was not possible in most cases. Thus, the most appropriate age ranges reported in national surveys were selected on a case-by-case basis in order to allow a meaningful comparison. Details can be found in **Annex F**. In total, nine national surveys were available for comparison, including all population groups covered by the intake assessment (n = 7). Of these, six national surveys (seven population

[10] P95 could not be calculated as the number of participants in this survey is below 60.

groups) report on total sugars, three national surveys (three groups) on free sugars and five national surveys (three groups) on added sugars.

Overall, mean intakes for **total sugars** calculated by EFSA were in line with those reported in national surveys. Mean intakes calculated by EFSA across surveys, age groups and sexes were, in most cases, within +/– 12% the values reported in national surveys. Exceptions were values calculated by EFSA for toddlers in France, which were 19 and 15% lower than national values reported for males and females, respectively.

For **added sugars,** EFSA values were generally lower than national values, across all surveys and population groups (up to 25%) possibly owing to the type of food composition data used and the different definitions of added sugars applied across countries. Exceptions were national values reported in the survey in Portugal, which were 11% lower than EFSA values for the older adults and did not differ from those calculated by EFSA for children. Added sugars intake reported for male and female children in Spain (ENALIA, 3–9 years), were, respectively, 49% and 46% higher than those estimated by EFSA. This substantial difference could be attributed to the type of food composition data and the different definition of added sugars used in the national publication.

Similar to added sugars, EFSA values for **free sugars** were generally lower than national values, across all surveys and population groups (up to 21%). Exceptions were national values reported in the survey in Portugal, which were between 8% and 17% higher than EFSA values for adults and older adults of both sexes.

4.5. Uncertainty analysis

Sources of uncertainty and their potential impact on the final intake estimates, where possible, are identified and discussed below.

Consumption data

Uncertainties and limitations arising from the use of the EFSA Comprehensive Food Consumption Database have been described in detail elsewhere (EFSA et al., 2011), and relate to the following methodological aspects:

- **Sampling strategy and response rate:** Using sampling strategies which are convenient (e. g. use of household as sampling unit rather than individuals, target recruitment through universities, pharmacies or factories vs. using national population registers) and low response rates may lead to survey samples which are not representative of the general population at national level. This could lead to over- or underestimation of the intakes in the general population at national level.
- **Representativeness over different weekdays and seasons:** Surveys not covering weekdays and weekend days, or conducted on one season only, may not capture habitual intakes mostly for foods which are consumed in one season only or on special occasions (e.g. weekends). However, most surveys in the Comprehensive Database, especially those conducted more recently, cover a whole year period with an appropriate proportion of weekdays and weekend days.
- **Methodology used to assess dietary intakes:** dietary recall vs. food records (see **Annex B**).
- **Use of standard portion sizes:** This can lead to over- or underestimation of the actual quantity consumed.
- **Inclusion of consumption surveys covering only few days**: This leads to overestimation of high percentiles of chronic intake, whereas it is expected to minimally affect mean intakes of nutrients widely distributed in the diet, such as dietary sugars. For foods not consumed daily, intakes could be over- or underestimated depending on whether consumption days are captured in the survey. This has also an impact on the number (and percentage) of consumers of non-core food groups identified in the surveys.
- **Other systematic errors**: Underreporting has been shown to be associated with sex, age, educational level and BMI (e.g. obese subjects and male subjects underreport more frequently than lean subjects and females). Underreporting also varies among food categories: Foods with high sugars or fat content and sweeteners added to beverages are more prone to be underreported (EFSA, 2009).

Composition data

- The EFSA Nutrient Composition Database contains data on total sugars from national food composition databases up to 2012. Recipes and ingredients (which can affect the sugar content of food products) might change to a certain extent over time, which could lead to either underestimation or overestimation of the actual intake of total sugars. However, major contributing food categories were checked in the Mintel's Global New Products Database for confirmation, which is expected to minimise the uncertainty associated with changes in recipes and ingredients over time.
- For this opinion, food composition data from 12 European countries were pooled, and thus, a consistent number of food products was taken into account per food category, leading to a more robust database which considers product variability, assuming a global food market. However, the use of national composition tables representing typical local products can introduce differences between the intake estimated by Member States and those estimated by EFSA for the present opinion, as shown in **Annex F**. Intakes of total sugars calculated by EFSA are generally lower than those calculated by Member States, with some exceptions.
- Composition tables contain average values for a food category, which may under- or overestimate the actual sugar content of a certain food product consumed by one subject. However, it is expected that the uncertainty introduced by this factor is minimised when mean intakes are calculated for the population.
- The classification of total sugars as added or free also involves assumptions, i.e. when the exact recipe of a product is unknown (e.g. cake) so that the amount of added and free sugars originating from the different ingredients could not be assigned. The classification of all the ingredients used for sweetening purposes as added sugars is expected to have no impact on the intake of free sugars, but could result in an overestimation of the consumption of added sugars that is proportional to the use of honey, syrups, fruit juices and fruit juice concentrates for sweetening purposes. The impact of this uncertainty on the overall intake estimates for added sugars is judged to be low. Similarly, when step 10 of the methodology is applied (the content of added or free sugars was assumed to be equal to 50% of total sugars, as indicated in **Annex C**), the free or added sugar content of the food could have been under- or overestimated.

Linkage of composition and consumption data

- Assumptions were made while assigning the total, free and added sugars content of foods to the consumption events. Some consumption records were only coded on a very generic level (FoodEx2 level 1 or 2) and it was not possible to identify the exact product consumed. In these cases, an average level of the lower FoodEx2 levels was assigned to the record (e.g. 'Alcoholic drinks' FoodEx2 level 1 category or 'Fine bakery wares' on FoodEx2 level 2).
- Both composition and consumption data were coded in the FoodEx2 system. Their matching was carried out through the linking categories, which took into consideration both the FoodEx2 basic codes on different levels and all possible sugar-related facet descriptors. However, 'sugar free' products and those made 'with reduced sugars' could not always be distinguished, which might have led to overestimation of the intake of total, free and added sugars. EFSA estimates of sugars intakes were generally lower than those calculated by Member States, and thus, it is expected that this factor does not introduce a major uncertainty in the intake estimates used in this opinion.

5. Methodological considerations when estimating intakes of dietary sugars and their sources and their relationship to disease endpoints in observational studies

5.1. Dietary assessment methods

Food frequency questionnaires (FFQs) are the most used dietary assessment method to estimate the intake of sugars and their sources in observational studies. Multiple 24-h recalls are sometimes used and, less commonly, diet records or dietary history.

Each dietary assessment method has its own characteristics and sources of errors, which are summarised in **Table 6**. Issues specific to the estimation of the consumption of dietary sugars from specific sources, total sugars and specific sugars types (e.g. free/added sugars, fructose) are further discussed in the following sections.

Table 6: Characteristics of dietary assessment methods and related sources of bias

	Diet records	24-h recalls	Food frequency questionnaires (FFQ)[a]	Diet history
Method	• Subjective real-time measure using open-ended, self-administered diet diary record • 'Weighed food consumption records' include weighing foods on scales • Participant literacy and full cooperation required; high burden • Children can contribute to the recording from around 10 years of age, but adults need to provide details of the foods consumed.	• Subjective retrospective measure using open-ended questionnaires administered by a trained interviewer • Participant literacy not required when interviewer-administered; low burden for the participant • Can be used to assess diets of children by questioning the parent/carer, but a problem arises if the parent/carer is not with the child all day. Children can provide some information themselves from around 10 years of age.	• Subjective retrospective measures using closed-ended questionnaires, self- or interviewer-administered • Participant literacy not required when interviewer-administered; low burden • Can be used to assess diets of children by questioning the parent/carer	• Subjective measures using open- and closed-ended questionnaires, administered by a trained interviewer • Low participant literacy required; high burden
Collected data	• Actual intake throughout a specific period; detailed • At least 2 separate days (preferably including a weekend day) needed to assess within-subject variability • If a suitable number of records are collected over a long period, usual intake can be estimated • Estimated records include careful description of amount of food • Foods need to be linked with nutrient composition data by trained staff	• Actual intake over the previous 24-h; detailed (open-ended) • At least 2 separate days (preferably including a weekend day) needed to assess within-subject variability • If a suitable number of recalls are collected over a long period, usual intake can be estimated • Foods need to be linked with nutrient composition data by trained staff	• Usual intake estimates over a relatively long period (e.g. 6 months, 1 year); level of details is variable depending on the purpose for which the FFQ was developed • Description of portion size with a choice of sizes or a modification of frequency to account for size • A standard list of foods is used to represent each food group, from this a representative nutrient intake for a portion of the food group is calculated	• Usual intake estimates over a relatively long period; level of details is variable depending on the purpose for which the questionnaire was developed • A FFQ or diet records may also be administered to verify information • Foods need to be linked with nutrient composition data by trained staff

	Diet records	24-h recalls	Food frequency questionnaires (FFQ)[a]	Diet history
Errors due to random within-person variation	• Foods consumed occasionally (twice a week or less; e.g. cakes or sweet beverages in occasional consumers) may be over- or underestimated and lead to subject misclassification • Generally reduces the strength of the association	• Foods consumed twice a week or less (e.g. cakes or sweet beverages in occasional consumers) may be over- or underestimated and lead to subject misclassification • Generally reduces the strength of the association	• Lower than with other dietary assessment methods if questions are well designed	• Describes usual diet so deals with within person variability as part of the method
Reporting errors	• Subjects may change their habitual intake for ease of recording or to increase social acceptability; selective reporting • May result in systematic within- and between-person errors; can bias the association in any direction	• Recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes; • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction	• Questionnaire misunderstanding, recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes • Errors due to FFQ design (e.g. a short FFQ may underestimate the true variation in dietary intake and the individual's total daily energy intake) • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction	• Recall bias and selective reporting may affect the identification of foods eaten and the estimation of portion sizes • Long interview may tire the respondent and affect accuracy • Interviewers bias • May result in systematic within- and between-person errors; can bias the association in any direction
Handling of measurement errors	• Errors due to random within-person variation can be limited if adequate number of days of recording are collected. • Weighed food records provide most accurate measures of portion sizes. A good description can be made if food not weighed. • Use of a food portion size atlas or similar information can aid description	• Errors can be limited if interviewers are well-trained, use adequate probing questions (e.g. regarding commonly forgotten foods such as adds-on (e.g. sugar, honey added by the consumer at the table), snacks, beverages) and by using an automated system. • Pictures/models can help improving the accuracy of portion size recalls	• Regression calibration (preferably derived from an internal calibration study based on a random sample of the main study)	• Errors can be limited if interviewers are well-trained, use adequate probing questions (e.g. regarding commonly forgotten foods such as adds-on (e.g. sugar, honey added by the consumer at the table), snacks, beverage) • Pictures/models can help improving the accuracy of portion size recalls

(a): Only studies using semi-quantitative FFQ were eligible for this opinion.

5.1.1. Sources of error in estimating the intake of dietary sugars

5.1.1.1. Food consumption data

Misreporting of food intake is a common problem in subjective dietary assessment methods and it is difficult to quantify. Selective reporting and recall bias may affect the identification of foods eaten and the estimation of portion sizes, in particular when using FFQs and 24-h recalls. Sources of sugars perceived as less healthy (e.g. SSBs, fine bakery wares, confectionery) may be more prone to selective underreporting (Poppitt et al., 1998), while those perceived as healthy (e.g. fruits and vegetables) may be overreported (Miller et al., 2008). Foods and beverages consumed between meals (e.g. snacks) and add-ons (e.g. sugar, honey added at the table) are also more prone to underreporting (Millen et al., 2009; Gemming and Ni Mhurchu, 2016). This can affect estimates of both sugars from specific sources and specific sugar types. For instance, intake of added sugars may be underestimated due to selective underreporting of significant contributors to added sugars intakes that are perceived as less healthy, as well as unintentional omissions (Poppitt et al., 1998). The direction and magnitude of the error (i.e. over- vs. underestimation) can be difficult to predict for exposures such as total sugars or total fructose, for which food contributors may be affected by reporting biases in opposite directions.

FFQs focusing on specific sources of sugars (e.g. SSBs) rather than on the whole diet can be quicker to administer and may appear more reliable for the specific source. However, such questionnaires do not allow the estimation of total energy intake (TEI), diet quality and the possibility to adjust for these factors (Section 5.1.3) (Cade et al., 2002).

5.1.1.2. Food composition data

The content of total sugars is available in most food composition databases (FCDs) because of its mandatory declaration on food labels. A source of error in the intake estimates relates to the quality and representativeness of the FCD used for the calculation of intake estimates, especially when it does not contain the foods/drinks consumed by the population under study (Ahuja and Perloff, 2008) or has not been regularly updated to reflect product reformulation and market trends (e.g. use of sugar substitutes) (Sylvetsky and Rother, 2016; Samaniego Vaesken et al., 2019).

In contrast to total sugars, the content of free and added sugars is not readily available in most FCDs. Methods have been developed to classify sugars in foods as added or free based on the ingredient lists or recipes (e.g. disaggregation method, 10-step systematic method) (Kibblewhite et al., 2017; Amoutzopoulos et al., 2018; Wanselius et al., 2019; Yeung and Louie, 2019). A common limitation of these methods is the reliance on food composition information which may not be available for all food products consumed or may be outdated due to changing formulations. These methods require assumptions (e.g. regarding the proportion of specific ingredients) and subjective decisions (e.g. when using borrowed values from similar food products) to be made, which may introduce biases. The method used to assign content of added and free sugars to foods is seldomly described in observational studies and thus the extent of potential inaccuracies is difficult to assess. Also, the use of different definitions and nomenclatures across studies hampers comparisons.

Similarly, sugar types (e.g. fructose, sucrose, glucose) are not readily available in most FCDs. Whereas some FCDs may rely on food analysis, others are built borrowing values from other countries or even from other regions of the world. This information is often not provided in studies' methods.

5.1.2. Assessment of measurement error and risk of bias

Elements considered when assessing errors of sugars intake estimates and related risk of bias in the relationship between the exposure and the health endpoint include the followings:

- Validity and reproducibility of the dietary assessment methods

The use of a tool which has been validated for the study population is critical to minimise errors in the intake estimates. Ideally, the questionnaire is validated for the intake of the nutrient of interest and for energy intake against objective measures. Urinary excretion of fructose and sucrose have been proposed as biomarkers of sugars intake (see Section 5.2). The doubly labelled water method can be used to validate dietary assessment methods for energy. However, biomarkers of sugars intake are limited and seldomly used as reference for validation to date (Section 5.2). The doubly labelled water method is also rarely used for validation of TEI. Instead, dietary assessment methods are commonly validated against each other. In that case, validation data are not necessarily available for the exposure of interest but for related dietary variables which are used as proxy indicators (e.g. validity

data on total carbohydrates for sugars or sources of sugars; validity data on main fructose food sources for fructose). Data on the reproducibility of the method, by comparing its results at different time points, are also important to assess its reliability.

- Repetition of the dietary assessment to assess habitual intake

In studies on sugars intake and incidence of chronic diseases, intake estimates should represent long-term intakes. Intake estimates based on a single dietary measurement do not allow to capture changes in subjects' consumption habits over time. Although macronutrient intakes can be assumed to be relatively stable over adulthood, consumption habits of individual foods may change rapidly. In studies investigating the association between a particular food source of sugars and the risk of disease, repeated dietary assessment is recommended to obtain a more representative estimate of individuals' habitual consumption.

- Measures to address potential systematic errors

It has been described that underreporting of food intake happens more commonly and to a greater extent in overweight and obese individuals than in normal weight subjects (Macdiarmid and Blundell, 1998; Murakami and Livingstone, 2015; Wehling and Lusher, 2019). Other factors such as smoking habits, level of education, social class, social desirability, physical activity and dietary restraint have also been associated with misreporting of food intake (Macdiarmid and Blundell, 1998; Tooze et al., 2004; Hebert et al., 2008). Although several methods have been applied to account for misreporting of energy intake, including the exclusion of implausible reporters (e.g. based on arbitrary cut-offs regarding energy intake estimates) or the adjustment or stratification of analysis according to the plausibility of reporting, these methods are not equivalent and their ability to minimise the impact of differential reporting bias on the observed nutrient–health relationships is unclear (Jessri et al., 2016; Ejima et al., 2019). Analyses taking different approaches of accounting for misreporting to assess stability of results (i.e. sensitivity analysis) are recommended.

- Calibration

In some studies, two methods (e.g. FFQ and diet records) are used in combination, so that a shortcoming of one method may be compensated to a certain extent by the second method, which can increase the accuracy of the intake estimates. Measurement errors in self-reported sugars intake may also be assessed, and possibly corrected for, using a biomarker of sugars intake (Section 5.2). However, available markers need further validation and have seldomly been used in epidemiological studies so far (Kuhnle et al., 2015; Tasevska, 2015).

- Temporal proximity of the intake estimation to the incidence of the disease

Intake measurements taken close to the incidence of the disease may be at risk of being influenced by changes in the dietary habits of the individual related to the underlying condition (reverse causality). Sensitivity analyses excluding incident cases identified during the first years of follow-up allow to address this concern.

5.1.3. Consideration of energy intake and other dietary factors in observational analyses

A general methodological issue when investigating the association between nutrient intakes, including sugar (or sugars from specific sources), and health endpoints is the risk for confounding by energy intake, intake of other nutrients and/or associated dietary patterns.

Several statistical approaches are available to account for energy intake in nutrient-disease risk models (Willett et al., 1997). The choice of the model requires consideration of the hypothesis investigated, i.e. whether energy intake may act as a confounder or as a mediator of the relationship. The characteristics and interpretation of the different models are outlined in **Table 7**.

Table 7: Models applied to account for energy intake in observational studies and their interpretation[(a)]

	Characteristics	Interpretation
Multivariable model, unadjusted for TEI	• Intake variable: nutrient (food) intake estimate	• The association may be confounded by TEI when TEI is associated with disease risk • The model allows for the mediation of TEI in the exposure–disease relationship
Multivariable model, adjusted for TEI	• Intake variable: nutrient (food) intake estimate • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, bias in the risk estimates may result from incomplete control of confounding by TEI
Nutrient residuals model	• Intake variable: residuals from the regression of the nutrient (food) intakes of the individuals on their total energy intakes • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, adjustment for TEI occurs before categorisation
Multivariable nutrient density model	• Intake variable: energy intake from the nutrient (food) divided by the total energy intake of each individual • TEI included as a covariate	• Apparent effect of the nutrient (food) while maintaining TEI constant (i.e. effect of the isocaloric substitution of the nutrient (food) with other macronutrients) • When the intake variable is categorised, adjustment for TEI occurs before categorisation • Lack of adjustment for TEI can bias the association in the opposite direction if TEI is associated with the disease
Energy partition model	• Intake variable: nutrient (food) intake estimate • Energy intake from other nutrients included as a covariate	• Apparent effect of the nutrient (food) while maintaining energy from other nutrients (foods) constant (i.e. reflects both the energy and non-energy contribution of the nutrient) • When the intake variable is categorised, bias in the risk estimates may result from incomplete control of confounding by TEI

(a): Adapted from (Willett et al., 1997).

Most observational studies consider TEI as a potential confounder of the association between sugars intake and disease risk. Sugars intake estimates are typically standardised for energy before categorisation, using the nutrient residual model or the nutrient density model adjusted for TEI.

In contrast, most studies investigating disease risk associated with sources of sugars (e.g. SSBs, FJs) provide models with and without adjustment for TEI, thus exploring the role of TEI as a potential mediator in the causal pathway between the consumption of the sugar source and the health endpoint. Notably, studies investigating disease risk associated with specific sources of sugars seldomly standardised the intake values for TEI (based on residuals from the regression on TEI or energy density) before categorising participants according to their intake. In this case, the adjustment is based on categorical variables, which may bias the intake–disease association due to incomplete control for confounding by TEI (Willett et al., 1997).

Confounding by dietary components is typically controlled by adjusting for individual dietary factors or for (aggregated) dietary pattern scores. As for other potential confounders, the adjustment strategy (e.g. choice of covariates, model selection) requires prior consideration, justification and sound statistical methods.

The incorrect use of these models in statistical analyses, but also measurement errors in dietary assessments, can increase, attenuate or even invert the true relationship. For instance, when the

nutrient density model is applied, the lack of adjustment for TEI, when it is associated with the disease, can invert the direction of the association (Willett et al., 1997). The fact that reporting errors in dietary assessments are usually biased and affect in different ways both the measurement of the nutrient of interest and the measurement of relevant covariates (e.g. TEI, intake of other nutrients or foods) makes it difficult to adjust for measurement error in regression analyses and also to predict the direction and magnitude of the bias of the nutrient–disease relationships.

Calibration and validation studies can be used to understand measurement error properties of different dietary assessment methods and apply adequate correction factors, so that well-designed and conducted studies can provide meaningful information about relationships between habitual consumption of specific components of the diet and disease endpoints, provided that appropriate statistical methods are used (Kipnis et al., 1997; Day et al., 2004).

5.2. Biomarkers of intake

5.2.1. Fructose and sucrose in urine

Urinary sucrose and fructose have been shown to correlate with the intake of dietary sugars but urinary glucose has not.

Urinary sucrose and fructose in 24-h urine samples (24uSF) cannot be used as a recovery biomarker because only a very small fraction of the sugars ingested are excreted, and thus, analytical values are quantitatively far from absolute intakes. Daily intake of dietary sugars, however, could be predicted from 24uSF by using calibration equations developed in feeding studies (Tasevska et al., 2005, 2009). This assumes that the biases of the biomarker are stable between individuals and across populations (Tasevska, 2015).

Calibrated measures of 24uSF have been used to assess the measurement error of dietary self-reports (dietary food records, 24-h recalls, FFQs) in the OPEN (Tasevska et al., 2011) and NPAAS (Tasevska et al., 2014a) cohorts, both regarding the accuracy of the measurements and their relationship with the risk of disease. Two and three individual, complete 24-h urine samples were available in the OPEN and NPAAS cohorts, respectively. Correlation coefficients between calibrated 24uSF and self-reported intake for total sugars were low for all dietary instruments (between 0.2 and 0.6), and generally lower for women than for men, suggesting that women misreported sugars consumption more than men. The average from multiple (2 and 3 days) 24-h dietary recalls was found to perform better than dietary food records or FFQs, also in relation to disease risk (Tasevska, 2015).

Urinary sucrose and fructose in spot urine samples and in overnight urine collections have been proposed to classify individuals in categories of intake for use in observational studies to investigate the relationship between sugars intake and disease risk, rather than to quantify habitual consumption of dietary sugars (Kuhnle et al., 2015; Ramne et al., 2020). The use of a composite measure of added sugars intake and urinary fructose and sucrose in overnight samples has also been explored (Freedman et al., 2010; Ramne et al., 2020).

Both spot urine and 24-h collections reflect recent intakes (in the previous 6–8 h up to the previous day), so that the number of collections needed to adequately capture habitual intakes (or how well habitual intakes are captured by a single urine collection) could vary widely depending on intra- and inter-individual day-to-day variation in sugars intake.

The Panel acknowledges the potential of fructose and sucrose in urine as a reliable biomarker of intake for dietary sugars. The Panel notes, however, that calibration equations to calculate the intake of dietary sugars from 24uSF have been developed in few studies with small sample sizes, and that the assumption that biases in the biomarker are stable between individuals and across populations needs to be ascertained. The Panel also notes that the validity of sucrose and fructose concentrations in spot urine samples and overnight urine collections as biomarkers of intake, either when used alone (as surrogate markers to classify individuals in categories of intake) or in combination with self-reported intakes (for calibration purposes), needs further exploration of the potential sources of error associated with these measurements, as well as of their (random, non-random) impact on subject misclassification in epidemiological studies (Davy and Jahren, 2016; Ramne et al., 2020).

5.2.2. Carbon stable isotope ratio

The carbon stable isotope ratio ($^{13}C/^{12}C$ or $\delta\ ^{13}C$) measured in biological samples (e.g. serum, urine, hair) has been proposed as a biomarker of added sugars intake in populations consuming added sugars mainly refined from C4 plants which are naturally rich in ^{13}C (e.g. maize, sugar cane, sorghum),

as in North America. However, correlations between sugars intake and δ ^{13}C may be biased by many confounding factors, including other dietary nutrients naturally enriched with ^{13}C (including maize starch, oils and protein), and the performance of this biomarker has not been yet investigated under controlled feeding conditions. In addition, δ ^{13}C in biological samples may be of little use in geographical areas largely depending on sugar beet, a C3 plant, as source of added sugars (e.g. Europe, Japan) (Dragsted et al., 2018).

6. Overview of dietary reference values and recommendations

While setting dietary reference intakes (DRIs) for carbohydrates in 2005, the US Institute of Medicine (IoM) concluded that the data available at the time on dental caries, behaviour, cancer, risk of obesity and risk of dyslipidaemia were insufficient to set a UL for total or added sugars. An upper limit of intake for added sugars of 25E% was suggested by considering that the intake of some micronutrients was below the DRI in US population subgroups exceeding that level of added sugars (IoM, 2005).

Other national and international authoritative bodies have given recommendations for individuals or proposed population goals for dietary sugars. Dietary goals or recommendations for a nutrient are based on considerations of health effects associated with its consumption, as well as 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 (EFSA NDA Panel, 2010b). An overview of population goals or recommendations for dietary sugars established by individual bodies can be found in the protocol for this opinion (see **Appendix A** in the **Protocol**). A tabulated summary is given in **Table 8**.

In 2010, when establishing DRVs for carbohydrates and dietary fibre, the EFSA NDA Panel (EFSA NDA Panel, 2010a) concluded that the data available at the time on dental caries, micronutrient density of the diet, body weight, blood lipids, glucose and insulin responses and risk of type 2 diabetes were insufficient to set a UL for total or added sugars. Different from other authoritative bodies, EFSA did not establish dietary goals or recommendations for dietary sugars (e.g. a limit of intake) because this is part of national nutrition policies and in the remit of individual EU Member States, and not under EFSA's remit.

In Europe, some countries provide qualitative recommendations for consumers to limit the intake of dietary sugars and/or their sources, including sweets, desserts and sugar-containing beverages (sugar-sweetened soft and fruit drinks, fruit juices and dairy drinks), whereas others provide quantitative recommendations for added or free sugars (typically < 10 E%), and more rarely for total sugars (from 15 to 20 E%). Further information on existing recommendations for dietary sugars and their sources in European countries can be found in the portal of the European Commission on Food-Based Dietary Guidelines[11] and **Annex F** of this opinion.

Table 8: Summary of existing population goals or recommendations for dietary sugars or their sources

Guideline	Target population	Sugar fraction	Population goal/ Recommendation	Basis (endpoint)
German Nutrition Society (Hauner et al., 2012)[(a)]	General population	SSBs	Limit consumption	Obesity Risk of T2DM
Nordic Council of Ministers (2014)	General population	Added sugars	Recommendation for individuals of < 10 E%	Micronutrient density
Health Council of the Netherlands (2015)	General population	SSBs	Limit consumption	Obesity Risk of T2DM
SACN (2015)	General population (> 2 years)	Free sugars	Population goal of ≤ 5 E%	Energy intake
ANSES (2016)	Adults	Total sugars[(b)]	Recommendation for the adult population of ≤ 100 g/day	Fasting triglycerides

[11] https://ec.europa.eu/jrc/en/health-knowledge-gateway/promotion-prevention/nutrition/food-based-dietary-guidelines

Guideline	Target population	Sugar fraction	Population goal/ Recommendation	Basis (endpoint)
HHS/USDA (2015)[(c)]	General population	Added sugars	Recommendation for individuals of < 10 E%	Micronutrient density
WHO (2015)	General population	Free sugars	Recommendation for individuals of < 10 E% < 5E% conditional	Body weight Dental caries
American Heart Association (Vos et al., 2016)	Children	Added sugars	Recommendation for individuals of 25 g/day ≥ 2 years Avoid < 2 years	Energy intake Adiposity Dyslipidaemia CVD risk
ESPGHAN (Fidler Mis et al., 2017)	Children	Free sugars	Recommendation for individuals of ≤ 5 E% ≥ 2 years (lower for < 2 years)	Dental caries Weight gain (SSBs) CVD and T2DM (fructose)

FBDG: food-based dietary guidelines; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; SSBs: sugar-sweetened beverage.

(a): Since the protocol was published, the German Nutrition Society in consensus with the German Obesity Society and the German Diabetes Society, updated its recommendation in 2019 and endorsed the WHO (2015) recommendation, stating that the intake of free sugars should be limited to less than 10% of total energy intake (Ernst et al., 2019).

(b): Excluding lactose and galactose.

(c): Since the protocol was published, HHS/USDA has updated its recommendation, keeping the same bases to establish a limit of 10 E% for added sugars (HHS/USDA, 2020).

7. Hazard identification: methodological considerations

As specified in the protocol, subquestions 4 and 5 were planned to be answered by performing systematic reviews and, possibly, dose-response meta-analyses if the available data allowed doing so. The conceptual framework for the systematic reviews on sugars intake in relation to disease endpoints and other endpoints is summarised in **Figure 5**.

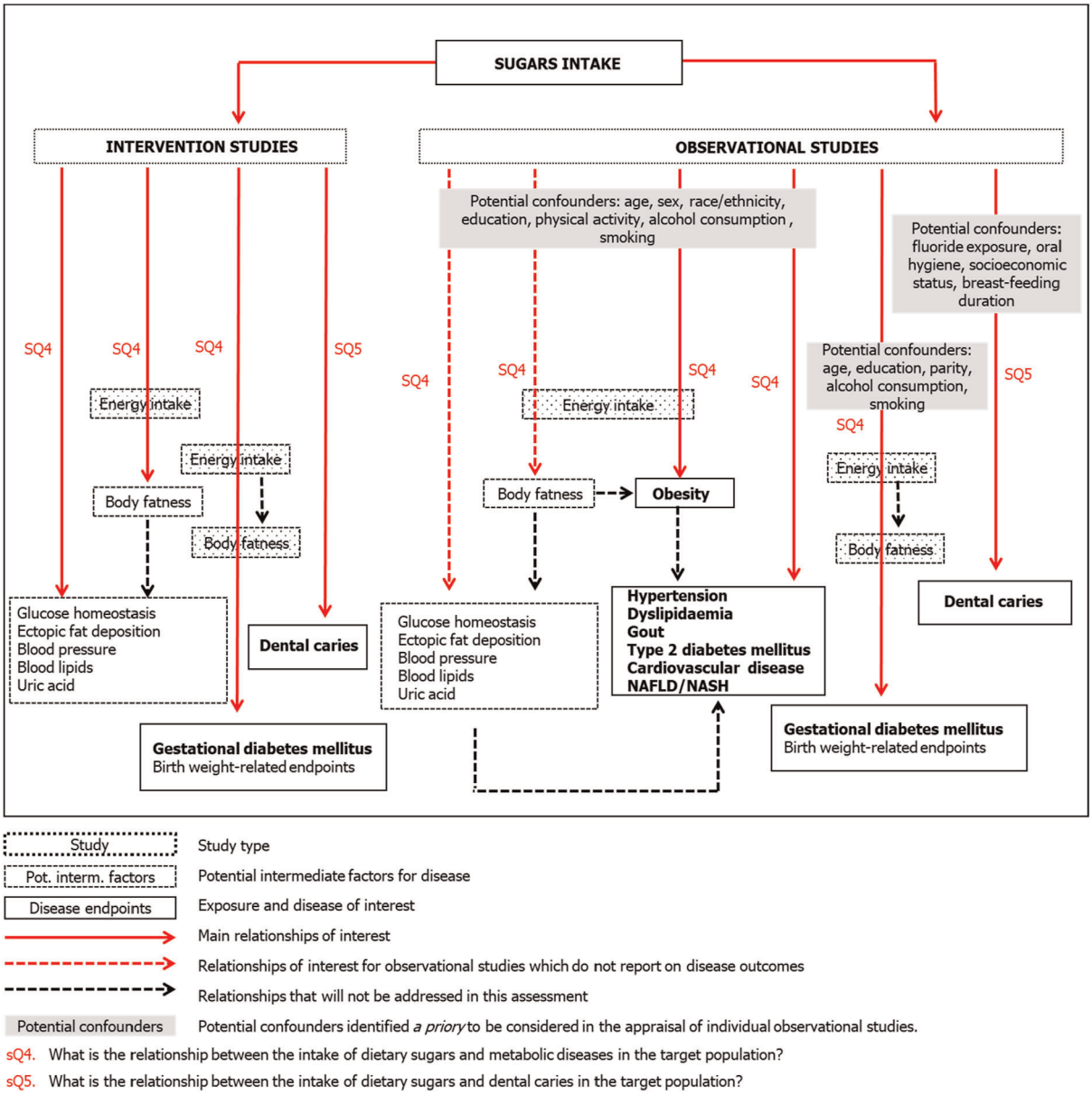


Figure 5: Conceptual framework for the systematic reviews on sugars intake in relation to disease endpoints and other endpoints

7.1. Literature searches

Literature searches were designed to identify studies published in English and conducted in humans. Specific search strings were used in Cochrane Library, Embase, PubMed and Scopus to limit by type of study and publication type. Date limits were applied based on previous systematic reviews as described in Section 9.2 of the protocol.

Literatures searches for sub-Q4 (metabolic diseases) were designed to address each type of endpoint. The searches were conducted on 23 July 2018. The results by endpoint and database were combined and exported into EndNote reference manager software, as well as all individual references cited in published reports from national and international authorities/bodies addressing the health effects of sugars, and in systematic reviews and meta-analyses published since 2010 on this topic. A variation of the method described in Bramer et al. (2016) was performed to identify duplicates in EndNote. After de-duplication, a total of 23,811 records were identified and imported into DistillerSR® Web-Based Systematic Review Software (Evidence Partners, Ottawa, Canada).

Literature searches were conducted for subquestion 5 (dental caries) on 24 and 25 July 2018 as described above. A total of 2,141 records were identified after removing the duplicates and imported into DistillerSR®.

Literature searches were updated on 28 and 31 August 2020 for subquestion 4 and on 13 and 16 October 2020 for subquestion 5 using the same methodology as described for the original searches. The complete search strings used in the bibliographic databases, the results of the updated literature searches and details on how the new studies identified were used for this scientific opinion can be found in **Annex A**.

Briefly, a full incorporation of the new evidence into the scientific assessment was not possible within the agreed timeline owing to the high number of pertinent studies identified and the high number of exposure–endpoint tandems for which new evidence became available. Therefore, in consultation with the mandate requestor, the Panel decided to incorporate into the assessment new publications meeting the inclusion criteria only when:

a) the BoE from the original search did not support a positive relationship between the exposure and the risk of disease and
b) the BoE from the updated search could change that conclusion.

In all other circumstances (e.g. when there was already evidence from the original search for a positive and causal relationship between the exposure and the risk of disease; or when the new evidence was unlikely to change conclusions of no support for a positive and causal relationship between the exposure and the risk of disease), the new studies are only summarised and discussed narratively in **Annex A**. The Panel acknowledges that this approach is conservative but considers it appropriate for a safety assessment.

7.2. Study selection and requests for additional information

The eligibility criteria for the selection of human intervention and observational studies on metabolic diseases and dental caries are listed in Section 9.1 of the protocol.

The flow charts for the selection of intervention and observational studies on metabolic diseases and dental caries are shown in **Appendix C**. For metabolic diseases, after full-text screening and exclusions during data extraction, the final number of articles included in the assessment was 156, of which 61 reported results from 49 intervention studies, and 95 referred to observational studies. Nine additional publications on observational studies identified through the update of the literature search were incorporated into the assessment, leading to a total of 104 publications reporting on 66 individual cohorts. For dental caries, 12 publications met the inclusion criteria: One was an intervention study and 11 articles reported on seven individual cohort studies.

At full-text screening and during data extraction, authors were contacted for additional information, where appropriate. Details about this process and the decisions taken based on the additional information provided are given in **Annex G**. For all the references on dental caries, authors were contacted to provide individual data for dose-response analyses (Section 10).

Details on the references excluded at full-text screening and the reasons for exclusion are given in **Annex H**. In some cases, the exclusion refers only to certain exposures, endpoints or specific exposure–endpoint combinations, and not to the whole study.

7.3. Strategies for data extraction and analysis

7.3.1. Intervention studies on metabolic diseases

A total of 49 intervention studies reported in 61 publications were included after full-text screening. Of these, 43 were conducted in adults and six in children and/or adolescents. A list of the studies reported in more than one reference, the main reference that is used as unique identifier for the study in this opinion and the endpoints used for the present assessment that are not extracted from the main reference but from linked references can be found in **Appendix D**.

The studies included were very heterogeneous in several aspects including the type of research question investigated, the dietary conditions in which they were conducted regarding the target energy intake, the fraction of the diet that was manipulated, the type of sugar or sugar source investigated, the type of control used, the study design (parallel, cross-over), the study population, the endpoints assessed and the variables used for the assessment and the duration of the intervention.

7.3.1.1. Research question

The intervention studies included were originally designed to answer one or more of the following questions:

Q1: The effect of the **amount of sugar from one or more sources**. These are studies comparing a type of sugar (e.g. sucrose) or a sugar source (e.g. honey, HFCS) to a 'zero' sugar control, which could be another energy-equivalent macronutrient (e.g. starch) or an energy-reduced or energy-free control (e.g. water, artificially sweetened beverages, no intervention) and studies comparing different amounts of the same type of sugar (e.g. fructose, glucose, sucrose).

Q2: The effect of the **type of sugar**. These are studies comparing the same amount of different monosaccharides (e.g. fructose vs. glucose).

As per protocol, the main question to be addressed to derive a UL for dietary sugars is the effect of the amount of sugars on the endpoint (**Q1**). A secondary objective was, where data allowed, to assess the effect of different types of sugars (**Q2**) and the effect of the amount of sugars from one or more sources **(Q1)**. Other questions that the studies included were originally designed to address are:

Q3: The effect of **sugars given as monosaccharides or as disaccharides**. These are studies comparing mixtures of glucose and fructose as either sucrose (as disaccharides) or HFCS (as monosaccharides).

Q4: The effect of **replacing one source of sugars by another**. These are studies comparing the same amount of foods containing different types and amounts of sugars (e.g. 20% of energy from the diet as fruits and vegetables or as fruit juices; 70 g of either sucrose or honey, the latter containing about 46 g of mixed sugars; same amount of HFCS and rare sugars syrup, the latter containing less sugars and a different monosaccharide composition), studies comparing the same amount of sugars with different monosaccharide composition (e.g. sucrose vs. corn syrup, sucrose vs. fructose or glucose) and studies comparing the effect of the same amount of a monosaccharide (e.g. fructose) from different sources (e.g. as free fructose, from sucrose, from HFCS).

However, these questions are not relevant for the present assessment.

The complete list of intervention studies that passed the full-text screening step and the question that each study investigated can be found in **Appendix E**.

7.3.1.2. Target energy intake

As per protocol, studies aiming at energy restriction or weight loss were excluded. The studies included could be classified in four main groups in relation to the dietary conditions in which they were conducted:

a) Isocaloric with neutral energy balance: Studies designed to maintain body weight by matching total energy intake to energy requirements (i.e. neutral energy balance) in all study arms
b) Isocaloric with positive energy balance: Studies designed to increase energy intake (i.e. positive energy balance) in all study arms
c) Hypercaloric: Studies designed to increase energy intake in the sugar arm (i.e. positive energy balance) and to maintain body weight in the control arm (i.e. neutral energy balance)
d) *Ad libitum:* Studies providing no instructions or restrictions regarding total energy intake to all study arms.

7.3.1.3. Fraction of the diet that is manipulated in the study

An inclusion criterion for intervention studies was the quantification of the amount of sugars provided. However, the amount of sugars reported in the publication that was consumed in the study arms (expressed in g/day or as E%) may refer to the whole diet (for whole-diet interventions) or only to the fraction of the diet that was manipulated (e.g. some beverages, some foods and beverages, some solid foods). The only study in which the whole diet was manipulated used a total liquid diet replacement (Thompson et al., 1978). In all other cases, only a fraction of the diet, variable from study to study, was the subject of the intervention, and thus, only the amount of sugars consumed with that fraction of the diet is reported in the publication. Only in few instances, there was enough information provided to calculate the amount of sugars consumed from the whole diet (total sugars) in all the study arms.

The amount of sugars provided with the intervention always refers to added sugars, except for studies using honey (free sugars, Majid et al. (2013)), studies which targeted non-milk extrinsic sugars (free sugars, Markey et al. (2016); Umpleby et al. (2017)) or a whole liquid diet (total sugars as free sugars, Thompson et al. (1978)).

7.3.1.4. Type of sugar investigated

The sugars administered to intervention arms were as follows: fructose, glucose, mixtures of glucose and fructose, sucrose, HFCS, corn syrup, rare sugars syrup, honey, fruit juice, sugar-sweetened beverages, non-milk extrinsic sugars, simple carbohydrates. For data analysis, the intervention has been classified as follows with respect to the type of sugar administered:

a) Glucose
b) Fructose
c) Mixtures of glucose and fructose, where these monosaccharides are in an approximate ratio of 1:1 as found in mixed diets (including sucrose, HFCS, honey, sugar-sweetened beverages, fruit juice, non-milk extrinsic sugars, simple carbohydrates)

Study arms using corn syrup (Thompson et al., 1978), rare sugars syrup (Hayashi et al., 2014) or fruit juice (Hollis et al., 2009; Houchins et al., 2012) were not considered for answering Q1 or Q2 as they were planned to investigate Q4 only (see also Section 7.3.1.6 on data selection).

7.3.1.5. Type of control

During data extraction, the type of controls used in the studies were classified as follows: water, artificial sweeteners, no sugar, starch, fat and mixed macronutrients. For data analysis, these arms were assigned a zero value for the amount of (added or free) sugars given with the intervention.

7.3.1.6. Data selection

Mean effect estimates were computed for each study by selecting one intervention arm and one reference arm, as follows:

Q1. Effect of the **amount of sugar**. Comparisons are made between:

a) one arm with a zero (added or free) sugars value (reference) and one arm with a sugars value > 0 (intervention), which could be any type of sugar; if more than one arm with zero (added or free) sugars is available for a given study, the arm being more comparable to the intervention is selected as reference (e.g. ASSD is selected as reference for SSSD, rather than water or no intervention); if two or more arms with a sugars value > 0 are available for the same study, the arm with the highest sugars value is selected as intervention; if the highest sugars value corresponds to two or more arms investigating different types of sugars, sucrose or fructose were selected as intervention rather than HFCS, corn syrup or glucose because sucrose and fructose are the main energy-containing sweeteners used in Europe, at least until the end of the sugar quota.
b) two arms with different doses of the same sugar (e.g. sucrose); if more than two arms are available for the same study, the arm with the lowest dose (reference) is compared to the arm with the highest dose (intervention); if the same doses are investigated for different sugars within a study, sucrose or fructose were selected rather than HFCS or glucose for the reasons given above.

Q2. Effect of the **type of sugar**. Comparisons are made between arms which provide the same dose of glucose (reference) and fructose (intervention).

The main characteristics of the intervention studies on metabolic diseases included in the assessment and the study arms selected to address each question are shown in **Appendix E**.

The amount of sugars provided with the intervention always refers to added sugars, except for studies using honey (free sugars, Majid et al. (2013)), studies which targeted non-milk extrinsic sugars (free sugars, Markey et al. (2016); Umpleby et al. (2017)) or a whole liquid diet (total sugars as free sugars, Thompson et al. (1978)).

The four intervention studies (seven comparisons; (Lowndes et al., 2014a,b; Angelopoulos et al., 2015) which compared the effect of sugars administered as either sucrose or HFCS (Q3) were kept in the body of evidence because they could also address Q1, Q2 or both. However, the four studies that could only answer Q4 about the source of sugars (e.g. honey vs. sucrose; fruits and vegetables vs.

fruit juice) will be not considered further (Yaghoobi et al., 2008; Houchins et al., 2012; Hayashi et al., 2014; Rasad et al., 2018).

7.3.1.7. Data analysis

In most intervention studies, and particularly in those conducted under controlled energy conditions, the amount of sugars given with the intervention to each subject is adjusted to total energy intake and expressed as E%. In other studies, the intervention is a fixed amount of sugars expressed in g/day. To make meaningful comparisons across studies, amounts of sugars in g/day were transformed into amounts of sugars as E% using mean total energy intakes for the study group at baseline reported in the individual studies whenever possible. If no information on total energy intake at baseline was available, assumptions were made based on sex (1,800 kcal was assumed for females; 2,200 kcal was assumed for males and 2,000 kcal was assumed for females and males combined). However, the same E% from sugars in different studies could correspond to very different E% from sugars in the whole diet, depending on the energy contribution of the dietary fraction that was manipulated to total energy intake and on the macronutrient composition of the dietary fraction that was not manipulated. For most of the studies included, such information is not available. In addition, the target dose of sugars to be administered with the intervention, rather than the amount of sugars consumed (often not reported in studies conducted ad libitum) was used for data analysis.

In this context, the only variable that could be investigated in relation to Q1 for different endpoints was the target (rather than the achieved) difference in sugar intakes between study arms, assuming that the dietary fraction that was not manipulated in the studies is comparable across arms regarding the macronutrient composition and, thus, the sugar content both at baseline and at the end of the intervention. The second assumption is that between-arm differences in endpoint variables reflect the change that would occur in a group of individuals increasing their sugar intake. This was effectively so in studies where the intervention aimed at increasing sugars intake, but not in studies where the intervention aimed at reducing sugars intake.

A correlation coefficient of 0.82 has been used to calculate the precision of the mean effect in cross-over studies and in parallel studies when the between-arm difference was computed using changes between baseline and end of the intervention. In both cases, the correlation coefficient is necessary to account for the dependency between two measurements of the same outcome variable (e.g. body weight, fasting blood glucose) in the same individual. Owing to the uncertainty in the level of correlation between repeated measurements for all the outcome variables considered in this assessment and the limited evidence that is available to provide an accurate and precise estimate for each of them, an Expert Knowledge Elicitation (EFSA, 2014) was conducted with the members of the Working Group on sugars. Estimates of the plausible range for the correlation coefficient (between 0.50 and 0.99) and of the value that with highest probability corresponds to the true mean across endpoints (0.82) were elicited. A sensitivity analysis using the extremes of the plausible range has also been conducted when estimating the pooled mean effects (forest plots) and the parameters of the dose-response models.

Further details on the statistical analysis of RCTs can be found in **Annex L**.

7.3.2. Observational studies on metabolic diseases including pregnancy endpoints

A total of 104 publications reporting on 66 different cohorts were included after full-text screening. These comprise mostly prospective cohort (PCs) and three prospective case-cohort (PCCs) studies. For convenience, PCs will be used as umbrella term for observational studies in the text, unless reference is made to specific studies with a PCC design.

A summary of the cohorts, together with the references reporting on each cohort, the general characteristics of the subjects recruited at baseline, the exposures and endpoints assessed and the methods used for the exposure assessment can be found in **Appendix J**.

7.3.2.1. Exposure

The studies included have investigated either dietary sugars from all sources or specific sources of sugars. In the former, quantified sugar intakes are used as independent variables in the studies, whereas studies on specific sources of sugars (e.g. sugar-sweetened soft drinks, fruits, chocolate, jam) generally use the amount of food as independent variable.

Standard exposure categories were defined for data extraction as shown in **Table 9**. The exposure described in the studies was approximated to the closest standard category to allow comparisons across studies. The same terminology was used for data extraction in intervention studies, where appropriate.

Table 9: Exposure categories for data extraction

Exposure category	Includes	Excludes
Total sugars	Monosaccharides (i.e. glucose, fructose and galactose) and disaccharides (i.e. sucrose, lactose and maltose)	Sugar alcohols (polyols), other substances used as sugar replacers and other mono- or disaccharides present in the diet in marginal amounts
Added sugars	Mono- and disaccharides used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table	Sugars from intact fruit, vegetables and milk; sugars naturally present in honey, syrups, fruit juice and fruit juice concentrates
Free sugars	Mono- and disaccharides added to foods by the manufacturer, cook or consumer plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.	Sugars from intact fruit, vegetables and milk
Sucrose	Sucrose naturally contained in foods and sucrose added to foods and beverages	–
Fructose	Free fructose plus half of sucrose	–
Free fructose	Fructose naturally present as monosaccharide in foods and beverages and fructose added to foods and beverages as monosaccharide	Fructose in sucrose
Free glucose	Glucose naturally present as monosaccharide in foods and beverages and glucose added to foods and beverages as monosaccharide	Glucose in sucrose
Sugar-sweetened soft drinks (SSSDs)	Carbonated and non-carbonated sugar-sweetened drinks such as soda, iced tea, sports drinks and energy drinks or any subgroup thereof	Alcoholic beverages, milk and milk beverages, coffee and hot tea, fruit drinks and fruit juices
Sugar-sweetened fruit drinks (SSFDs)	Fruit squashes, cordials, lemonades, punches or any combination of these	SSSDs and fruit juices
Sugar-sweetened fruit juices (SSFJs)	Fruit juices, concentrates and nectars with added sugars or any combination of these	Fruit drinks and 100% fruit juices
100% fruit juices (100% FJs)	Unsweetened fruit juices	SSFDs and SSFJs
Total fruit juices (TFJs)	SSFJs and 100% FJs	SSSDs and SSFDs
Fruit juices (FJs)	100% FJs, SSFJs or TFJs	SSSDs and SSFDs
Artificially sweetened soft drinks (ASSDs)	Sugar-free carbonated and uncarbonated drinks such as soda, iced tea, sports drinks and energy drinks or any subgroup thereof	Sugar-sweetened soft drinks, alcoholic beverages, milk and milk beverages, coffee and hot tea, fruit drinks and fruit juices
Sugar-sweetened beverages (SSBs)	Water-based beverages and fruit juices with added sugars. Include SSSDs, SSFDs, SSFJs and TFJs (when SSFJs and 100% FJs are not reported separately) or any combination thereof	100% fruit juices (except if SSFJs and 100% FJs are not reported separately)
Artificially sweetened beverages (ASBs)	Sugar-free, water-based sweetened beverages	Water-based beverages and fruit juices with added sugars

Dietary sugars

Sugars in the diet have been classified in observational studies considering their chemical structure (e.g. glucose, fructose, lactose, maltose, sucrose), whether they are consumed as monosaccharides, disaccharides or both (e.g. free fructose vs. total fructose), whether they occur naturally in foods or have been added to foods (e.g. 'natural' fructose vs. added fructose), whether they come from solid foods or from liquids, or a combination of the above (e.g. added free fructose).

This heterogeneity in the classification of the exposure results in a high number of specific exposure–endpoint couples which cannot be systematically addressed within the time and resources available. In addition, for several exposure–endpoint couples, only one study was available. Therefore, the Panel took the following decisions regarding data extraction:

a) Not to extract data on lactose, maltose and galactose. The rationale for this decision are as follows:

   i) Maltose is a very minor component of the diet and galactose is only found in small amounts in fruits and vegetables (Acosta and Gross, 1995).
   ii) Lactose, maltose or galactose is generally not used as sweeteners and was not used in any of the intervention studies included in the assessment.
   iii) There is no hypothesis by which lactose or maltose *per se* could increase the risk of metabolic diseases other than contributing to total sugars in the diet or the glucose pool in the body.

b) Not to extract data on added sucrose, added fructose or added sugars from specific foods (e.g. beverages, cereals, milk, sweets, table sugar). The reasons for this decision are:

   - The study reporting on added sucrose also reports on added sugars from all sources and sucrose from all sources (Tasevska et al., 2014b).
   - The study reporting on added fructose also reports on fructose from all sources and this was extracted as the exposure of interest (Bahadoran et al., 2017).
   - The very few studies which report on added sugars from specific foods also report on added sugars from all sources, which was extracted as the exposure of interest. In addition, the food groups for which the intake of added sugars was reported were not comparable across studies (**Appendix J**).

c) Not to extract data on added sugars from solids and/or added sugars from liquids when data on added sugars from all sources were available.
d) Not to extract data on added free fructose because the only study reporting on this exposure also reports on fructose from all sources, which was extracted as the exposure of interest (Tasevska et al., 2014b).

Data have been extracted, where available, for the following categories of dietary sugars: total sugars, added sugars, free sugars, sucrose, fructose (as monosaccharide and bound to glucose), free fructose (as monosaccharide) and free glucose (as monosaccharide) from all dietary sources. Data have also been extracted for added sugars from solids and/or liquids from studies not reporting on added sugars from all sources.

Sources of sugars

When the exposure category used in the studies as independent variable for analysis was the amount of a food source for which the sugar content had not been quantified, the following approach was followed for data extraction and analysis.

For beverages, the nomenclature of the exposure of interest was standardised as described in **Table 9**. When the amount of SSSDs, SSFDs, SSFJs, TFJs and 100% FJs consumed was reported, either for each beverage group separately or for any combination of these groups, data were extracted for the most aggregated exposure category available within the SSBs category (e.g. for SSSD and SSFD combined rather than for the two categories separately) and within the FJ category (for fruit juices combined rather than for each individual juice type; for TFJs rather than for 100% FJs or SSFJs separately). Using data from the EFSA food composition and consumption databases, the sugar content in these beverages was assumed to be 10 g/100 mL (round number).

Data were not extracted for the following beverages:

a) Combined categories including beverage groups with very different sugar content and for which a reliable estimate of the sugar intake was not feasible, not knowing the relative

contribution of each of the beverage groups to the combined exposure (e.g. categories including coffee and tea not specifying if sweetened or unsweetened; categories including both SSSD and ASSD combined; categories including plain milk, milk shakes and flavoured milk).

b) Vegetable juices, either alone or in combination with fruit juices, because the sugars content is significantly lower compared with other beverages (mean 3.7 g/100 mL) and their relative contribution to total juices is unknown.

c) Milk, because the intake is typically reported for skim and whole milk separately and there is no hypothesis by which lactose *per se* could increase the risk of metabolic diseases.

Data were not extracted for individual **solid foods** or food groups for the following reasons:

a) Combined categories included foods or food groups with very different sugar content. Not knowing the relative contribution of each food or food group to the combined exposure, reliable estimates of sugars intake were not feasible (e.g. sweets and deserts, candies and cakes).

b) Foods for which sugar intakes could have been calculated were either small contributors to total sugar intakes, were investigated in relation to the metabolic disease endpoints for other reasons than their sugar content or both (e.g. individual fruits, chocolate, syrups, jams).

c) The few studies quantifying sugar intakes from individual solid foods or food groups were heterogeneous regarding the exposure of interest and the endpoint assessed, so that only one study was available for each specific exposure–endpoint relationship. In addition, these studies were also reporting on (total/added/free) sugars from all sources, which was extracted as the exposure of interest.

Artificially sweetened beverages

Health effects of artificially sweetened beverages (ASBs) consumption are out of the scope of this assessment. Data on ASBs from the same PCs reporting on SSBs have been extracted in evidence tables whenever available to explore whether (and the extent to which) any relationship between SSBs and risk of disease could be attributed to the sugar fraction of these beverages in these particular studies. However, it should be noted that such data do not allow drawing conclusions about the relationship between the intake of ASBs and risk of disease because the systematic reviews conducted for this assessment did not address that question (e.g. evidence for ASBs has not been systematically collected).

7.3.2.2. Data selection

Data have been extracted in evidence tables from the PCs included in the assessment for all exposures and endpoints of interest with the following exceptions:

1) When data for the same cohort, exposure and endpoint were reported in more than one publication, the publication with the longest follow-up was kept.
2) If two publications reported on the same cohort, exposure and endpoints which are closely related (e.g. BMI and BMI z-scores), the publication reporting on the endpoint which was more appropriate for the study population was kept (e.g. BMI z-scores rather than BMI for adolescents).
3) Data from publications on single cohorts (e.g. EPICOR, HPFS) that are part of pooled analysis in other publications (e.g. EPIC and Harvard Pooling Project in relation to SSBs and CHD risk, respectively) have not been extracted to avoid considering these cohorts twice.

7.3.2.3. Data analysis

Data from PCs were meta-analysed by EFSA to explore linear and non-linear dose-response relationships between exposures and endpoints of interest in comprehensive uncertainty analyses whenever possible (see Section 8.1.3). Details on the statistical analysis of observational studies on metabolic diseases can be found in **Annex M**.

For dose-response relationships explored in individual studies by the authors, only PCs reporting on measures of risk across categories of intake (and not PCs reporting on continuous exposure–endpoint relationships) have been considered. This is because in the former, linearity of the dose-response relationship is not assumed but tested.

7.3.3. Studies on dental caries

One publication reporting on a human intervention study and 11 publications reporting on seven prospective cohort studies met the inclusion criteria for this assessment. Although only studies investigating the relationship between quantitative amounts of dietary sugars intake and dental caries were included, data on frequency of consumption were also extracted from these studies when available.

Individual data were requested from the authors of all prospective cohort studies. This was to explore the possibility of conducting pooled analyses to identify dose-response relationships between the intake of sugars and risk of dental caries and/or levels of intake at which the risk of dental caries is not increased.

7.4. Appraisal of the internal validity of the included studies

As specified in the protocol, a customised version of the OHAT/NTP risk of bias (RoB) tool was used to appraise the internal validity of eligible studies.[12] The appraisal addressed eight RoB questions for RCTs and five RoB questions for prospective cohort studies (PCs) and prospective case-cohort studies (PCCs) (**Table 10**). Questions related to randomisation (for intervention studies) and confounding (for observational studies) and questions related to detection bias for the exposure and the endpoint were considered the most critical for the allocation of studies to RoB tiers (i.e. key questions). For each study and exposure–outcome relationship, the RoB questions were answered by choosing one of the options depicted in **Figure 6**.

Table 10: Sources of bias and the corresponding questions used to address them, by study design(a)

Selection bias	**RCTs**	**PCs/PCCs**
1. Was administered dose or exposure level adequately randomised?	X*	
2. Was allocation to study groups adequately concealed?	X	
3. Did selection of study participants result in appropriate comparison groups?		(b)
Confounding bias		
4. Did the study design or analysis account for important confounding?		X*
Performance bias		
5. Were the research personnel and human subjects blinded to the study group during the study?	X	
Attrition/Exclusion Bias		
6. Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection bias		
7. Can we be confident in the exposure characterisation?	X*	X*
8. Can we be confident in the outcome assessment?	X*	X*
Selective Reporting Bias		
9. Were all measured outcomes reported?	X	(c)
Other Sources of Bias		
10. Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	X	X

RCTs: randomised controlled studies; PC: prospective cohort studies; PCC: prospective case-cohort studies.
(a): Adapted from OHAT/NTP RoB tool (NTP, 2019).
(b): This question from OHAT/NTP RoB tool was not retained as it was not applicable to the study designs included in the assessment.
(c): Because this question was found to be seldomly relevant for the observational studies included in the assessment, it was addressed under question 10 'other sources of bias' as selective reporting.
*: Key questions, i.e. questions considered as the most critical for the allocation of studies to RoB tiers.

[12] Available online: https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/riskbias/index.html

++	**Definitely Low** risk of bias	There is direct evidence of low risk-of-bias practices (May include specific examples of relevant low risk-of-bias practices)
+	**Probably Low** risk of bias	There is indirect evidence of low risk-of bias practices OR it is deemed that deviations of low risk-of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
-/NR	**Probably High** risk of bias	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g. not reported or 'NR') provided about relevant risk-of bias practices
--	**Definitely High** risk of bias	There is direct evidence of high risk-of-bias practices (May include specific examples of relevant high risk-of-bias practices)

(a): Source: OHAT/NTP RoB tool[13]

Figure 6: Answer format for the risk of bias (RoB) questions[(a)]

The judgements to the RoB questions were combined into an overall RoB judgement for each study and exposure–outcome relationship, according to the OHAT/NTP 3-tier system (**Table 11**). As a result, studies were classified as being at low (tier 1), moderate (tier 2) or high (tier 3) RoB.

Table 11: Tiering approach, by study design

	RCTs	PCs/PCCs
Tier 1, low risk of bias	Study rated as 'definitely low' or 'probably low' risk of bias for the key questions[(a)] **AND** Most other applicable questions answered 'definitely low' or 'probably low' risk of bias	Study rated as 'definitely low' or 'probably low' risk of bias for the key questions[(b)] **AND** At least one of the other applicable questions answered 'definitely low' or 'probably low' risk of bias
Tier 2, moderate risk of bias	Study met neither the criteria for tiers 1 or 3	Study met neither the criteria for tiers 1 or 3
Tier 3, high risk of bias	Study rated as 'definitely high' or 'probably high' risk of bias for the key questions[(a)] **AND** Most other applicable questions answered 'definitely high' or 'probably high' risk of bias	Study rated as 'definitely high' or 'probably high' risk of bias for at least two of the key questions[(b)] **AND** At least one of the other applicable questions answered 'definitely high' or 'probably high' risk of bias

RCTs: randomised controlled studies; PCs: prospective cohort studies; PCCs: prospective case-cohort studies.
(a): Key questions, i.e. questions considered most critical for the allocation of studies to RoB tiers for RCTs, related to randomisation (question 1), exposure characterisation (question 7) and outcome assessment (question 8).
(b): Key questions, i.e. questions considered most critical for the allocation of studies to RoB tiers for PCs and PCCs, related to confounding (question 4), exposure characterisation (question 7) and outcome assessment (question 8).

The appraisal forms, including the explanations for expert judgements, can be found in **Annex I**. As foreseen by the OHAT/NTP guidance, the criteria for the RoB questions were customised in the light of the specificities of the review questions. For RCTs, minimal adaptations to the original tool were introduced, mostly to accommodate the appraisal of studies with a cross-over design (questions 1, 2 and 8), the special characteristics of the exposure of interest (question 5) and the outcome assessment (question 6). For observational studies, the criteria to rate the confidence in the exposure characterisation (question 4) and in the outcome assessment (question 5) were adapted to encompass the methods for dietary assessment and outcome ascertainment used in eligible studies, and associated risk of bias. To that end, the criteria for the appraisal of the exposure characterisation captured the critical elements outlined in Section 5. The question addressing 'other threats' to internal validity (question 7) was used to address the risk of bias related to potential over-adjustment of the model in the statistical analysis and selective reporting **(Annex I)**.

The outcome of the appraisal of human studies in relation to the risk of bias can be found in **Annex K**.

[13] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

8. Hazard identification: chronic metabolic diseases

8.1. Body of evidence

8.1.1. Intervention studies

A summary of the main characteristics of the randomised controlled trials (RCTs) on metabolic diseases included in the assessment, the identification of the questions that each study could address (Q1–Q4) and the study arms used in this opinion as intervention and control to address Q1 (effect of the amount of sugar) and Q2 (effect of fructose vs. glucose) can be found in **Appendix E**.

A summary of the results of the intervention studies on metabolic diseases per endpoint cluster is shown in **Appendix F**. The results are presented in line with the primary objective of the study and according to the data analyses performed by the authors.

The intervention studies included in the body of evidence can be summarised as follows:

a) Studies providing different amounts of sugar (e.g. fructose; mixtures of fructose and glucose as sucrose, sugars from SSBs, honey; non-milk extrinsic sugars, simple carbohydrates from the whole diet). Of these, four studies targeted free sugars and the rest manipulated only the added sugars fraction (Q1).
b) Studies providing similar amounts of fructose and glucose (Q2).

These studies allow investigation of the following exposures in relation to the endpoints of interest:

a) Added and free sugars
b) Fructose
c) SSBs (as mixtures of glucose and fructose in beverages)

In the RCTs available, the sugar fraction manipulated was either added sugars or free sugars. In this context, an assumption will be made that the sugar fraction not manipulated in the study remained constant through the intervention and comparable among study arms. This applies to sugars in intact fruits, vegetables and milk in all the studies and to sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates when used as such by the consumer in all the studies except those assessing free sugars. That was the case in the few RCTs which reported on the amount of total sugars in the background diet. The sugar fraction not manipulated with the intervention in those studies ranged from 2.5 to 12E%, and the intake of total sugars across arms ranged from 2.5 to 50E%.

It should be noted that, since added sugars are a fraction of free sugars, and free sugars are a fraction of total sugars, changes in the intake of added sugars in an intervention will also imply changes in the intake of free and total sugars. However, sugars in whole fruits, vegetables and milk have not been manipulated with the intervention in any of the studies, and this is an important fraction of total sugars intake. Therefore, the Panel considers that these studies do not allow conclusions on total sugars as a whole.

Conversely, since the intakes of added and free sugars widely overlap, the Panel considers that RCTs addressing Q1 can be combined to draw conclusions on added and free sugars, even if the majority of the studies manipulated only the added sugars fraction. The Panel also considers that the data available from RCTs do not allow comparison of health effects based on the classification of dietary sugars as added or free.

From the only study which investigated 100% FJs vs. a sweetened drink or no drink (Hollis et al., 2009), the sweetened drink was selected as the high sugar arm for comparability across studies. This single study was considered insufficient to draw conclusions from RCTs on fruit juices.

For studies conducted in usual consumers of SSBs who were asked to replace these with non-caloric alternatives, the target for the control was assumed to be the usual consumption of SSBs at baseline and the target for the intervention the complete removal of those beverages.

It should be noted that RCTs conducted under isocaloric conditions aim to investigate the effect of sugars in isocaloric exchange with other macronutrients (primarily starch) and thus independently from their energy content, whereas RCTs conducted ad libitum investigate the effect of introducing sugars to (or removing sugars from) the diet in free living conditions. This includes the contribution of sugars to TEI but also the effect of any dietary modifications resulting from the intervention (e.g. changes in TEI and/or the composition of the diet), which were generally not controlled for.

8.1.2. Observational studies

The main characteristics of the observational studies included in the assessment are in **Appendix J**. The results by type of exposure and endpoint are shown in the evidence tables (**Annex J**).

The PC studies included in the body of evidence (BoE) allow investigation of the following exposures in relation to the endpoints of interest:

a) Total sugars
b) Added sugars, sucrose as a surrogate exposure for added sugars and free sugars (and non-milk extrinsic sugars) from all sources.
c) Fructose, either as total fructose or as free fructose from all sources
d) SSBs, including (a) SSSDs, SSFDs, SSFJs or any combination of these; and (b) TFJs when combined with SSSDs and/or SSFDs
e) Fruit juices, including 100% FJs or TFJs.

It is acknowledged that the above-mentioned classification is data driven. Like intervention studies, few PCs have investigated the relationship between free sugars from all sources (DONALD, (Herbst et al., 2011) and (Goletzke et al., 2013b); Mr and Ms Os (Liu et al., 2018); and/or free sugars from liquids (KoCAS, (Hur et al., 2015); DONALD, (Goletzke et al., 2013b)) and the endpoints of interest. Only the Mr and Ms Os cohort investigated both added sugars and free sugars from all sources. Therefore, studies on free sugars will be assessed together with studies on added sugars to draw conclusions on both sugar fractions because these two exposures widely overlap. As for RCTs, the Panel considers that the data available from PCs do not allow comparison of health effects based on the classification of dietary sugars as added or free.

In the PCs available, SSFJs were always considered under SSBs, i.e. in combination with SSSDs and/or SSFDs, whereas only a few PCs include TFJs under SSBs, always in combination with SSSDs and SSFDs. In this context, SSBs mostly denote water-based beverages with added sugars, under the assumption that 100% FJs were a minor contributor to the combined intake. In all PCs addressing FJs, these were reported by the authors (either in the publications or following clarification upon EFSA's request) as 100% FJs or TFJs. The Panel notes that, as for food consumption surveys, study participants might not have the knowledge or information to differentiate between fruit juices with no added sugars and fruit nectars with added sugars, and/or the question in FFQs may have not been specific enough to retrieve that information. However, the Panel notes that, although 100% FJs and SSFJs (e.g. nectars) differ in the content of added sugars, the amount of free sugars in these beverages is similar, and thus, 100% FJs and TFJs will be considered together under FJs for the purpose of this opinion.

PCs investigating the relationship between a food source (SSBs, FJs) and an endpoint allow conclusions on the food source and not necessarily on the sugar fraction of the source. Data on ASBs from the same PCs reporting on SSBs will be summarised in the text and discussed when drawing overall conclusions on hazard identification in order to explore whether any relationship between the intake of SSBs and risk of disease could be attributed, at least in part, to the sugar fraction of these beverages. However, the Panel wishes to reiterate that such data do not allow drawing conclusions about the relationship between the intake of ASBs and risk of disease because the systematic review was not set for that purpose, ASBs being out of the scope for this assessment.

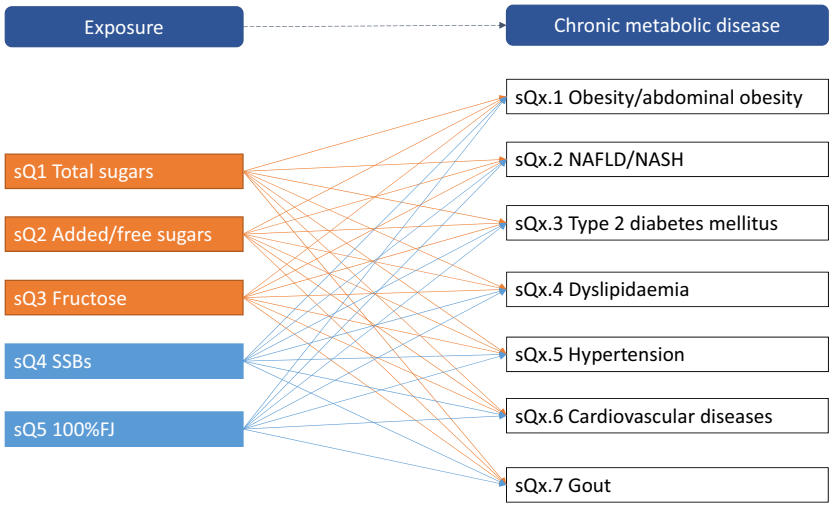
In PCs where the exposure has been introduced in multivariable regression models as a **continuous variable**, adjustments for TEI have been conducted in different ways and at different steps in the process. A review of the methods used to adjust for TEI in nutritional epidemiology, together with their strengths, limitations and potential for confounding of the association between the intake of the nutrient and the endpoints associated with TEI can be found in Willett et al. (1997) and in Section 5.1.3 of this scientific opinion. Most PCs on dietary sugars (total, added and free sugars; glucose and fructose) have investigated these nutrients keeping TEI constant in the analysis (i.e. in isocaloric exchange with other macronutrients), whereas most PCs on specific sources of sugars (SSBs and FJs) have explored whether these could be associated with the endpoint with and without considering their contribution to TEI (i.e. keeping and not keeping TEI constant). It should be noted, however, that in most PCs that have analysed the exposure as a **categorical variable**, the intake of dietary sugars has been standardised for TEI before assigning individuals to categories of intake, whereas the intake of beverages has not. In the first case, TEI is kept constant in the analysis, testing the hypothesis that dietary sugars may be associated with disease risk by mechanisms other than contributing to excess energy intake. In the second, TEI is not kept constant in the analysis because

introducing TEI as a covariate later in the process results in incomplete adjustment for TEI. This approach addressed the hypothesis that specific sources of sugars may be associated with disease risk also by contributing to excess energy intake.

8.1.3. Principles applied to assess the body of evidence: evidence integration and uncertainty analysis

The hazard identification step aims at identifying adverse health effects, i.e. increased risk of chronic metabolic diseases, caused by the intake of dietary sugars. The following question is addressed: Is the intake of (total/added/free) sugars (and/or their sources, e.g. SSBs, FJs) positively and causally associated with the risk of chronic metabolic diseases at the levels of sugar intake and in the population subgroups investigated in the studies eligible for this assessment?

The question is broken down into a series of subquestions (sQ) addressing specific exposure–disease relationships, as illustrated in **Figure 7**.



Each arrow represents one specific subquestion. Five types of exposure and seven metabolic diseases have been identified based on the evidence availability resulting from the study selection process. sQx = subquestion by exposure.

Figure 7: Exposure–disease relationships investigated for hazard identification

Within each sQ, randomised controlled trials (RCTs) and prospective cohort studies (PCs) are organised in separate lines of evidence (LoE), which are classified in the following hierarchical order (**Figure 8**):

- **Standalone (main) LoE:** Studies on disease endpoints (e.g. incidence of hypertension, incidence of T2DM). These studies could, on their own, answer the sQ directly.
- **Standalone (surrogate) LoE:** Studies on endpoints which are surrogate measures of the disease risk (e.g. blood pressure for hypertension, fasting glucose for T2DM). These studies also could, on their own, answer the sQ, on the assumption that a sustained increase in the surrogate measure over time (e.g. blood pressure) would eventually lead to an increased risk of disease (e.g. hypertension). However, the Panel is aware of the uncertainty inherent in this assumption and this will be considered in the overall uncertainty analysis for each sQ.
- **Complementary LoE:** Studies on endpoints which are relevant to the disease but less direct than those included in standalone LoE (e.g. risk factors, upstream indicators, other biologically related endpoints). These studies, on their own, cannot answer the sQ but can be used as supporting evidence to the standalone LoEs.

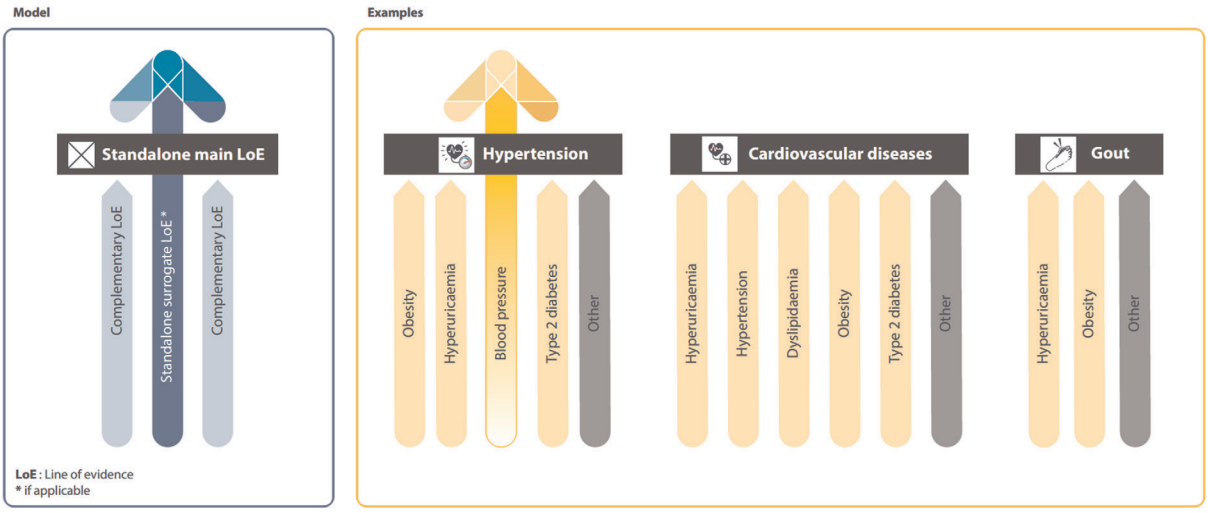
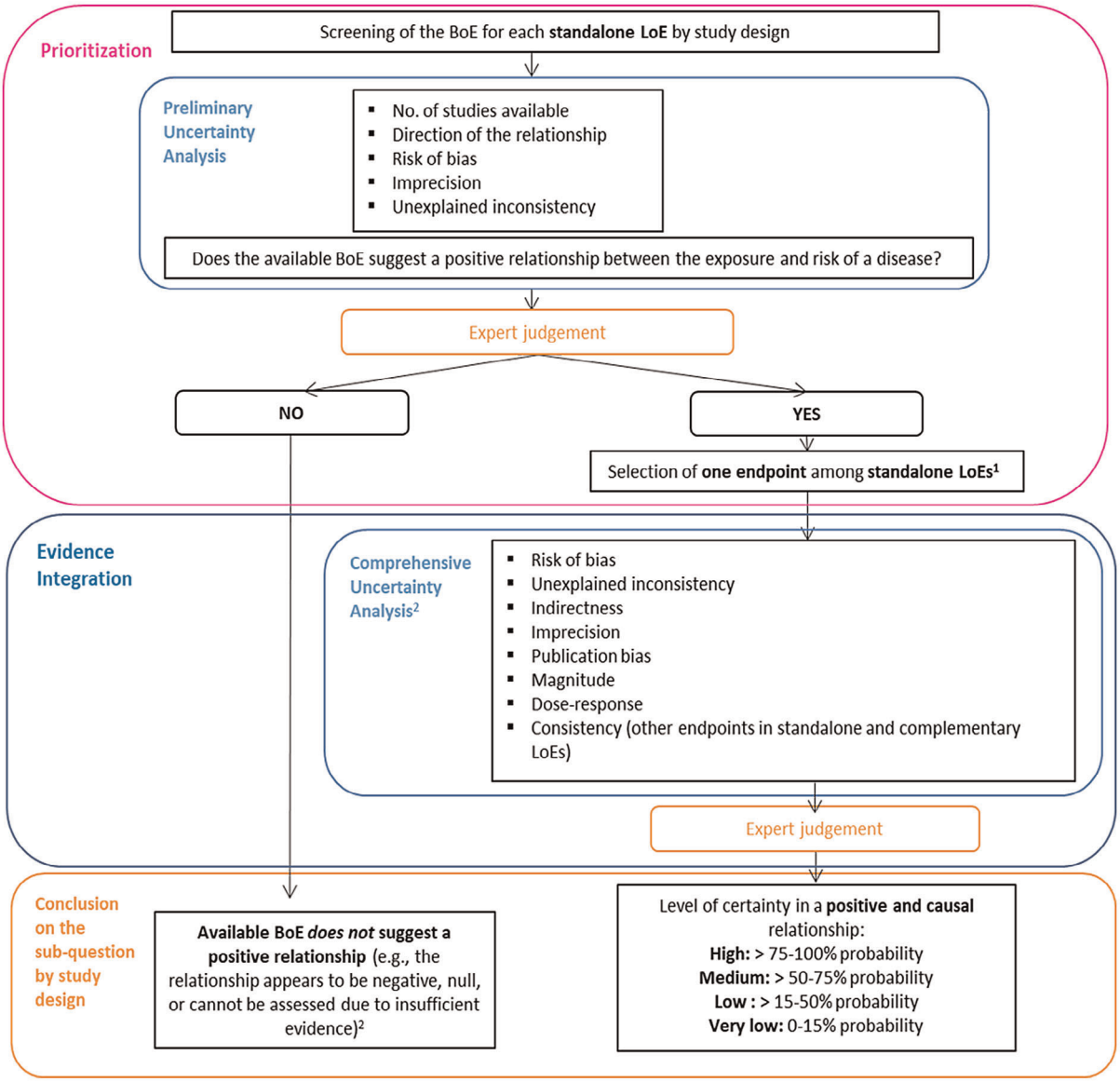


Figure 8: Graphical representation of standalone and complementary lines of evidence with some examples

Conclusions on each sQ are reached by study design (RCTs separately from PCs), by considering the uncertainties in the BoE and in the methods and by integrating the relevant LoEs. A stepwise approach is applied as illustrated in **Figure 9**. It involves a prioritisation step to identify sQs for which the available BoE suggests a positive relationship between the exposure and risk of disease based on a preliminary uncertainty analysis (UA) and expert judgement. A comprehensive UA (adapted from the OHAT approach as described below) is then applied to the selected sQs to express the level of certainty that a positive and causal relationship exists (see **Figures 10 and 11**). The Panel considers that sQs for which the available BoE does not suggest a positive relationship (e.g. the relationship appears to be negative, null or cannot be assessed due to insufficient evidence) cannot be used to inform the setting of a UL/safe level of intake for dietary sugars or to provide advice on quantitative intakes for their sources (i.e. SSBs and FJs) based on safety considerations. These sQs will be used to identify data gaps and research needs, where appropriate.



[1]For subquestions with more than one standalone LoE, and for standalone LoEs with endpoints which are biologically related, the comprehensive uncertainty analysis is undertaken for the endpoint with the highest level of evidence for a positive relationship with the exposure. The endpoint will be selected by expert judgement i.e. considering the number of studies available, and the strength, consistency and biological plausibility of the relationship.
[2]Complementary LoEs are assessed and discussed considering the factors underpinning the preliminary UA to provide a complete picture of the evidence base available for the sQ and inform the identification of data gaps. Yet, in the absence of evidence from Standalone LoE, evidence from complementary LoEs cannot be used to conclude on a positive and causal relationship between the exposure and the risk of disease.

Figure 9: Stepwise approach for evidence integration and uncertainty analysis applied to each subquestion by study design

The prioritisation step focuses on standalone LoEs. Data from complementary LoEs are not considered at this step because, on their own, they cannot answer the sQ and thus cannot be used to conclude on a positive and causal relationship between the exposure and the risk of disease. However, when the BoE for standalone LoEs does not suggest a positive relationship between the exposure and the risk of disease, complementary LoEs will nevertheless be assessed and discussed considering the factors underpinning the preliminary UA as depicted in **Figure 9**, in order to provide a complete picture of the evidence base currently available for the sQ and inform the identification of data gaps.

In the preliminary UA, the judgement applied to determine whether the BoE suggests a positive relationship between the exposure and the risk of disease includes considerations around the statistical

significance of study results. EFSA recommends that less emphasis is placed upon the reporting of statistical significance and more on statistical (point) estimation (i.e. effect estimate) and associated interval estimation (i.e. confidence interval) (EFSA Scientific Committee, 2011). In fact, point estimates and related confidence intervals are reported in evidence tables and plots, and full use of them is made during the judgement. However, for practical reasons, the terms 'non-significant' and 'significant', which usually imply making reference to a conventional cut-off for the p value of the statistical test applied, are used when reporting the results of individual studies in the preliminary UA.

The principles for the UA (**Figure 10**) have been derived from the OHAT 7-step framework for systematic review and evidence integration (NTP, 2019). The latter includes three steps to reach conclusions on hazard identification: (i) 'rating the confidence[14]' in the body of evidence, i.e. expressing the likelihood that the true effect is reflected in the apparent relationship (step 5); (ii) translating confidence ratings into 'level of evidence' for 'health effect' or 'no health effect' (step 6); (iii) integrating evidence from human and animal studies, along with other relevant data (e.g. mechanistic data) (step 7).

The following adaptations have been applied to the OHAT approach:

a) The assessment is restricted to the identification of adverse health effects in the BoE, i.e. positive and causal relationship between the exposure and risk of disease. This involves a prioritisation step, as described above, and a comprehensive UA to conclude on the level of certainty for the positive and causal relationship identified in the BoE. In contrast to OHAT, whenever a positive relationship is not identified for an sQ at the prioritisation step, no comprehensive UA is undertaken and no conclusions are made about other possible relationships (i.e. null denoting no health effect; negative, denoting a beneficial health effect) (see **Figure 10**).
b) Consequently, this assessment combines steps 5 and 6 from OHAT. The final level of certainty expresses the probability that a positive and causal relationship exists between the exposure and risk of disease, considering the limitations in the BoE and in the methods used to address it. The Bradford Hill criteria on causality as used in the OHAT approach (strength, consistency, temporality, biological gradient, biological plausibility, experimental evidence for causal association; Table 14 in OHAT handbook (NTP, 2019) are applied to judge on causality.
c) In line with OHAT's principles, the BoE on a particular sQ is given an initial level of certainty based on study design. In the OHAT's framework, the 'initial confidence rating' is expressed through four qualitative descriptors, i.e. 'high', 'moderate', 'low', 'very low'. It is assigned by considering four features of the design i.e. exposure is experimentally controlled, exposure occurs prior to the endpoint, endpoint is assessed at individual level and an appropriate comparison group is included in the study. As a result, OHAT proposes that RCTs start with a 'high' confidence rating (likely to comply with all four the above-mentioned criteria), while prospective cohort studies (where the exposure is unlikely to be controlled) start with a 'low' to 'moderate' confidence rating (Table 8 in OHAT handbook (NTP, 2019), depending on whether the exposure precedes the outcome or not. The Panel agrees with the rationale behind this initial rating but notes that qualitative descriptors bear some ambiguity (EFSA Scientific Committee, 2018). Therefore, OHAT's 'initial confidence ratings' have been translated into 'initial levels of certainty' expressed as approximate probabilities (**Figure 10**).
d) Similarly, the final level of certainty for a positive and causal relationship between the exposure and risk of disease is expressed in terms of probabilities, rather than using qualitative descriptors (**Figure 10**).
e) Among the criteria considered to downgrade the certainty in the BoE, the evaluation of indirectness is restricted to how the endpoint assessed in the studies relates to the main (disease) endpoint. External validity will be considered when drawing overall conclusions on hazard identification (Step 7 in OHAT). The other criteria, i.e. risk of bias across studies, unexplained inconsistency, imprecision and publication bias, are used according to OHAT's principles. Criteria for downgrading the certainty in the BoE will be considered first and will be systematically addressed in comprehensive UAs.
f) Among the criteria considered to upgrade the certainty in the BoE, consistency is assessed by considering the consistency in the evidence available on endpoints which are biologically

[14] The concept of 'confidence' as used in OHAT framework is equivalent to the concept of 'certainty' in EFSA's terminology (EFSA guidance on U).

related under each sQ (i.e. standalone LoEs and complementary LoEs which pertain to the sQ of interest, as outlined in **Table 12**). At this step, the consistency across LoEs is considered for each type of study design separately. Consistency of the evidence across study designs is considered in a final integration step (see below and **Figure 10**). The other criteria, i.e. magnitude, dose-response, residual confounding and other related factors, are used according to OHAT's principles. Criteria for upgrading the certainty in the BoE will be systematically considered but only reported on when deemed relevant to the BoE.

g) The level of certainty in a positive and causal relationship between the exposure and disease risk in this assessment is based on human data alone. Consistent with the OHAT framework, mechanistic data and mode of action are not required to reach hazard identification conclusions for each specific exposure–disease endpoint. This information will be discussed narratively when summarising the overall conclusions on hazard identification. However, different from the OHAT framework, it will not be used to upgrade or downgrade the level of certainty on the relationship between the intake of dietary sugars and disease risk because mechanistic data have not been systematically searched for or appraised, as foreseen in the protocol.

h) A comprehensive UA will not be undertaken on a BoE consisting of less than three independent studies because some criteria that should be considered to downgrade the certainty in the BoE cannot be assessed (e.g. heterogeneity). In that case, the initial level of certainty assigned to the relationship will be 'very low' (0–15% probability) to reflect the limited BoE available. In this case, the characteristics of the available studies (e.g. sample size, magnitude of the effect, risk of bias) and the biological plausibility of the relationship (including mode of action) will be considered to upgrade the level of certainty where appropriate. When the BoE for an exposure–disease relationship is limited to one or two studies, data supporting its biological plausibility become a critical feature of the available evidence that could increase the Panel's level of certainty on the relationship.

i) Step 7 in OHAT is not applied.

A schematic representation of the approach for assessing the final level of certainty in the hazard identification conclusions by study design is provided in **Figure 10**.

Initial level of certainty by study design	Factors decreasing certainty	Factors increasing certainty	Final level of certainty
High: > 75-100% probability RCTs Moderate: > 50-75% probability PCs *assessing the exposure (or change thereof) prior to the endpoint* Low: > 15-50% probability PCs *assessing changes in the exposure and concurrent changes in the endpoint* Very low: 0-15% probability	• risk of bias across studies (limitations to internal validity) • Unexplained inconsistency (heterogeneity) • indirectness of the endpoint to the main (disease) endpoint • imprecision • publication bias	• large magnitude of the effect (or a strong association/response) • dose-response (monotonic or not) • residual confounding or other factors that would increase certainty in the estimated effect (for PCs only) • consistency (across endpoints in standalone and complementary LoEs)	**High:** > 75-100 % probability **Moderate:** >50-75 % probability **Low:** > 15-50% probability **Very low:** 0-15 % probability

(a): Adapted from OHAT (NTP, 2019).

Figure 10: Approach applied to assign the final level of certainty in a causal relationship(a)

This type of approach cannot be implemented according to fixed objective criteria – expert judgement is needed, which implies some subjectivity in each decision. However, it provides a reproducible and transparent framework for expressing uncertainty in the evidence and in the methods.

Hazard identification conclusions for each sQ across study designs will be primarily based on the evidence with the highest certainty on the relationship. Consistent results across study designs can result in higher certainty on the causality of a positive relationship (**Figure 11**). Limitations in the BoE regarding the external validity of the results with respect to the exposure level and setting (population subgroup) will be discussed in the hazard characterisation step (Section 11).

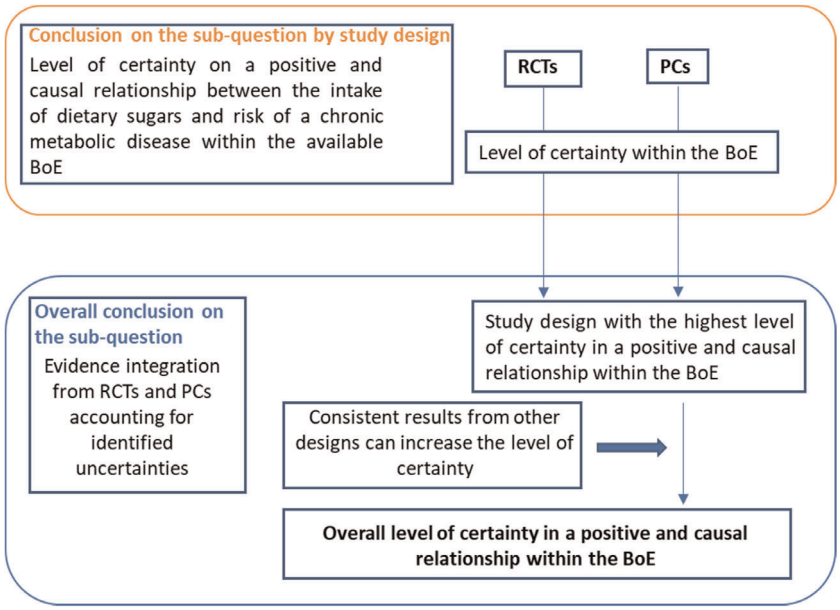


Figure 11: Approach for evidence integration and uncertainty analysis across study designs applied to each subquestion

Table 12 outlines the subquestions (sQ) and the LoEs considered in relation to each metabolic disease. The table also provides information on the eligible studies by type of design and exposure, the number and type of studies available for each LoE and identifies data gaps in the BoE.

For the risk of obesity, two disease endpoints are included in the standalone (main) LoE: (a) incidence of obesity based on BMI cut-offs, and (b) incidence of abdominal obesity based on WC cut-offs, as either one on its own could answer the sQ. Measures of body weight/BMI and WC are included in the standalone (surrogate) LoE. Measures of body fat and abdominal fat are considered as complementary LoEs.

Changes in skeletal muscle fat and visceral adipose tissue are considered in a complementary LoE for the sQ on the risk of NAFLD/NASH because these two variables are reported in studies which investigate the effect of sugars on liver fat.

Measures of glucose homeostasis have been grouped in LoE which follow the natural history of type 2 diabetes, i.e. from those that are expected to be impaired first to those expected to be impaired later in time:

a) Measures of insulin sensitivity obtained either in steady-state conditions (during an euglycaemic hyperinsulinaemic clamp) or in non-steady state conditions (e.g. during an intravenous glucose with frequent sampling/minimal model assessment (IVGTT)).
b) Indices of insulin sensitivity/resistance and indices of insulin secretion/beta cell function, either derived from the fasting state (e.g. HOMA-IR, HOMA-beta) or from an OGTT (e.g. Matsuda index of insulin sensitivity).
c) Measures of glucose tolerance, either derived from the fasting state (fasting glucose and insulin) or from an oral glucose tolerance test (OGTT), including glucose and insulin at 120 min and areas under the curve (AUC) for glucose and insulin.
d) Measures of blood glucose control, including fructosamine, glycated albumin and glycated haemoglobin.

LoE c) is considered standalone (surrogate) because cut-off values for fasting glucose and for glucose at 120 min during an OGTT are used for the diagnosis of diabetes. Within this LoE, measures of fasting insulin and insulin at 120 min during an OGTT will be considered as complementary. In contrast, LoEs (a) and (b) are considered complementary because, on their own, they cannot answer the sQ about the risk of T2DM. Although measures of blood glucose control (LoE d) are relevant endpoints, these are not expected to change significantly in non-diabetic individuals (RCTs in diabetics were not eligible). Indeed, the four RCTs with an appropriate duration that investigated the effect of added sugars on measures of blood glucose control, with sugar doses ranging from 6 to 24 E%, did not show significant differences between the high and low sugar arms on fructosamine (Gostner et al., 2005; Stanhope et al., 2009), glycosylated albumin (Swanson et al., 1992) or glycated haemoglobin (Hernandez-Cordero et al., 2014). Consequently, this LoE will not be considered further.

Risk of T2DM is considered as complementary LoE for the risk of dyslipidaemia because high fasting TG and low HDL-cholesterol are characteristic of insulin resistance states (such as the metabolic syndrome) and T2DM.

For LoEs with more than one endpoint (e.g. measures of glucose tolerance, blood lipids) studies reporting on at least one endpoint which is pertinent to the LoE (e.g. fasting glucose, HDL-cholesterol) have been counted. Studies reporting on multiple endpoints that belong to the same LoE (e.g. total cholesterol, triglycerides and HDL-cholesterol; incidence of obesity, incidence of abdominal obesity) have been counted only once.

Table 12: Subquestions for hazard identification, lines of evidence and number of studies included by study design

sQ1: Is the intake of **total sugars** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) Randomised controlled trials (RCTs) providing different amounts of total sugars through the manipulation of free sugars and sugars in intact fruits, vegetables and milk – None
b) Prospective cohort studies (PCs) on total sugars from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ1.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**3**
LoE3. Complementary	Body fat, abdominal fat	0	2
sQ1.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	**1**
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity (sQ1.1)	sQ1.1.	sQ1.1
sQ1.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**4***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	**1**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
sQ1.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c and derived indices	0	**2**
LoE3. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
sQ1.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	SBP and/or DBP	0	**1**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0	0

LoE4. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
sQ1.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint), CHD or stroke	0	**8**
LoE2. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ1.3)	sQ1.3	sQ1.3
LoE4. Complementary	Risk of dyslipidaemia (sQ1.4)	sQ1.4	sQ1.4
LoE5. Complementary	Risk of hypertension (sQ1.5)	sQ1.5	sQ1.5
LoE6. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ1.5)	LoE3 for sQ1.5	LoE3 for sQ1.5
sQ1.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ1.5)	LoE3 for sQ1.5	LoE3 for sQ1.5
LoE3. Complementary	Risk of obesity (sQ1.1)	sQ1.1	sQ1.1

sQ2: Is the intake of **added and free** sugars positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) Randomised controlled trials (RCTs) providing different amounts of added and free sugars from foods, beverages or food and beverages
b) Prospective cohort studies (PCs) on added sugars, sucrose (as surrogate for added sugars) and free sugars from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ2.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**11(+2)**	**8**
LoE3. Complementary	Body fat, abdominal fat	5	4
sQ2.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**4**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/3	0
LoE4. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
sQ2.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**4**
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**17**	**2**
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	5	2
LoE4. Complementary	Measures of insulin sensitivity	7	0
LoE5. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
sQ2.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**24**	**3**
LoE3. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
sQ2.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	0
LoE2. Standalone (surrogate)	SBP and/or DBP	**10**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/7	0
LoE4. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
sQ2.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**

LoE2. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ2.3)	sQ2.3	sQ2.3
LoE4. Complementary	Risk of dyslipidaemia (sQ2.4)	sQ2.4	sQ2.4
LoE5. Complementary	Risk of hypertension (sQ2.5)	sQ2.5	sQ2.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ2.5)	LoE3 for sQ2.5	LoE3 for sQ2.5
sQ2.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	0
LoE2. Complementary	Incidence of hyperuricaemia/ uric acid (LoE 3 for sQ2.5)	LoE3 for sQ2.5	LoE3 for sQ2.5
LoE3. Complementary	Risk of obesity (sQ2.1)	sQ2.1	sQ2.1

sQ3: Is the intake of **fructose** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing similar intakes of fructose and glucose from foods, beverages or food and beverages
b) RCTs comparing different amounts of fructose from foods, beverages or food and beverages
c) PCs on fructose, free fructose and free glucose (as comparator for free fructose) from all sources

LoE	Endpoints	RCTs (n)	PCs (n)
sQ3.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	0
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**2**	**2**
LoE3. Complementary	Body fat, abdominal fat	1	1
sQ3.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	2/2	0
LoE4. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
sQ3.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**3**
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**10**	0
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	5	1
LoE4. Complementary	Measures of insulin sensitivity	6	0
LoE5. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
sQ3.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	0
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**10**	**1**
LoE3. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
sQ3.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**3**
LoE2. Standalone (surrogate)	SBP and/or DBP	**5**	**2**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/5	0
LoE4. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
sQ3.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ3.3)	sQ3.3	sQ3.3
LoE4. Complementary	Risk of dyslipidaemia (sQ3.4)	sQ3.4	sQ3.4
LoE5. Complementary	Risk of hypertension (sQ3.5)	sQ3.5	sQ3.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ3.5)	LoE3 for sQ3.5	LoE3 for sQ3.5

sQ3.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ3.5)	LoE3 for sQ3.5	LoE3 for sQ3.5
LoE3. Complementary	Risk of obesity (sQ3.1)	sQ3.1	sQ3.1

sQ4: Is the intake of **SSBs** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing different amounts of SSBs or mixtures of fructose and glucose in beverages
b) PCs on SSBs or on added sugars from beverages

LoE	Endpoints	RCTs (n)	PCs (n)
sQ4.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**10**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	**6(+2)**	**21**
LoE3. Complementary	Body fat, abdominal fat	4	6
sQ4.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	**3**	0
LoE3. Complementary	Skeletal muscle fat/visceral adipose tissue	2/2	0/1
LoE4. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
sQ4.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**14***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	**7**	1
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	3	2
LoE4. Complementary	Measures of insulin sensitivity	3	0
LoE5. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
sQ4.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**5**
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	**7**	**4**
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
sQ4.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**7**
LoE2. Standalone (surrogate)	SBP and/or DBP	**4**	**1**
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0/3	1/0
LoE4. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
sQ4.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**10**
LoE2. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ4.3)	sQ4.3	sQ4.3
LoE4. Complementary	Risk of dyslipidaemia (sQ4.4)	sQ4.4	sQ4.4
LoE5. Complementary	Risk of hypertension (sQ4.5)	sQ4.5	sQ4.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ4.5)	LoE3 for sQ4.5	LoE3 for sQ4.5
sQ4.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid	LoE3 for sQ4.5	LoE3 for sQ4.5
LoE3. Complementary	Risk of obesity (sQ4.1)	sQ4.1	sQ4.1

sQ5: Is the intake of **FJs** positively and causally associated with the risk of chronic metabolic diseases at the levels of intake and in the population subgroups investigated in the studies eligible for this assessment?
Eligible studies by exposure:

a) RCTs comparing different amounts of fruit juices – None
b) PCs on fruit juices

LoE	Endpoints	RCTs (n)	PCs (n)
sQ5.1. Risk of obesity			
LoE1. Standalone (main)	Incidence of obesity, incidence of abdominal obesity	0	**2**
LoE2. Standalone (surrogate)	Body weight/BMI, waist circumference	0	**10**
LoE3. Complementary	Body fat, abdominal fat	0	3
sQ5.2. Risk of NAFLD/NASH			
LoE1. Standalone (main)	Incidence of NAFLD/NASH	0	0
LoE2. Standalone (surrogate)	Liver fat	0	0
LoE3. Complementary	Skeletal muscle fat and visceral adipose tissue	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
sQ5.3. Risk of Type 2 diabetes mellitus			
LoE1. Standalone (main)	Incidence of T2DM	0	**9***
LoE2. Standalone (surrogate)	Measures of glucose tolerance	0	0
LoE3. Complementary	Indices of insulin sensitivity/beta-cell function	0	0
LoE4. Complementary	Measures of insulin sensitivity	0	0
LoE5. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
sQ5.4. Risk of dyslipidaemia			
LoE1. Standalone (main)	Incidence of high total-c, LDL-c, TG or low HDL-c (cut-offs)	0	**1**
LoE2. Standalone (surrogate)	Total-c, LDL-c, TG, HDL-c or derived indices	0	0
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE4. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
sQ5.5. Risk of hypertension			
LoE1. Standalone (main)	Incidence of hypertension	0	**2**
LoE2. Standalone (surrogate)	SBP and/or DBP	0	0
LoE3. Complementary	Incidence of hyperuricaemia/uric acid	0	0
LoE4. Complementary	Risk of obesity (sQ5.1)	sQ1.1	sQ1.1
LoE5. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
sQ5.6. Risk of cardiovascular diseases (CVDs)			
LoE1. Standalone (main)	Incidence and mortality: CVD (composite endpoint) or as CHD or stroke	0	**3**
LoE2. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1
LoE3. Complementary	Risk of Type 2 diabetes mellitus (sQ5.3)	sQ5.3	sQ5.3
LoE4. Complementary	Risk of dyslipidaemia (sQ5.4)	sQ5.4	sQ5.4
LoE5. Complementary	Risk of hypertension (sQ5.5)	sQ5.5	sQ5.5
LoE6. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ5.5)	LoE3 for sQ5.5	LoE3 for sQ5.5
sQ5.7. Risk of gout			
LoE1. Standalone (main)	Incidence of gout	0	**2**
LoE2. Complementary	Incidence of hyperuricaemia/uric acid (LoE 3 for sQ5.5)	LoE3 for sQ5.5	LoE3 for sQ5.5
LoE3. Complementary	Risk of obesity (sQ5.1)	sQ5.1	sQ5.1

BMI, body mass index; CHD, coronary heart disease; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; LoE, line of evidence; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCs, prospective cohorts; RCTs, randomised controlled trials; SBP, systolic blood pressure; sQ, subquestion; T2DM, type 2 diabetes mellitus; TG, triglycerides; total-c, total cholesterol.
*: Includes prospective case-cohort studies. Grey cells denote the absence of eligible studies. Number of studies in standalone LoEs are in **bold**.