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Sugar intake of children in the "Childhood Obesity Project" trial

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Table of content

1. Abbreviations

BMI	Body mass index
CHOP	Childhood Obesity Project
CVD	Cardiovascular diseases
FMI	Fat mass index
FS	Free sugar
HDL-C	High density lipoprotein cholesterol
HOMA	Homeostasis model assessment
LDL-C	Low density lipoprotein cholesterol
NCD	Non- communicable diseases
OR	Odds ratio
SSB	Sugar sweetened beverages
TC	Total cholesterol
TEI	Total energy intake
TG	Triglycerides
TS	Total sugar
WHO	World Health Organization

2. Publications

This thesis consists of the following publications:

Publication I:

Associations of sugar intake with anthropometrics in children from ages 2 until 8 years in the EU Childhood Obesity Project.
Aumueller N, Gruszfeld D, Gradowska K, Escribano J, Ferré N, Rousseaux D, Hoyos J, Verduci E, ReDionigi A, Koletzko B, Grote V**.** *Eur J Nutr (2019).*
https://doi.org/10.1007/s00394-019-02107-0

Publication II:

Influence of total sugar intake on metabolic blood markers at 8 years of age in the Childhood Obesity Project.
Aumueller N, Gruszfeld D, Gradowska K, Escribano J, Ferré N, Martin F, Poncelet P, Verduci E, ReDionigi A, Koletzko B, Grote V**.** *Eur J Nutr (2020).*
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3. Introduction

Non- communicable diseases (NCDs) are the most prevalent cause of deaths worldwide (1, 2). In 2016, about 41 million deaths worldwide were caused by NCDs, with the majority due to four main conditions: cardiovascular disease (CVD) (44% of all NCD deaths), cancer (22%), chronic respiratory disease (9%), and diabetes (4%) (1). Although the risk of dying between ages 30 and 70 from any of those four main NCDs decreased from 22% in 2000 to 18% in 2016, it is still a major health concern (1). Obesity and overweight are important risk factors for several NCDs, such as CVD and diabetes (2). Obesity and overweight are widely prevalent: In 2014, 39% of adults were overweight and 13% obese (2). In children a worldwide increase of overweight and obesity prevalence during the last few decades was observed: in 2000 the percentage of overweight or obese children younger than 5 years of age was 4.9% whereas it increased to 5.9% by 2018 (3). It is suggested that this increasing trend will continue and rise up to a worldwide prevalence of 11% by 2025 (2). In 4 to 7-year-old European children, percentage of overweight ranged in 2012 from 8% to 30% and obesity from 1% to 13%. In Germany and Belgium were lowest rates observed and highest in southern European countries, such as Greece and Spain (4).

In addition to overweight and obesity, elevated blood pressure and dyslipidemia are further risk factors for CVDs, favoring the development of atherosclerotic plaques (2, 5 , 6). An increasing prevalence of dyslipidemia and high blood pressure has been reported in childhood (7). The presence of these risk factors during childhood has been associated with increased risks of dyslipidemia, hypertension, and CVD in adulthood (8-10). Another risk factor for CVDs is hyperglycaemia (11), which increases the likelihood of developing insulin resistance and diabetes (12, 13). Due to the high prevalence of NCDs, their early onset, and the propagation of their development by overweight/obesity and altered lipid and glucose metabolism in childhood, factors enhancing or causing the development of NCDs and their risk factors in young ages need to be identified.

Sugar intake as proposed risk factor for NCDs, and mediating factors

Several lifestyle factors have been identified as risk factors for NCDs or as mediators for NCDs such as overweight/obesity, or altered glucose or lipid metabolism. These include air pollution, tobacco use, physical inactivity, alcohol abuse, and a poor quality diet (1, 14). Several health institutes focus on nutrition and encourage people to improve their diet to decrease the prevalence of overweight/obesity, altered glucose or lipid metabolism, and NCDs (2, 15, 16). Beside recommendations of e.g. increasing vegetable, fruit, and fiber intake and limit salt and meat intake, one important characteristic of a healthy diet is to limit sugar intake (16, 17). Most health institutes differentiate between three types of sugars: first, "total sugar" (TS), which comprises all mono- and disaccharides; second, "added sugar", which includes all types of sugars, which are added to food or beverages during food production, processing, or preparation; and lastly "free sugar" (FS), which consists of added sugar and sugars naturally prevalent in honey, syrups, and fruit juices (17). In general, naturally and added sugars are metabolized in the same way by the body. Nevertheless, food products with 'added sugar' or FS have, in general, a lower nutrient density compared to food products with naturally occurring sugar (18).

During the last few decades, high sugar intakes have become highly prevalent in adults as well as in children (17, 19). In a review by Azaïs-Braesco et al., which included data from 10 European countries, TS intake in adults (N~20,000) ranged from 15 to 21% of total energy intake (TEI) and from 16 to 26% in children (N~9,000) (20). In a Dutch survey performed between 2007 and 2010, energy percentage from TS in men and women (7 to 69 years) was estimated as 22% and 14% from FS. Sugar consumption in adults was reported to be lower than in children: in children (7 to 8 years) TEI from TS was 28% and 20% from FS (21). In German children (3 to 18 years) from the DOrtmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study, 24 to 28% of TEI came from TS and 15 to 18% from FS (22). In the multicentric European Identification and

prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS (IDEFICS) study including children from 2 to 9 years of age (from Germany, Sweden, Estonia, Spain, Cyprus, Italy, Hungary, Belgium), energy from TS was estimated as 23% and FS as 18%, ranging in FS intake from 13% in Italy to 27% in Germany (23).

There is increasing concern that high intakes of sugar, particularly added sugar, FS, and sugar-sweetened beverages (SSB), favor the development of overweight and obesity (17, 24, 25), as well as alter lipid and glucose metabolism by contributing to high triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) , and low high-density lipoprotein cholesterol (HDL-C) concentrations (26-32). This is in line with altered concentrations of insulin, glucose, and high homeostasis model assessment (HOMA) levels (33-35). Therefore, the American Heart Association recommended in 2017 to limit added sugar intake in adults to ≤25g (100 kcal or about 6 teaspoons) per day (36). In 2015 the World Health Organization (WHO) focused on FS and recommended for children and adults to decrease the contribution of FS intake to TEI below 10% and suggested to aim at a lower energy intake from FS of less than 5% (17). Those recommendations are, however, mainly based on research results investigating sugar intake on dental health. Studies examining the effect of increasing sugar intake on various outcomes, such as overweight and obesity, CVD, and diabetes, are still inconclusive (17).

Despite these recommendations, sugar intakes in children and in adults are generally above the recommendation of 10% of TEI from FS. In the European Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS (IDEFICS) study, less than 20% of children were beyond 10% of TEI from FS and in a Dutch survey, only 5% of children met the WHO recommendation (21). While sugar intakes in children and adults are currently high and in general above the recommendations, sugar consumption seems no longer to rise, but even partly to decrease (22, 37). Health institutes expect that due to the reduction in sugar intake a decrease in NCDs and their risk factors will be achieved (17, 25, 36).

Outline of this doctoral thesis

The objective of this doctoral thesis is to examine whether sugar intake in early childhood has an influence on two different risk factors of NCDs: overweight and obesity, and unfavorable blood markers of lipid and glucose metabolism. This compromises also different types of sugars and sugar intake from major sugar contributing food groups, as milk products, fruit products, confectionaries, SSBs, and bread and cereals. First, the association of TS and FS intake from SSBs and fruit juices with anthropometric measures and the development of overweight and obesity is determined in a longitudinal analysis from 2 to 8 years of age. Afterwards the effects of TS and TS from major food groups on blood markers of lipid and glucose metabolism will be investigated at 8 years of age.

Data is drawn from the "Childhood Obesity Project" trial (CHOP), a European multicenter double- blind randomized nutritional intervention trial during the first year of life with long-term follow-up. Healthy term infants born after uncomplicated singleton pregnancies were recruited in five European countries (Belgium, Germany, Italy, Poland, Spain) and randomized to a higher or lower protein content formula (38). In addition, a reference group of breastfed children was recruited. Participating children were followed up until the age of 11 years. The primary aim of the CHOP study was to investigate how lower or higher protein content formula influences the growth development of children. Data from 2 to 8 years of age were used in the analysis of this doctoral thesis. Nutrition was assessed by 3-day-weighed food protocols, which is considered as the method that assesses dietary intake most precisely [36]. An outline of the specific research questions and methodological approaches will be presented in the following.

Publication I

In the first publication of this thesis, the focus lies on the association of TS intake with overweight and obesity. Several studies indicate that increasing sugar intake is linked to higher weight gain in children and adults (17, 25). Yet, published studies are still

inconclusive as to whether an association of the nutrient sugar itself with anthropometric measures exists or whether the reported associations are due to increased TEI during a diet with high sugar intake (39, 40). Te Morenga et al. concluded in their meta-analysis that the effect of sugar intake on body fatness is due to altered energy balance and less due to physiological mechanisms of mono- and disaccharides (39). This is supported by several other researchers (41, 42). Nevertheless, randomized controlled trials and cohort studies, especially in children, are limited and cover often only a short age period (39, 42). Additionally, results may vary depending on age, type of sugar examined (e.g. TS, FS, added sugar, or specific sugars like fructose), form of sugar intake (e.g. liquid or solid), and whether an adjustment for TEI was performed (39-41). Therefore, this association is optimally investigated in a cohort with the possibility to examine longitudinal changes, different forms of sugar intake, and with and without adjustment for TEI. As all this information are available in the CHOP study, the trial was suitable for the investigation of the association of sugar intake with anthropometrics.

Nutrition in the CHOP study was assessed yearly from 2 to 6 years and at 8 years of age by 3-day-weighed food protocols. On the basis of the German food composition database (BLS II, Federal Institute for Risk Assessment [BfR]; www.bfr.bund.de) nutrient intakes were calculated, because it was the most comprehensive and most appropriate database at the time of study planning. As nutrition data and anthropometry were measured at several time points, a longitudinal analysis was performed.

When looking at sugar intake and its relation to weight, which is highly correlated to TEI, it is important to take TEI into consideration in the analysis. There are four techniques, which are widely used to adjust for energy intake: the energy- adjusted/ residual method, the standard multivariate method, the energy partition method, and the multivariate nutrient density method (43). 1) In the energy- adjusted/ residual method (SugarResidual / SugarResidual + TEI), the TEI is regressed on the investigated nutrient and the residuals from this regression are used in further analysis. If the outcome of the further analysis is

highly TEI dependent, like overweight, it is recommended to additionally adjust for TEI in the analysis. 2) In the standard multivariate method ($Sugar_{Cal}$ + TEI) the calories from the investigated nutrient are included into the model and additionally adjusted for TEI. 3) The energy partition method ($Sugar_{Cal}$ + $OtherMacronutrients_{Cal}$) includes calories from the investigated nutrient and the calories from all other macronutrients. 4) The multivariate nutrient density method ($Sugar_{\%}$ + TEI) uses the energy percentage of the investigated nutrient and adjusts additionally for TEI. For every macronutrient or nutrient analysis, it should be carefully considered which method fits best for the hypothesis of the investigation (43). As in this doctoral thesis increasing intake of calories from sugar intake, and for example not the increasing energy percentage from sugar intake compared to other nutrients, should be investigated, the energy-adjusted/residual method was chosen. Another advantage of this method is that it takes the high correlation between TEI and the outcome BMI as well as the high correlation of sugar intake with TEI into consideration, which makes it suitable for the analysis of this thesis.

It was shown that on an energy-equivalent basis, increasing TS is associated with lower BMI and fat mass index (FMI) z-score (BMI and FMI standardized for age and gender). Contrary, in an ad libitum diet with increasing TS, without adjustment for TEI, an association with increasing zBMI and zFMI was observed. Neither increasing the SSB intake, nor increasing the fruit juice consumption was associated with zBMI or zFMI on an energy-equivalent basis. No changes over time were seen. Therefore, no indication is provided that TS intake of children increasingly affects BMI or FMI on an energy-equivalent basis. This supports the conclusion of Te Morenga et al. and Rippe et al. (39, 41, 42). Attention should be directed more on reducing TEI to prevent overweight. Nevertheless, dietary products with high sugar intake, especially with free sugars, are often accompanied by a high energy density and low nutritional density and add unnecessary and dispensable energy (18).

Publication II

The second part of this doctoral thesis investigates the influence of sugar intake on blood risk markers of disorders such as CVD and diabetes. This comprises blood lipids, including triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and the TG/HDL-C ratio, as well as markers of glucose metabolism, including insulin, blood glucose, and the homeostasis model assessment (HOMA) as a marker for insulin resistance. There are several physiological mechanisms explaining how increase in sugar intake might lead to unfavorable blood markers of blood lipid or glucose metabolism: high fructose intake has been shown to stimulate hepatic fat synthesis (44, 45), leading to increased circulating concentrations of TG and TC, while endothelial lipoprotein lipase activity in adipose tissues decreases, which reduces peripheral lipid clearance (44-46). In addition, some sugar types, such as glucose and maltose, are rapidly absorbed and utilized. This rapid absorption induces a quick increase of plasma glucose and insulin levels, which may cause insulin resistance, inflammation, and increased long-term cardiovascular risk (45).

Some epidemiological studies reported a significant association of high dietary sugar intakes with unfavorable TG, LDL-C, HDL-C, TC, TG/HDL-C ratio, insulin, glucose, and HOMA values (26-35). In a meta-analysis by Te Morenga et al. investigating mainly adults, a high sugar diet was associated with increased TG, LDL-C, and TC concentrations (26). However, these results may also be influenced by dietary advice within the studies and less due to increasing sugar intake (26). High quality randomized control trials and cohort studies are limited in children (26). Therefore, studies in children are especially needed to identify whether sugar intake in children is associated with blood markers of lipid and glucose metabolism. Hence, those associations were investigated in this doctoral thesis using data of the CHOP study.

In the CHOP study, both nutritional intake and blood markers were assessed at follow-up at 8 years of age. Therefore, a cross-sectional analysis was applied using linear regression models. Our analysis shows that HDL-C is the only blood marker which was significantly and negatively related to sugar intake. This was mainly driven by increased sugar intake from SSBs. For none of the other blood markers of lipid or glucose metabolism an association with sugar intake in 8-year-old children was observed. However, even the association with HDL-C was weak. A potential association of sugar intake, particularly from SSBs, with long-term NCD risk should be explored in further studies.

Contribution to the publications

For both publications I developed the specific research questions and conducted a statistical analysis plan to investigate those research questions. In accordance to the specific hypotheses, I adapted the pre-existing dataset, which was already collected and entered into the database by the different co-authors/partners from the five study countries. Following my statistical analysis plan, I analyzed the processed dataset using SAS 9.4. Both manuscripts were drafted by me and reviewed from all coauthors. I incorporated suggestions from co-authors and finalized both manuscripts for publication in the peer-reviewed scientific journals. I was in charge of the submission process to the journals and was responsible for the revision of the manuscripts according to the suggestion made during the peer-review process. In all steps I was supported by my supervisor.

4. Summary

Introduction:

High sugar intake has been suggested to be involved in the development of overweight and obesity and several associated NCDs such as diabetes and CVD. The aim of this doctoral thesis is to investigate whether a higher sugar intake in children is associated with two different risk factors of NCDs, i.e. overweight and obesity, and unfavorable blood markers of lipid and glucose metabolism.

Methods:

Data was drawn from the CHOP trial, a randomized controlled nutritional intervention trial in the first year of life with long- term follow-up. Infants from five European countries (Belgium, Germany, Italy, Poland, Spain) were randomized to feeding with a higher or lower protein content formula, and an additional breastfed reference group was recruited. Nutrition was assessed yearly from 2 to 6 years of age and again at age 8 years using 3-day-weighed food protocols. Anthropometric measurements were taken from 2 to 8 years of age, at the same time as nutrition assessments. A longitudinal analysis was performed to investigate the influence of sugar intake on age and gender standardized body mass index (BMI) and fat mass index (FMI) over time. A cross-sectional analysis at 8 years of age examined the association of sugar intake with several blood markers of lipid and glucose metabolism.

Results:

While increasing TS intake in an ad libitum diet was positively associated with BMI and FMI z-score, a negative association was observed on an energy-equivalent basis (zBMI: -0.033; 95% CI: -0.061, -0.005, zFMI: - 0.050; 95% CI: - 0.089, - 0.011 at an increase of 100 kcal from TS). Looking at blood markers, an increased consumption of 100 kcal from TS was significantly associated with a HDL-C z-score decrease (-0.14; 95% CI: -0.01, - 0.27). Increase of TS intake from SSBs showed the strongest association with a decrease in HDL-C z-score (-1.67; 95% CI: -0.42, -2.91). For none of the other investigated

markers of lipid or glucose metabolism a significant association with TS increase or TS increase of major food groups was observed.

Conclusions:

Results indicate that increasing TS intake in childhood does not affect overweight or obesity on an energy-equivalent basis. Additionally, on an energy-equivalent basis only HDL-C was unfavorably influenced by increasing TS intake and this association was very weak. The analysis of the current thesis suggests that increasing TS on an energy-equivalent basis in childhood have little impact on the investigated risk factors of NCDs. Therefore, for prevention of NCD risk factors in early childhood the reduction of TEI should be rather focused on. Nevertheless, a diet with a high sugar intake is generally not recommended, since dietary products with high sugar intake, especially with free sugars, are often accompanied by a low nutritional density and add unnecessary and dispensable energy.

5. Zusammenfassung

Einleitung:

Es wird angenommen, dass eine hohe Zuckeraufnahme an der Entstehung mehrerer nicht-übertragbarer Krankheiten, wie kardiovaskulären Erkrankungen und Diabetes, beteiligt ist und ebenfalls Übergewicht und Adipositas fördert, das als Risikofaktor für verschiedene nicht-übertragbare Krankheiten gilt. Ziel dieser Dissertation ist es, zu untersuchen, ob eine zunehmende Zuckeraufnahme bei Kindern mit zwei unterschiedlichen Risikofaktoren für nicht-übertragbare Krankheiten assoziiert ist: Übergewicht und Adipositas und unvorteilhafte Blutmarker des Lipid- und Glukosestoffwechsels.

Methoden:

Die verwendeten Daten stammen aus der CHOP-Studie, einer randomisiert kontrollierten Ernährungsstudie im ersten Lebensjahr mit einer langfristigen Nachuntersuchung der teilnehmenden Kinder. Neugeborene aus fünf Europäischen Ländern (Belgien, Deutschland, Italien, Polen, Spanien) erhielten eine Formula mit niedrigeren oder höheren Proteingehalt. Zusätzlich wurde eine Referenzgruppe mit gestillten Säuglingen rekrutiert. Die Ernährung wurde mit 3-Tage-Wiegeprotokollen jährlich im Alter von 2 bis 6 Jahren und erneut im Alter von 8 Jahren erfasst. Durch eine zeitlich parallele Erfassung der Anthropometrie konnte eine Längsschnittanalyse durchgeführt werden, um den Einfluss der Zuckeraufnahme auf geschlechts- und altersstandardisierten Body Mass Index (BMI) und Fat Mass index (FMI) über die Zeit zu betrachten. Blutmessungen und Ernährungsdaten waren nur im Alter von 8 Jahren zum gleichen Zeitpunkt verfügbar. Daher wurde zu Untersuchung des Zusammenhangs zwischen Zuckeraufnahme und verschiedenen Blutmarkern des Lipid- und Glukosestoffwechsels eine Querschnittsanalyse angewandt.

Ergebnisse:

Während eine erhöhte Gesamtzuckeraufnahme in einer ad-libitum-Ernährung positiv mit zBMI und zFMI assoziiert war, wurde auf energieäquivalenter Basis eine negative Assoziation beobachtet (zBMI: -0,033; 95% CI: -0,061, -0,005, zFMI: - 0.050; 95% CI: - 0.089, - 0.011 bei einem Anstieg von 100 kcal von Gesamtzucker). Weiterhin war eine Zunahme von 100 kcal Gesamtzucker signifikant mit einer Abnahme des z-Scores von HDL-C assoziiert (-0,14; 95% CI: -0,01, -0,27). Die erhöhte Aufnahme von Gesamtzucker durch zuckerhaltige Getränke zeigte die stärkste Assoziation mit einer Abnahme der HDL-C Konzentration (-1,67; 95% CI: -0,42, -2,91). Keiner der anderen Blutfett- oder Glukosestoffwechsel-bezogenen Marker zeigte eine signifikante Assoziation mit einer erhöhten Gesamtzuckeraufnahme.

Schlussfolgerungen:

Die Ergebnisse deuten darauf hin, dass eine zunehmende Gesamtzuckeraufnahme auf energieäquivalenter Basis keinen Einfluss auf Übergewicht oder Adipositas in der Kindheit hat. Darüber hinaus wurde auf energieäquivalenter Basis nur HDL-C durch eine erhöhte Zuckeraufnahme ungünstig beeinflusst und dieser Zusammenhang erwies sich als eher schwach. Die Analyse der aktuellen Doktorarbeit legt nahe, dass eine erhöhte Gesamtzuckeraufnahme auf energieäquivalenter Basis im Kindesalter wenig Einfluss auf die untersuchten Risikofaktoren von nicht-übertragbaren Krankheiten hat. Deshalb sollte für die Prävention von Risikofaktoren von nicht-übertragbaren Krankheiten in Kindern eher auf die Reduzierung der Energiegesamtaufnahme Fokus gelegt werden. Dennoch wird grundsätzlich von einer Ernährung mit hoher Zuckeraufnahme abgeraten, da Produkte mit hohem Zuckergehalt, besonders mit vielen freien Zuckern, oft mit einer niedrigen Ernährungsdichte einhergehen und zur Ernährung entbehrliche und austauschbare Energie hinzufügen.

6. Publication I

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ORIGINAL CONTRIBUTION

Associations of sugar intake with anthropometrics in children from ages 2 until 8 years in the EU Childhood Obesity Project

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Abstract

Purpose We determined the association of total sugar intake with body weight and fat mass in children on an energy-equivalent basis and potential changes in the association from 2 to 8 years of age.

Methods Data were available from the Childhood Obesity Project Trial initiated in 2002. Sugar intake was measured by 3-day weighed food protocols at 2, 3, 4, 5, 6, and 8 years of age. Body mass index (BMI) and fat mass index (FMI) were available at the same time points. To investigate the association of sugar intake with anthropometrics over time, linear mixed models were applied. Odds ratios for having a high BMI or FMI (above one standard deviation) were estimated by logistic random-effects models. To control for total energy intake, the residual method was chosen and models were additionally adjusted for total energy intake.

Results Data were available for 809 children with in total 2846 observations. In an isocaloric model, an increase of 100 kcal from sugar per day was significantly associated with lower zBMI (− 0.033; 95% CI −0.061, − 0.005) and zFMI (− 0.050; 95% CI − 0.089, − 0.011). In addition, a 100 kcal higher sugar intake was related to lower odds of having a high zBMI (OR 0.743; 95% CI 0.611, 0.903).

Conclusion This study provides no indication that increased total sugar intake positively affects BMI on an energy-equivalent basis. Whether the negative association of sugar is due to physiological effects or points more to macronutrient preferences or a reporting bias (lower sugar intake) in children with higher BMI can be debated.

Clinical trial registry ClinicalTrials.gov Identifier: NCT00338689; Registered: June 19, 2006. URL: http://clinicaltrials.gov/ct2/show/NCT00338689?term=NCT00338689&rank=1.

Keywords Sugar intake · Children · Overweight · BMI · Nutritional epidemiology

Abbreviations

BMI	Body mass index
CHOP	Childhood Obesity Project
EI	Energy intake
FMI	Fat mass index
OR	Odds ratio
WHO	World Health Organization

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Introduction

Childhood obesity increased worldwide in the last decades. While the prevalence of overweight and obesity in children aged under 5 years was 4.9% in 2000, 5.4% in 2010, 5.7% in 2015, and 5.9% in 2018 [1], current trends predict an increase up to 11% worldwide by 2025 [2]. Based on World Health Organization (WHO) criteria, the prevalence of overweight and obesity in 4–7 years old children in Europe in 2012 ranged from 8 to 30% and 1 to 13%, respectively, with lowest rates in Belgium and Germany and highest in Southern European countries, like Spain and Greece [3].

Nutrition is an important factor influencing obesity in children and adults [2, 4]. Since sugar intake is high among children [4–6], sugar was brought into focus as a possible risk factor for overweight and obesity. Especially, sugar-sweetened beverages are considered to increase body weight, due to their additional energy contribution and lower and shorter feeling of satiety compared to sugar intake from solids [7]. In addition to the additional energy intake (EI) and shorter feeling of satiety, the nutrient sugar itself might also influence physiological mechanisms potentially facilitating weight gain [8]. The postprandial increase in glucose and insulin concentrations in the blood might be mechanisms linking higher sugar intake with higher body weight as described in the carbohydrate–insulin model by Ludwig and Ebbeling [9].

The WHO recommended to lower sugar intake mainly due to observed effects on dental caries. They recommended to limit the free sugar intake in children to below 10% of EI and suggested to further lower EI from free sugar to below 5% [4]. Free sugar includes sugars added to foods or beverages by the consumer, cook or manufacturer, and, furthermore, sugars naturally present in fruit juices, honey, and syrups [4]. Despite the WHO recommendations, results from published studies are still inconclusive, whether a relation between sugar itself and anthropometrics exists. Results seem to differ between type of sugar assessed (e.g., free, added, specific sugars like fructose, or total sugar), age of children, and whether the sugar intake was accounted for total EI or not [10–12]. Therefore, further studies, especially with longitudinal data, are needed to investigate the relationship. This study aims to determine the association of total sugar intake with anthropometric measures in a European multicenter study over a period of 6 years in early childhood.

Methods

Study design

The CHildhood Obesity Project (CHOP) is an ongoing double-blind randomized intervention trial in five European countries (Belgium, Germany, Italy, Poland, and Spain) and is described in detail elsewhere [13]. Briefly, CHOP was established to investigate the differential effect of a lower and a higher protein-content formula and breastfeeding on growth in children. Healthy infants born after uncomplicated singleton pregnancies between October 2002 and July 2004 were recruited ($N = 1678$) and followed until 11 years of age ($N = 583$). Informed consent was obtained from the parents at enrollment. The trial was approved by the local ethics committees, registered (https://clinicaltrials.gov: NCT00338689) and follows the Declaration of Helsinki.

Nutritional assessment

Dietary intake was assessed at the ages of 2, 3, 4, 5, 6, and 8 years using weighed dietary records on 3 consecutive days (1 weekend day and 2 week days). Parents were instructed to weigh foods and leftovers, and had the opportunity to compare the consumed food with standardized and weighed portion sizes in an alternative dietary record from 3 years onwards. Food consumed outside home and not prepared by parents were recorded by others, i.e., instructed educators. Protocols were validated by a trained dietician, entered into the database, and checked for quality by standard operating procedures [14]. Afterwards, nutrient intakes were calculated based on the German food composition database, BLS 3.01 (Bundeslebensmittelschlüssel Version 3.01). Items missing in the BLS were added by study dieticians, using nutrient content from the food manufacturer or other nutritional databases. Sugar was calculated as the sum of all mono- and disaccharides, including both natural and added sugars [15]. Free or added sugars are not recorded in the German food composition database and no manual estimation of free and added sugars was performed on the food product level. Whereas free sugar is easily defined for sweetened beverages and fruit juices, a lot of assumptions are needed to estimate added or free sugar in other food products. Due to this, we decided to primarily analyze the effect of total sugar intake and additionally the effects of sweetened beverages and fruit juices. Nevertheless, approximate free sugar intake was calculated to have some comparison to the current WHO recommendations and to other published studies. To estimate the free sugar intake, we used the sum of sugar calories from confectionary products, sweets, sweetened milk products, sweetened beverages, sweetened cereals, sweetened fruit products (including fruit juices), honey, and syrups. Detailed information about the food groups can be found elsewhere [15].

Anthropometry (outcome variable)

Anthropometric measures were taken at each follow-up visit by trained study nurses, following the standard operating procedures based on the WHO growth reference study for school-aged children and adolescents [16]. Body mass index [BMI = weight (kg)/height $(m)^2$] was calculated and standardized on the WHO reference population to compute age- and sex-specific BMI z scores (zBMI) [17]. Fat mass index [FMI = total body fat mass (kg)/height $(m)^2$] was calculated by the Slaughter equation out of triceps and subscapular skinfolds, measured three times by a Holtain caliper [18]. Detailed equations and application in the CHOP study have been reported previously elsewhere [19]. Due to missing external reference, FMI has been standardized by gender and age to create age- and sex-specific z scores (zFMI).

Covariates

Potential risk factors or confounders were assessed at baseline by questionnaire. Maternal pre-pregnancy weight (kg) and height (cm), maternal age (years), smoking, and alcohol drinking during pregnancy (yes/no) were reported by the mother. Parental education was assessed by questionnaire and categorized in accordance to the International Standard Classification of Education and categorized in low, middle, and high [20]. Physical activity was measured by the SenseWear Armband 2 (Body Media Inc., Pittsburgh, PA, USA) on 3 consecutive days for at least 20 h per day. Physical active was classified by average Metabolic Equivalents of Task > 1.5, which is described in detail elsewhere [21]. In addition, time played outside (h) was assessed by questionnaire.

Statistical analysis

Data were validated, and tested for plausibility and macronutrient intake and observations with total EI, protein, fat or carbohydrate intake higher than three times the standard deviation by the measurement time point and country were excluded. To check for possible misreporting, total caloric intake was compared to energy expenditure, calculated from height and weight, as described in detail by Gomes et al. [22]. Children were afterwards grouped in correct reporting, under- and over-reporting (correct reporting: 75%, under-reporting: 12%, and over-reporting: 13%).

Mixed models with random intercepts and random linear slope over age for each child were applied to investigate the association of sugar with anthropometric measures. Models were tested for further outliers, high residuals and leverage. Studentized residual plots were used to identify potential outliers and Cook's distance plots and a cut-off value of Cook's distance of more than $4/N$ ($N = 3100$) were applied to assess high leverage and those observations were excluded.

To control for total EI, the residual method was applied with the advantage to detect associations between total sugar itself and body composition unconfounded by total EI. Therefore, residuals from the linear regression of EI on total sugar intake were used as sugar marker in the mixed model on anthropometrics which was additionally adjusted for total EI, resulting in the base model: anthropometric outcome ~ Total sugar residuals + total EI + country + gender + misreport. This method is considered as an isocaloric model and the same procedures were applied for the other macronutrients (protein, fat, and oligo and polysaccharides). Further on, other covariates (maternal pre-pregnancy weight and height, maternal age, smoking and alcohol drinking during pregnancy, parental education, physical activity, and formula intervention) and zBMI at specific time points and zBMI gain of the child until 2 years of age were considered as possible covariates and included stepwise into the mixed model. These covariates were tested for improvement of the model fit by likelihood-ratio tests. In addition, possible interactions of total sugar residuals with age or covariates were checked for model improvement. Beside total sugar intake from all food groups, sugar intake from SSBs and fruit juices and their relation to anthropometrics were separately investigated. Both were also included as sugar residuals into the models. In a next step, zBMI and zFMI were categorized as high (≥ 1 SD) or normal (< 1SD). Odds ratios (OR) were calculated by logistic random-effects models, using total sugar residuals as continuous exposure.

As a sensitivity analysis, we repeated the model procedures using only participants with valid nutrition data from at least three time points. In addition, we performed a sensitivity analysis including only normal-weight children. All analyses were conducted in SAS 9.4 and a p value of ≤ 0.05 was selected as significance threshold.

Results

Nutrition data were available for 850 children with 3100 observations in total. Observations with total energy intake, protein, fat, or carbohydrate intake values higher than three times the standard deviation were afterwards omitted. Due to high residuals or Cooks distance over three, 28 children had to be excluded, resulting in an analyzing data set of 809 children with 2846 observations (2 years: $N = 688$, 3 years: $N = 481$, 4 years: $N = 464$, 5 years: $N = 416$, 6 years: $N = 440$, and 8 years: $N = 357$). Participation rate on dietary assessment of those children who had anthropometric data at the respective time point decreased from 86% at 2 years to 66% at 8 years of age. Measurements for all six time points were available for 143 children (5 time points: 163 children, 4

time points: 128 children, 3 time points: 94 children, 2 time points: 98 children, and 1 time point: 183 children). In general, children in the analysis data set did not differ in sex, country, formula distribution, maternal age, and pre-pregnancy BMI compared to the full cohort (Supplementary Table 1). However, more mothers with high education decided to participate in the nutritional assessment and were also less likely to drop out during follow-up. Of the 809 participants in the analysis data set, 53% were female and most children lived in Italy (27%) and Spain (27%) (Table 1). zBMI and zFMI were stable from 2 to 6 years of age, but increased at 8 years of age. About 21% and 15% of the children had a zBMI and zFMI above one standard deviation. Highest percentage of children with a high zBMI was at 8 years of age (29%) and at 4 years for a high zFMI (18%).

Children's caloric intake increased over the years (2 years: 1097 kcal; 8 years: 1520 kcal). Total EI was in general adequate compared to the estimated total energy expenditure. About 12% of all 3-day protocols were considered to underreport energy intake and 13% to overreport. Total sugar intake increased from 2 to 8 years of age from 69 to 80 g, carbohydrates from 135 to 186 g, protein from 44 to 58 g, and fat from 42 to 61 g. The energy % and carbohydrate % of total sugar slightly decreased from 25 to 51% at 2 years, respectively, to 21% and 43% at 8 years. The roughly estimated energy % of free sugar was on average 13% with little variation over time. Energy % from SSBs was about 2.5% at younger ages and increased to 3.6% at 8 years, while energy % from fruit juices stayed more or less constant at 3%.

The best fitting model on the relation of total sugar intake with child BMI consisted of country, formula, gender, zBMI at 1 year, maternal education, maternal pre-pregnancy BMI, smoking during pregnancy, and misreporting. No effect was observed for formula intervention. Results of the mixed model analysis with continuous outcomes are presented in Table 2. Adjusted for total EI, total sugar residuals were inversely associated with zBMI and zFMI: in the fully adjusted model, an increase of 100 kcal from total sugar was related to a decrease of zBMI (−0.036; 95% CI −0.009, −0.064) and zFMI (−0.049; 95% CI −0.011, −0.087). In the same models, an increased total EI of 100 kcal from any food source was significantly related to a 0.055 (95% CI 0.044, 0.066) higher zBMI and 0.058 (95% CI 0.043, 0.074) higher zFMI. Looking at OR, an increase of 100 kcal from total sugar in an isocaloric setting was related to lower odds of having a high zBMI (OR 0.742, 95% CI 0.604, 0.912) and a high zFMI (OR 0.825, 95% CI 0.669, 1.018), while

Table 1 Baseline characteristics for a subset of CHOP participants

Age in years		2 (*N* = 688)	3 (*N* = 481)	4 (*N* = 464)	5 (*N* = 416)	6 (*N* = 440)	8 (*N* = 357)	Total cohort
Male	*N* (%)	322 (47)	224 (47)	220 (47)	195 (47)	202 (46)	163 (46)	380 (47)
Country								
Germany	*N* (%)	111 (16)	70 (15)	54 (12)	45 (11)	53 (12)	46 (13)	126 (16)
Belgium	*N* (%)	90 (13)	63 (13)	65 (14)	54 (13)	56 (13)	41 (11)	105 (13)
Italy	*N* (%)	200 (29)	152 (32)	141 (30)	136 (33)	127 (29)	76 (21)	216 (27)
Poland	*N* (%)	124 (18)	76 (16)	71 (15)	61 (15)	77 (18)	75 (21)	144 (18)
Spain	*N* (%)	163 (24)	120 (25)	133 (29)	120 (29)	127 (29)	119 (33)	218 (27)
Anthropometry								
BMI (kg/m^2)	Mean (SD)	16.1 (1.2)	15.9 (1.3)	15.8 (1.3)	15.8 (1.7)	15.8 (1.7)	16.7 (2.2)	16.0 (1.5)
zBMI	Mean (SD)	0.2 (0.9)	0.3 (0.9)	0.3 (0.9)	0.3 (1.0)	0.2 (1.0)	0.4 (1.1)	0.3 (1.0)
FMI (kg/m^2)	Mean (SD)	2.4 (0.6)	2.4 (0.6)	2.4 (0.7)	2.5 (1.0)	2.5 (1.0)	3.1 (1.5)	2.5 (0.9)
zFMI	Mean (SD)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)
Dietary intake								
Total energy intake (kcal)	Mean (SD)	1 097 (231)	1 199 (231)	1 297 (227)	1 365 (232)	1 429 (236)	1 520 (240)	1 290 (274)
Total sugar (g)	Mean (SD)	69 (23)	74 (23)	78 (23)	80 (23)	82 (23)	80 (25)	76 (24)
Carbohydrates (g)	Mean (SD)	135 (33)	149 (34)	161 (32)	171 (36)	179 (36)	186 (36)	160 (39)
Protein (g)	Mean (SD)	44 (12)	46 (12)	49 (12)	51 (13)	54 (12)	58 (12)	50 (13)
Fat (g)	Mean (SD)	42 (12)	47 (12)	51 (13)	54 (13)	56 (13)	61 (14)	51 (14)
Energy percentage from total sugar (E%)	Mean (SD)	25.0 (6.2)	24.7 (5.9)	24.2 (5.7)	23.5 (5.7)	22.9 (5.4)	21.0 (5.4)	23.8 (5.9)
Proportion of total sugar on carbohydrates (%)	Mean (SD)	50.5 (10.4)	49.6 (10.2)	48.7 (10.3)	46.9 (9.9)	45.9 (9.7)	42.9 (9.9)	47.9 (10.4)
Energy percentage from free sugar (E%)	Mean (SD)	12.5 (7.1)	13.5 (6.7)	13.3 (6.4)	13.1 (6.2)	13.1 (5.8)	12.8 (5.6)	13.0 (6.4)

BMI body mass index, *FMI* fat mass index, *CHOP* CHildhood Obesity Project

Table 2 Mixed model coefficients for total sugar intake and their association with anthropometrics

	zBMI		
Base model[1]	β-coefficient	95% CI	*p* value
Total sugar (100 kcal)	−0.033	−0.061 to (−0.005)	0.0215
Total energy intake (100 kcal)	0.057	0.046–0.068	<0.0001
Adjusted[2]			
Total sugar (100 kcal)	−0.036	−0.064 to (−0.009)	0.0092
Total energy intake (100 kcal)	0.055	0.044–0.066	<0.0001
	zFMI		
Base model[1]	β-coefficient	95% CI	*p* value
Total sugar (100 kcal)	−0.050	−0.089 to (−0.011)	0.0123
Total energy intake (100 kcal)	0.063	0.048–0.079	<0.0001
Adjusted[2]			
Total sugar (100 kcal)	−0.049	−0.087 to (−0.011)	0.0124
Total energy intake (100 kcal)	0.058	0.043–0.074	<0.0001

All values are β-coefficients (95% CIs)

zBMI standardized body mass index, *zFMI* standardized fat mass index

[1]Base model was only adjusted for gender, country, and misreporting

[2]Adjusted for gender, country formula, zBMI at 1 year, maternal education, maternal pre-pregnancy BMI, smoking during pregnancy, and misreporting

an increase of 100 kcal of total EI from any food source was associated with increased odds of having a high zBMI (OR = 1.345, 95% CI 1.233, 1.467) and zFMI (OR = 1.185, 95% CI 1.087, 1.292). Sugar intake from SSBs or fruit juices was not significantly associated with BMI or FMI (results not shown).

Since changes in total sugar intake in an isocaloric model have to be exchanged by other macronutrients, protein, fat, and oligo- and polysaccharides (total carbohydrates minus total sugar) have been analyzed with the mixed model using also the residual method and results are displayed in Table 3. Only protein showed a significant and positive effect on zBMI (0.073, 95% CI 0.009, 0.137) and zFMI (0.116, 95% CI 0.025, 0.206). Oligo- and polysaccharides were significantly related to increased zFMI (0.051; 95% CI 0.012, 0.089).

Models have been tested for interaction effects, but no interaction improved the model fit significantly, indicating that the associations neither differed across gender, country nor across years of age. Sensitivity analysis with children having valid dietary data of at least three different time points (528 children, 2467 observations) showed similar results without changes in significance (results not shown). Furthermore, in a sensitivity analysis including only

Table 3 Mixed model coefficients for macronutrients and their association with anthropometrics in an isocaloric model

	β-coefficient	95% CI	*p* value
zBMI			
Protein (100 kcal)	0.073	0.009–0.137	0.0250
Fat (100 kcal)	0.018	−0.009–0.045	0.1902
Oligo- and polysaccharides (100 kcal)	0.018	−0.009-0.045	0.1942
zFMI			
Protein (100 kcal)	0.116	0.025–0.206	0.0121
Fat (100 kcal)	0.005	−0.033 to 0.043	0.7835
Oligo- and polysaccharides (100 kcal)	0.051	0.012–0.089	0.0098

All values are β-coefficients (95% CIs)

Separate linear mixed models were applied for each macronutrient, using the residual method and adjusting for total energy intake. All separate models were adjusted for gender, country formula, zBMI at 1 year, maternal education, maternal pre-pregnancy BMI, smoking during pregnancy, misreporting, and total energy intake

zBMI standardized body mass index, *zFMI* standardized fat mass index

normal-weight children, the inverse relationship between total sugar intake and anthropometrics remained significant (results not shown).

Discussion

On an energy-equivalent basis, we observed an inverse relationship between total sugar intake and zBMI and zFMI, while protein was positively associated with zBMI and zFMI and oligo- and polysaccharides with increased zFMI. We observed a lower odds of having a high zBMI (OR 0.743, 95% CI 0.611, 0.903) with an increase of 100 kcal total sugar, which is the total sugar amount of about one mango, 150–200 g sweetened fruit yogurt, 15 gummi bears, or one glass of coke.

This inverse association of total sugar intake with BMI after energy adjustment has also been reported by several other studies partly with and partly without energy adjustment. Williams et al. observed a significant, negative relationship between sucrose intake and BMI at 3–4 years of age after energy adjustment [23]. At the follow-up at 7–10 years of age, the association remained negative, but was no longer statistically significant. In the Dortmund Nutritional and Anthropometric Longitudinally Designed Study, added sugar intake at 1 year was also inversely related to BMI at 7 years of age, but not to body fat [24]. In over 135,000 children and adolescents (10–16 years), Janssen et al. observed a significant, negative relation between sweets intake and BMI classification without energy adjustment [25]. This was confirmed in younger children and adolescents in the 1999–2004 National Health and Nutrition Examination Survey using energy adjustment, in which candy consumers were less likely to be overweight and obese than non-consumers [26].

There are some possible explanations for the inverse relation between sugar intake and anthropometrics. First of all, in an isocaloric setting, the increase of energy from sugar is accompanied by a reduced intake of protein, carbohydrates other than sugar, and fat. Investigating the influence of other macronutrients on body composition in the current study, protein intake was significantly associated with zBMI and zFMI, and oligo- and polysaccharides only with zFMI. In several studies, it was already shown that a high protein intake in young children is related to a higher body weight and fat mass, while carbohydrates showed often an inverse association [27–30]. Furthermore, in the CHOP study, it was shown that formula with higher compared to lower protein formula was positively associated with body fat in children from 1 to 6 years [19]. Possible mechanisms might be increased concentrations of growth factors, which stimulate growth and promote the proliferation of adipocytes [30]. Since protein was related to higher zBMI and zFMI in the present analysis and total sugar intake showed an inverse relation, while oligo- and polysaccharides was only positively related to zFMI and fat showed no significant association, this might point to general differences in metabolic response of macronutrients in children.

Another explanation for the seemingly protective effect of total sugar might be a metabolic pathway. Glucose, which is not immediately used for energy needs or for glycogen storage, can be converted into fat by an energetically costly de novo lipogenesis. Furthermore, fecal energy loss increases in a carbohydrate-overfeeding setting. Therefore, Astrup and Raben calculated that 68% more energy is required to result in 1 kg higher body fat with carbohydrate overfeeding (15–30% purified sucrose) compared to fat overfeeding [31]. However, our cohort may not be totally comparable to a carbohydrate-overfeeding setting.

The observed relation may also be a result of reporting bias. It was shown that people with higher weight are more likely to underreport their EI [22] and children with high BMI in the present cohort may have also underreported their intake of high-sugar foods and drinks. However, in the current analysis we adjusted for misreporting to take reporting bias into account. In addition, the inverse relation between sugar and anthropometrics might be attributable to reverse causation. Since high-fat and high-sugar products are thought to increase adiposity, parents of children with overweight or obesity might limit intake of those products to lose weight [32]. This was also seen in our study, as energy contribution from sugar was lower in overweight and obese children compared to normal-weight children. On the other hand, we have only few children that are overweight or obese in our cohort (11%) and observed the inverse relation nonetheless. In addition, the association remained significant after excluding overweight and obese children. The approximated energy percentage from free sugar in the CHOP cohort was 13% and is clearly above the WHO recommendation of 10% [4], but far lower than free sugar intake of other study populations in European countries [6, 33, 34]. In the Netherlands in 2007–2010, energy percentage from free sugar in children (7–8 years) was 20% [34], and in Germany, about 17% (3–10 years) [6]. In the multicentric European IDEFICS study, free sugar intake of 2–9-year-old children were estimated as 18E% ranging from 13E% in Italy to 27E% in Germany [33]. Possible reasons for the lower free sugar intake might be the low intake of SSBs and fruit juices in the current population compared to other populations. While free sugar intake from SSBs and fruit juices per consumer was about 11% each of total EI in the IDEFICS study [33], energy percentage from SSBs and fruit juices was only 3% each in the current population. Thus, SSBs and fruit juices were consumed more rarely and in smaller amounts in our study population, and free sugar intake was preferably consumed by sweets and milk products.

There are several studies which report no significant [35–37] or positive associations [38, 39] of sugar intake with anthropometric measures. Furthermore, in a non-isocaloric model, allowing total EI to increase, total sugar intake was positively associated with anthropometrics in various studies [10, 12], as well as in the present study, indicating that the positive relation between sugar intake and anthropometrics in ad libitum models is mainly due to increasing EI. Inconsistent results might be explained by overall different intake levels, types of sugar, and whether they are taken up in solid or liquid form [10, 40]. Effects might also change with age in the transient period from childhood to adolescence as indicated by Rolland-Cachera et al. for protein [30]. Therefore, types of sugar, intake type and amount, and age of participants have to be considered during comparison of studies or planning of future studies.

Strengths and limitations

The current study has some limitations. Foremost, the number of participants decreased over the follow-up period from 688 children at 2 years to 357 at 8 years. This limits the power of our analysis. However, the mixed model analysis chosen is capable of handling missing data and unweighted designs. Families with higher education were more likely to stay in the study and families with a lower education are more likely to have a poorer diet [41]. Therefore, our results may be biased and generalizability is limited. Furthermore, we could not clearly separate total sugar into natural, added, and free sugars due to the chosen dietary assessment and nutrition database used. This limits the possibility to compare our results to the WHO recommendations and some studies. Nevertheless, we estimated free sugar intake based on the main contributing food sources and additionally compared free sugar intake from SSBs and fruit juices in the current study to other populations to give the reader the possibility to classify our results.

One major strength is the multicenter and longitudinal design of the CHOP study. Due to yearly assessment, we were able to include six time points during childhood in our analysis. This resulted in a robust model and allowed us to identify potential changes in the association of sugar intake with anthropometric measures across time. Accurate anthropometric measurements based on standard operating procedures across study sites by trained study nurses reduced potential bias. A major strength is the high-quality dietary assessment. Weighed dietary records on 3 consecutive days are considered as the most precise method of dietary intake assessment in children [14].

Conclusion

In the present study, we observed inverse relation between total sugar intake and zBMI and zFMI in an isocaloric model, while increased protein intake was related to higher zBMI and zFMI in early childhood. Therefore, results provide no indication for positive associations of total sugar intake with BMI beyond adding energy. Furthermore, the study points to either different physiological mechanisms of macronutrients influencing body composition or different macronutrient preference of children with higher zBMI and zFMI compared to children with lower zBMI and zFMI. It has to be considered that in the present study, total sugar was investigated, including also sugar from fruits and milk products. Total sugar intake in our cohort was comparable to other developed countries, but this association might not be transferable to higher total sugar intake levels. The relation was only present children on an energy-equivalent basis and the study is not recommending to increase sugar consumption in children.

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Author contributions NA analyzed the data, drafted and finalized the manuscript. DG, KG, JE, NF, DR, JH, EV, AR, BK, and VG conducted the study and entered data at study sites and critically reviewed the manuscript. BK designed the research and critically reviewed the manuscript. VG designed the research, participated in the data analysis, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL CONTRIBUTION

Influence of total sugar intake on metabolic blood markers at 8 years of age in the Childhood Obesity Project

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Abstract

Purpose We aimed to characterize the association of dietary sugar intake with blood lipids and glucose-related markers in childhood.

Methods Data from the multicentric European Childhood Obesity Project Trial were used. Three-day weighed dietary records were obtained at 8 years of age along with serum concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), glucose, and insulin. Total sugar intake comprised all mono- and disaccharides; different sugar sources were defined. Linear regression models were applied to investigate the cross-sectional association of total sugar intake with blood lipids and glucose-related markers with adjustment for total energy intake using the residual method.

Results Data were available for 325 children. Children consumed on average 332 kcal (SD 110) and 21% (SD 6) of energy from total sugar. In an energy-adjusted model, an increase of 100 kcal from total sugar per day was significantly associated with a z score HDL-C decrease (− 0.14; 95% CI − 0.01, − 0.27; p value = 0.031). Concerning different food groups of total sugar intake, 100 kcal total sugar from sweetened beverages was negatively associated with z score HDL-C (− 1.67; 95% CI − 0.42, − 2.91; p value = 0.009), while total sugar from milk products was positively related to z score HDL-C (1.38, 95% CI 0.03, 2.72; p value = 0.045). None of the other blood lipids or glucose-related markers showed a significant relationship with total sugar intake.

Conclusion Increasing dietary total sugar intake in children, especially from sweetened beverages, was associated with unfavorable effects on HDL-C, which might increase the long-term risk for dyslipidemia and cardiovascular disease.

Clinical trial registry ClinicalTrials.gov Identifier: NCT00338689; Registered: June 19, 2006. URL: https://clinicaltrials.gov/ct2/show/NCT00338689?term=NCT00338689&rank=1.

Keywords Sugar intake · Children · Blood lipids · Blood sugars · HDL

Abbreviations

BMI	Body mass index
CHOP	Childhood Obesity Project
CVD	Cardiovascular disease

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TEI	Total energy intake
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
NCD	Non-communicable disease
SSB	Sugar-sweetened beverage
TC	Total cholesterol
TG	Triglycerides
WHO	World Health Organization

Introduction

About 41 million deaths worldwide were caused by non-communicable diseases (NCDs) in 2016. The majority of those deaths are attributed to four main NCDs: cardiovascular disease (CVD) (44% of all NCD deaths), cancer (22%), chronic respiratory disease (9%), and diabetes (4%) [1]. Concerning CVDs, dyslipidemia and elevated blood pressure are major risk factors exacerbating the development of atherosclerotic plaques [2, 3]. Already in childhood, the prevalence of dyslipidemia and high blood pressure is increasing [4] and these risk factors during childhood predict higher risks of hypertension, dyslipidemia, and CVD in adulthood [5–7]. Elevated fasting glucose is another risk factor for CVDs [8], and hyperglycaemia in childhood is known to enhance the likelihood of developing insulin resistance and diabetes [9, 10]. Because of the early onset of NCDs and the propagation of its development by unfavorable metabolic risk factors in childhood, effective interventions need to be identified and implemented.

In addition to tobacco use, air pollution, physical inactivity, and harmful use of alcohol, a poor diet quality has been identified as a major risk factor for NCDs [1, 11]. A diet with high sugar intake has been suggested to lead to a poor diet quality [12]. Although sugar intake seems no longer to increase and even partly to decrease [13, 14], high sugar intake is still highly prevalent in the last few decades both in adults and children and lies above the World Health Organization (WHO) recommendation of free sugar intake beyond 10% of energy percentage [12, 15]. Previous studies indicated that high intakes of sugar and particularly added sugar (sugars added to foods or beverages during food production, processing, or preparation) [12], and sugar-sweetened beverages (SSB), are associated with unfavorable blood lipid and glucose concentrations [16–25]. This comprises high triglyceride (TG) and total cholesterol (TC) as well as low-density lipoprotein cholesterol (LDL-C), and low high-density lipoprotein cholesterol (HDL-C) concentrations [16–22], along with concentrations of glucose and insulin, and high homeostasis model assessment (HOMA) levels [23–25]. Results might differ between type of sugar assessed (e.g. total sugar, added sugar, or specific sugars such as fructose) and food sources of sugar intake (e.g. SSBs, liquid or solid) [16, 26, 27]. Nevertheless, results from published studies in children are still inconclusive [15, 26, 28] and the evidence for total sugar intake in children and its relation to NCD risk markers measured in the blood is limited. Therefore, we aimed to investigate the association of total sugar intake as well as major food sources of total sugar with blood markers related to different health outcomes, such as blood lipids and glucose-related markers, in 8-year-old children.

Methods

Study design

Data were used from the CHildhood Obesity Project (CHOP), a study that was originally set up as a double-blind randomized nutritional intervention trial during the first year of life in five European countries (Belgium, Germany, Italy, Poland, Spain). Details are described elsewhere [29]. Briefly, the aim of CHOP was to explore the effects of lower and higher protein supply with infant formula on growth and subsequent obesity risk. The study also included a reference group of breastfed children. Between October 2002 and July 2004, 1678 healthy infants born after uncomplicated singleton pregnancies were enrolled. Some children ($N=589$) were followed until 8 years of age. As investigated blood markers are time variable, and exposure and outcome were only measured at the same time at 8 years in children of the original intervention trial. Therefore, a cross-sectional design was chosen for the current investigation. Written informed consent was obtained from the parents at enrollment. Additionally, children gave their assent at 8 years of age. The trial was approved by the ethics committees and follows the Declaration of Helsinki (Registration number: NCT00338689).

Nutritional assessment

Dietary intake was assessed at 8 years of age using weighed dietary records on three consecutive days, including one weekend day. Foods and leftovers were weighed by parents, caregivers, or the children themselves following detailed instruction. Outside home, families had the opportunity to compare the amount of consumed food with standardized and weighed portion sizes mapped in an especially designed alternative dietary record. Returned dietary records were validated by trained dieticians, entered into the database, and checked for quality by standard operating procedures, which are explained more in detail elsewhere [30]. Briefly, trained dietitians checked the records, and in case of implausible or missing information, parents were asked to complete or clarify the records by phone. Additionally, each single day was checked for accuracy by a standardized score and data

entry was monitored by a food record and nutritionist [30]. Nutrient intakes were calculated using the German food composition database BLS 3.01 (Bundeslebensmittelschlüssel Version 3.01). The database was chosen as it was at the time of study beginning the most comprehensive and available one in all study countries. Items not listed in the BLS, including country-specific foods, were added to the food database by study dieticians on the basis of nutrient content from the food manufacturer or other nutritional databases. Total sugar content in each food product was calculated as a composition of mono- and disaccharides, including all natural and added sugars [31].

Blood markers

At the age of 8 years, venous blood was mainly drawn in the morning after at least 6 h fasting by trained study nurses applying same standard operating procedures. In Germany, however, blood was drawn in the afternoon without 6-h fasting in some cases. Blood samples were stored at − 70 °C and transported on dry ice to the central laboratory (Children's Memorial Health Institute, Warsaw, Poland). Insulin was measured with an immunoradiometric assay (DiaSource, Nivelles, Belgium). All other markers, LDL-C, HDL-C, TC, TG, and glucose, were measured in the laboratories of the local study centers according to the local hospital routines including measures of quality control. In all centers, enzymatic methods were used. TG/HDL-C-ratio and HOMA index [HOMA index = (insulin (μu/ml) × glucose (mg/dl))/405] were calculated. As methods could not be standardized across centers, it has to be assumed that differences between study centers are at least partially due to methodological differences. This has been taken into account by calculating z scores for the individual centers.

Covariates

Most potential risk factors or confounders were assessed at baseline by questionnaires. Maternal pre-pregnancy weight (kg), smoking, and alcohol drinking during pregnancy (yes/no) were reported by the mother; maternal height (cm) was measured at the study site. Parental education was assessed in accordance with the International Standard Classification of Education and categorized into low, middle, and high [32]. Anthropometric measures of the children were assessed by trained study nurses, following standard operating procedures [33] at 8 years of age. Body mass index [BMI = weight (kg)/height $(m)^2$] was calculated and standardized to the WHO reference population to compute age- and sex-specific BMI z scores (zBMI) [34]. Physical activity was measured with the SenseWear Armband 2 (Body Media Inc., Pittsburgh, USA) on at least three consecutive days for at least 20 h per day, as described in detail elsewhere [35]. Physical active was classified by average Metabolic Equivalents of Task > 1.5. Misreporting of TEI was classified based on the comparison to the child's individual energy expenditure, calculated from height and weight, as described in detail by Gomes et al. [36]. Based on this comparison, children were afterwards classified into either a correct reporting group, under-reporting group or over-reporting group (correct reporting: 70%, under-reporting: 27%, over-reporting: 3%).

Statistical analysis

Nutritional data were validated during data introduction by trained dietitians and checked for plausibility by comparing nutritional intake to individual weight-, height-, and age-dependent energy intakes and needs for vitamins and minerals, which is reported more in detail elsewhere [30]. Observations with values higher or lower than three times the standard deviation for outcome variables were identified, checked for possible unlikely values, and excluded in case of implausibility. To account for TEI, the residual method was chosen; TEI was regressed on total sugar calories and residuals were calculated. Those residuals were used in all following models and are referred to by naming sugar intake in the current analysis. The base model included country, sex, misreporting, and calories from total sugar. The following covariates were included stepwise into the base model and were tested for improvement of the model fit by improving adjusted R^2, square root of the variance of the residuals, having normally distributed residuals, and whether the respective covariate reached significance: zBMI of the child, education of parents, smoking and alcohol drinking during pregnancy, maternal pre-pregnancy BMI, and physical activity. Furthermore, total sugar intake in the final model was exchanged for intake by major food groups of total sugar, including total sugar from milk products, fruit products (including fruit juice), confectionary, SSBs, and bread and cereals. Total sugar from those food groups was also included as residuals into the model.

For sensitivity analyses, analyses were repeated with crude blood marker concentrations, which were not standardized. All analyses were conducted in SAS 9.4 and a p value of ≤ 0.05 was selected as significance threshold.

Results

Valid blood measurements were available for 438 children and nutrition data for 446 children at 8 years of age; both were available in 336 children. Eleven children were excluded due to implausible values in blood data. Thus, the analyzed data set consisted of 325 children from 5 different European countries, with the majority being from Spain and Italy (Table 1). Most parents had a high or medium level of

Table 1 Baseline characteristics for study participants with nutritional information and blood measurements at 8 years of age

Characteristics[a]	Analysis cohort ($N=325$)
Age (years)	8.0 (0.1)
Male	160 (49%)
Country	
Germany	24 (7%)
Belgium	35 (11%)
Italy	86 (26%)
Poland	71 (22%)
Spain	109 (34%)
Education of parents	
Low	26 (8%)
Middle	171 (53%)
High	127 (39%)
BMI	17.0 (2.8)
Dietary intake	
Energy intake (kcal/day)	1587 (278)
Energy percentage from fat	36 (9)
Energy percentage from protein	13 (4)
Energy percentage from carbohydrates	51 (9)
Total sugar (kcal/day)	332 (110)
Energy percentage from total sugar	21 (6)
Total sugar intake[b]	
Milk products (kcal/day)	64 (41)
Fruit products (kcal/day)	97 (62)
Sweetened beverages (kcal/day)	54 (53)
Bread and cereals (kcal/day)	18 (21)
Confectionary (kcal/day)	84 (54)
Blood marker[c]	
Glucose (mg/dl)	83.3 (8.4)
Insulin (µIU/ml)	9.3 (5.7)
HOMA index	1.8 (0.7)
TG (mg/dl)	64.5 (40.2)
TG (mmol/l)	0.74 (0.46)
HDL-C (mg/dl)	59.6 (15.1)
HDL-C (mmol/l)	1.55 (0.39)
TG/HDL ratio	1.1 (0.7)
TC (mg/dl)	167.5 (27.5)
TC (mmol/l)	4.35 (0.71)
LDL-C [mg/dl]	94.7 (25.0)
LDL-C (mmol/l)	2.46 (0.65)

HOMA High Homeostasis Model Assessment, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol

[a]Categorical variables are displayed as *N* (%) and continuous as mean (SD)

[b]Some food groups were not consumed by all children: milk products ($n=38$), fruit products ($n=49$), sweetened beverages ($n=197$), bread and cereals ($n=36$), confectionary ($n=40$)

[c]Missings: insulin (11), HOMA index (35), triglycerides (1), HDL-C (1), TG/HDL ratio (1), LDL-C (4)

education. Mean TEI at 8 years of age was 1587 (SD 278) kcal, with 332 (SD 110) kcal contributed from total sugar (21 energy % from total sugar). SSBs were consumed by 128 children (38%), whereas all other major total sugar-containing food products were consumed by most of the children. Most calories from total sugar were consumed as fruit products [mean intake 97 (SD 62) kcal/day; consumed by $n=276$] and confectionaries [84 (SD 54) kcal/day; $n=285$], followed by milk products [64 (SD 41) kcal/day; $n=287$], SSBs [54 (SD 53) kcal/day; $n=128$], and bread and cereals [18 (SD 21) kcal/day; $n=289$].

Mean serum concentrations of blood lipids and glucose-related blood markers are displayed in Table 1. There were differences between countries, with the highest mean concentrations of glucose and insulin in Poland (88 mg/dl) and Germany (15 µIU/ml), respectively, and lowest concentrations of both markers in Italy (glucose: 78 mg/dl, insulin 7 µIU/ml) (Supplementary Table 1). More favorable blood lipids (lower TG, TC, and LDL-C, and higher HDL-C concentrations) were generally seen in Italy and Spain and more unfavorable levels in Germany and Poland. Mean HDL-C concentrations ranged from 50 mg/dl (SD 11 mg/dl) in Poland to 64 mg/dl (SD 14 mg/dl) in Spain. Variations of blood values differed across countries. This supports the analysis of country-specific *z* scores. Blood marker concentrations were similar in both sexes. We also found BMI differences between countries, with the highest mean BMI in Spain (17.3 kg/m^2) and Italy (17.5 kg/m^2), and the lowest in Belgium (15.8 kg/m^2). This was partly in line with caloric intake, which was reported highest in Spain and Poland and lowest in Belgium. Concerning total sugar intake, most total sugar was consumed in Poland (23 energy % from total sugar) and least of all in Italy (18 energy % from total sugar). TEI was higher in boys compared to girls, but energy percentage from total sugar intake did not differ between sexes. Sugar intake from milk products was highest in Spain, while sugar intake from fruit products, bread and cereals, and confectionary was consumed mostly in Germany. Highest sugar intake from SSBs was observed in Belgium. Sugar intake from major food products was very similar in boys and girls.

Looking at the effects of total sugar intake and blood markers in the linear regression models, the covariates country, sex, zBMI, and misreporting showed either a significant improvement of model fit or confounding and were included in the final model. The fully adjusted models for each lipid marker or glucose-related marker are displayed in Table 2. An increase of total sugar intake by 25 g or 100 kcal per day was significantly associated with a lower HDL-C concentration *z* score (− 0.14; 95% CI − 0.01, − 0.27) which represents a decrease of 2.13 mg/dl (95% CI − 0.20, − 4.05 mg/dl), based on the mean and standard deviation across all countries. None of the other lipid markers or glucose-related markers was associated with total sugar intake.

Table 2 Linear regression coefficients for total sugar intake (per 100 kcal) and their association with markers of sugar metabolism and lipids

	β-coefficient of z score	95% CI	p value
Sugar metabolism			
Glucose	0.03	(− 0.10 to 0.16)	0.652
Insulin	− 0.00	(− 0.11 to 0.11)	0.980
HOMA index	− 0.02	(− 0.15 to 0.11)	0.770
Blood lipids			
TG	0.08	(− 0.03 to 0.19)	0.168
HDL-C*	− 0.14	(− 0.27 to (− 0.01))	0.031
TG/HDL-C-ratio	0.02	(− 0.10 to 0.14)	0.774
TC	− 0.10	(− 0.23 to 0.04)	0.155
LDL-C	− 0.03	(− 0.17 to 0.10)	0.624

All values are β-coefficients (95% CIs) for an increase of 100 kcal of total sugar

Separated models of markers of sugar metabolism and lipids were each adjusted for sex, country, zBMI, and misreporting. Outcome variables were included in the analysis as z scores by laboratory

TG triglycerides, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol

*Significant

Similar results with slightly larger confidence intervals were seen in unadjusted models and in the sensitivity analysis using crude blood marker concentrations (Supplementary Table 2). Considering the five main different food groups for total sugar intake (total sugar from milk products, fruit products (including fruit juice), confectionary, SSBs, and bread and cereals), an increase by 100 kcal or 25 g/day of total sugar intake from SSBs was significantly negatively associated with HDL-C z score (− 1.67; 95% CI − 0.42, − 2.91), while total sugar intake from milk products was borderline, positively related to HDL-C z scores (1.38; 95% CI 0.03, 2.72) (Fig. 1). Similar results were observed in unadjusted models: the negative association of sugar from SSBs with HDL-C stayed significant, but sugar intake from milk products was not significant (Supplementary Table 3).

Discussion

In the multicentric CHOP study, we observed a negative association of total sugar intake and total sugar intake from SSB with HDL-C blood concentrations in 8-year-old children. Other blood lipids and blood sugars were not significantly affected by total sugar intake. A major contributor for the negative association between total sugar intake and HDL-C levels was total sugar intake from SSBs. Total sugar intake from milk products was borderline, positively associated with HDL-C levels, which may reflect the close association of milk sugar and milk fat intake, with the latter being suggested to increase HDL-C [37–40].

The association of increasing sugar intake with decreasing HDL-C concentrations has been previously reported. Lee et al. observed a 0.26 mg/dl greater increase in HDL-C levels, comparing lower (< 10% of TEI) to higher added sugar consumption (> 10% of TEI) in 2379 girls aged 9 and 10 years [19]. In two other studies comparing added sugar consumption below 10% of TEI to one above 22.8% [22]

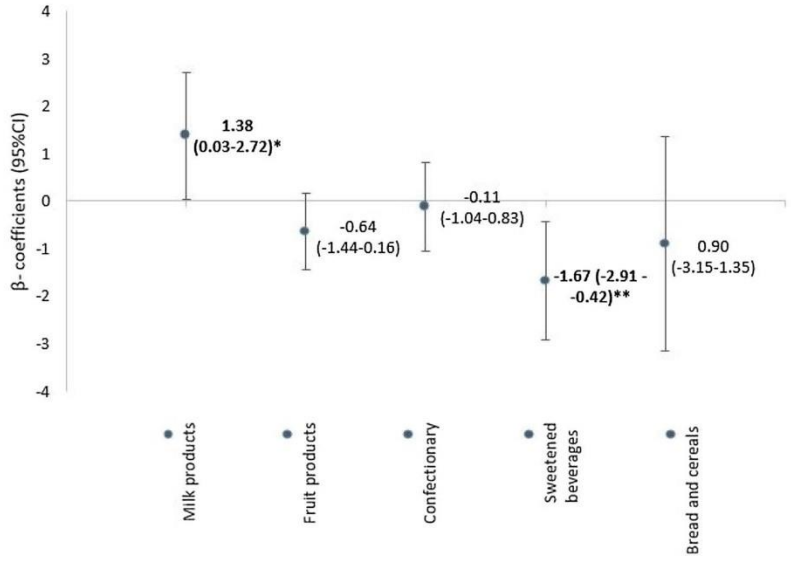

Fig. 1 Linear regression coefficients for sugar intake from major food groups and their association with z score HDL levels[1]. All values are β-coefficients (95% CIs) for an increase of 100 kcal of sugar from specific food groups; *$p = 0.045$, **$p = 0.009$. Models were adjusted for sex, country, zBMI, and misreporting. [1]HDL concentrations were included in the analysis after laboratory-specific standardization. *HDL-C* high-density lipoprotein cholesterol

and 30% [17], a decrease of 3.1 mg/dl and 4.5 mg/dl HDL-C concentration, respectively, was observed in a high added sugar diet in 4047 (12–19 years) and 2252 (13–18 years) adolescents. This is comparable to our observed HDL-C decrease of 2.13 mg/dl with a 100 kcal higher intake of total sugar. Furthermore, decreased HDL-C concentrations with increasing SSB consumption was also observed by other studies [20, 21]. In contrast, the increased HDL-C level seen with higher total sugar intake from milk products in our study is more likely related to the higher milk consumption and not to the sugar, as suggested by several other studies [37–39]. Furthermore, the association of sugar from milk products with HDL-C has to be interpreted with caution, as it was only borderline significant and reached no significance in the unadjusted model. Additionally, it has to be kept in mind that SBBs were consumed only by 128 children compared to 287 children consuming milk products.

No significant associations were observed between total sugar intake and TG, TC, TG/HDL-C ratio, or LDL-C levels in the current study. Whereas this was also seen in one other study [20], most other studies found significant relations between sugar intake and blood lipids other than HDL-C in children and adolescents [17, 18, 21, 22, 41]. TG were especially positively associated with increased sugar intake in a number of studies [17–19, 21, 22]. Additionally, increased TG/HDL-C ratio [17] and LDL-C [41] have been observed during increased sugar intake. A meta-analysis of randomized controlled trials by Te Morgenga et al. concluded that higher compared with lower sugar intakes were significantly associated with increased TG, TC, and LDL-C concentrations in adults [16].

We did not see a direct association of total sugar intake with fasting blood sugar levels. An association of sugar intake with glucose, insulin, and HOMA levels has been inconsistently reported [17, 23–26, 42, 43]. Overall epidemiological evidence on the effect of sugar intake on blood glucose metabolism is limited, and the current evidence on the influence of sugar intake on the development of diabetes, obesity, or CVD is inconclusive [26–28, 42, 44].

Possible causes for inconsistencies across studies might be due to the different types of sugars assessed across studies. While some studies investigated mainly total or added sugars, others focused on specific type of sugars such as fructose. Fructose is related to fat metabolism and might influence blood sugars and lipids in a different way as total sugars, which includes also other mono- and disaccharides [27, 45, 46]. Furthermore, different approaches to assess sugar intakes from different food groups might also contribute to inconsistent results across studies, along with the close association of lactose intake with the intake of other nutrients from dairy products. It was proposed that the effects of sugar intake may also differ depending on the food matrix and whether it is taken in solid or liquid form [24, 27].

Sugar intake in the CHOP trial is comparable to intake in other European countries [13, 31, 47]. Although sugar intake in Europe seems to plateau and even to decrease in some parts in children and in adults [13, 14], high sugar intake and free sugar intake above the WHO recommendations of 10% are widely prevalent [12]. Besides the potential unfavorable influence of increasing sugar intake on HDL-C concentrations, high sugar intake is suggested to promote the development of dental caries, overweight and obesity, and the metabolic syndrome [12]. Therefore, useful interventions and recommendations to reduce sugar intake are needed to prevent potential detrimental effects caused by a high sugar consumption.

Strengths and limitations

One strength of our study is accurate nutritional assessment, anthropometric measurements, and blood draw using the same standard operating procedures across study sites by jointly trained study nurses. We could explore effects of diet across five European countries. The technique used for dietary assessment is a major advantage of our study. Dietary records on three consecutive days were used, which are considered as the most precise method of dietary intake assessment in children for large studies [30].

One limitation is that most blood lipid and sugar concentrations were measured in different local laboratories, which may have added imprecision. Additionally, venous blood in Germany was mostly drawn in the afternoon without an at least fasting period of 6 h. To reduce the potential bias and measurement error, we calculated laboratory-specific standardized values. We did not separate natural and added sugars due to the chosen dietary assessment and nutrition database. Therefore, comparison of our results to those studies that focused on added sugars is challenging. Although 3-day weighed dietary records are considered as the most precise method of dietary intake assessment, correct estimation of sugar intake is still limited by self-reported data [48] and results have to be interpreted with caution. Furthermore, SSBs were consumed by less than half of the children, which has to be kept in mind while interpreting the results. Generalizability of the study result might be limited since predominantly families with middle and high education participated in the follow-up.

Conclusion

In a cross-sectional multicentic study in 8-year-old European children, increasing total sugar intake, especially from SSBs, was associated with an unfavorable decrease of HDL-C levels. The association between dietary sugar intake during

childhood, particularly from SSBs, and long-term cardiovascular risk warrants further research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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