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The role of dietary sugar intake in the development and management of diabetes mellitus – mediation and substitution analyses of observational studies

Dissertation

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Contributions at conferences

9th joint Diabetes and Metabolism Research Symposium Lille - Maastricht - Düsseldorf, Lille, France (2019)

Presentation: What if sugar is worse than just “empty calories”? A global causal mediation analysis

57th annual conference of the German Nutrition Society (DGE), Jena, Germany (2020)

Contribution in abstract book: Zucker – mehr als nur leere Kalorien? Ergebnisse einer globalen Mediationsanalyse

17th annual conference of the German Society for Epidemiology (DGEpi), Greifswald, Germany (2022)

Presentation: Association of a lifestyle score with cardiometabolic health among individuals with diabetes: a cross-sectional study

60th annual conference of the German Nutrition Society (DGE), Bonn, Germany (2023)

Presentation: Mediationseffekt von Übergewicht auf die prospektive Assoziation zwischen Saccharose im Urin und Diabetes-Inzidenz in einer Subgruppe der EPIC-Norfolk

18th annual conference of the German Society for Epidemiology (DGEpi), Würzburg, Germany (2023)

Presentation: Association of a lifestyle index with scores of diabetes-related distress, depression symptoms, health-related quality of life and well-being among individuals with new-onset diabetes: a cross-sectional study

Poster presentation: Risk phenotypes of diabetes as predictors for Covid-19-related death and severity: update of a systematic review and meta-analysis

59th annual meeting of the European Association for the Study of Diabetes (EASD), Hamburg, Germany (2023)

Short oral discussion: The mediating role of BMI and waist circumference on the prospective association between urinary sucrose and incidence of diabetes in a sub-cohort of the EPIC-Norfolk

58th annual meeting of the European Diabetes Epidemiology Group (EDEG), Pesaro, Italy (2024)

Poster presentation: Association of a lifestyle index with scores of patient-reported outcomes among individuals with recent-onset type 1 and type 2 diabetes – a cross-sectional study

19th annual conference of the German Society for Epidemiology (DGEpi), Dresden, Germany (2024)

Poster presentation: Cross-sectional association between substitution of carbohydrates with protein/fat and subcutaneous, visceral and liver adipose tissue volume in recent-onset diabetes

Zusammenfassung

Bisherige Erkenntnisse zeigen, dass der Zusammenhang zwischen Zuckeraufnahme und Typ-2-Diabetes (T2D) heterogen und unschlüssig ist. Es wird diskutiert, ob die Zuckeraufnahme allein aufgrund eines Kalorienüberschusses und dem damit eingehenden Übergewicht zu T2D führt. Zudem wird eine reduzierte Kohlenhydratzufuhr für das Diabetes-Management empfohlen. Allerdings ist bisher nicht hinreichend geklärt, inwiefern die Aufnahme anderer Nährstoffe bei Personen mit Diabetes mit der Verteilung des Fettgewebes assoziiert ist. Die vorliegende Dissertation hatte zum Ziel, 1) den Zusammenhang zwischen der Zuckeraufnahme und Diabetes auf globaler und individueller Ebene sowie die Auswirkungen von Adipositas auf diese Assoziation zu ermitteln und 2) die Substitution von Kohlenhydraten durch Fett und Protein in Verbindung mit dem Körper- und Leberfettgehalt zu untersuchen.

Zur Untersuchung des Zusammenhangs zwischen Zuckeraufnahme und Diabetes wurden eine ökologische Studie mit aggregierten Daten auf globaler Ebene sowie eine prospektive Studie mit Daten aus der *EPIC-Norfolk* auf individueller Ebene durchgeführt. In beiden Studien wurde eine kausale Mediationsanalyse durchgeführt, um den Einfluss von Adipositas auf diesen Zusammenhang zu untersuchen. Des Weiteren wurde eine Substitutionsanalyse mit Daten aus der Deutschen Diabetes-Studie (GDS) durchgeführt, um den Austausch von Kohlenhydraten durch Fett und Protein in Verbindung mit mittels MRT gemessenem subkutanem und viszeralem Fettgewebe sowie dem Fettgehalt der Leber zu untersuchen.

Die Ergebnisse zeigten, dass die Zuckeraufnahme sowohl auf globaler Ebene (Pro-Kopf-Zuckerkonsum) als auch auf individueller Ebene (objektiver Saccharose-Biomarker im Urin) mit einer höheren Diabetes-Prävalenz [β (95 % CI): 1.62 (0.71, 2.53)] bzw. höheren Inzidenz von T2D [HR: 1.14 (95 % CI: 0.95, 1.36)] assoziiert war. Diese Zusammenhänge lassen sich teilweise durch den Einfluss von Übergewicht erklären (~66 % auf globaler und ~20 % auf individueller Ebene). Darüber hinaus legen die Ergebnisse nahe, dass der Austausch von Kohlenhydraten durch mehrfach ungesättigte Fettsäuren bei Personen mit T2D mit geringerem viszeralen Fettgewebe und Leberfett verbunden war. Zudem konnte ein Zusammenhang zwischen dem Ersatz von Kohlenhydraten mit höherem glykämischem Index durch ungeradkettige oder sehr langkettige gesättigte Fettsäuren oder pflanzliche Proteine und einem geringeren Gehalt an Leberfetten bei Personen mit T2D festgestellt werden.

Zusammenfassend lässt sich festhalten, dass der Zusammenhang zwischen Zuckeraufnahme und Diabetes teilweise durch Übergewicht bestimmt wird. Es gibt jedoch Hinweise darauf, dass andere potenzielle direkte Mechanismen die Entwicklung von Diabetes beeinflussen können. Darüber hinaus scheint nicht allein eine Reduktion der Kohlenhydratzufuhr, sondern vielmehr die Qualität der dafür aufgenommenen Nährstoffe eine wesentliche Rolle bei der Akkumulation von Körper- und Leberfett zu spielen, insbesondere bei Personen mit T2D. Diese Dissertation betont die Relevanz der Kohlenhydrat- und Zuckeraufnahme in der Ernährung im Kontext mit der Prävention und Behandlung von Diabetes.

Summary

Previous evidence indicated that the association between dietary sugar intake and type 2 diabetes (T2D) is heterogeneous and inconclusive. In this context, it is discussed whether dietary sugar intake solely leads to T2D due to an excess of calories and thus obesity. Moreover, a restriction in carbohydrate intake appears beneficial in the management of diabetes. However, evidence on compensatory nutrient intake in individuals with diabetes in association with adipose tissue distribution is yet unclear. Therefore, this dissertation aimed to examine 1) the relationship between dietary sugar intake and onset of diabetes on a global and individual level and detect the impact of obesity on this association, and 2) the substitution of carbohydrates with fat and protein in association with body and liver fat content.

In order to investigate the association between dietary sugar intake and the onset of diabetes, we conducted an ecological study using aggregated data on a global level and a prospective study using data from the EPIC-Norfolk on an individual level. In both studies, causal mediation analysis was applied to examine the influence of obesity on this association. In addition, a cross-sectional substitution analysis was conducted using data from the German Diabetes Study (GDS) to investigate the replacement of carbohydrates with fat and protein in association with magnetic resonance imaging measured subcutaneous and visceral adipose tissue volumes and hepatic lipid content.

The findings demonstrated that dietary sugar intake was associated with a 1.6 % higher prevalence of diabetes on a global level using aggregated data on per capita sugar consumption [β (95 % CI): 1.62 (0.71, 2.53)], as well as with a higher incidence of T2D on an individual level using objective urinary sucrose biomarker [HR: 1.14 (95 % CI: 0.95, 1.36)]. These associations can be partly explained by the mediating influence of obesity (~66 % on a global and ~20 % on an individual level). Furthermore, the results indicated that substituting carbohydrates with polyunsaturated fatty acids was linked to lower visceral adipose tissue volume and hepatic lipid content in individuals with T2D. Similarly, replacing higher glycemic index carbohydrates with odd-chain or very-long-chain saturated fatty acids or plant-based protein was associated with lower hepatic lipid content in T2D.

In conclusion, the association between dietary sugar intake and the onset of diabetes is partially mediated by overweight or obesity. However, there is an indication that other potential direct sugar-related mechanisms may influence the development of diabetes. In addition, the findings indicate that not solely a restriction of carbohydrate intake, but rather the quality of the replacing nutrients play a crucial role in the accumulation of body and liver fat content, particularly in individuals with T2D. This dissertation highlights the importance of dietary carbohydrate and sugar intake in the context of diabetes prevention and management.

Abbreviations

24uSF	24-hour urinary sucrose and fructose
ADA	American Diabetes Association
BMI	Body mass index
CIA	Central Intelligence Agency
CKD	Chronic kidney disease
δ13C	Ratio of the two stable isotopes of carbon-13 and carbon-12
δ15N	Ratio of the two stable isotopes of nitrogen-15 and nitrogen-14
DDG	German Diabetes Society (Deutsche Diabetes Gesellschaft)
EPIC	European Prospective Investigation into Cancer
FAO	Food and Agriculture Organization of the United Nations
GDS	German Diabetes Study
GI	Glycaemic index
GL	Glycaemic load
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HL	Hepatic lipid
IDF	International Diabetes Federation
Kcal	Kilocalories
LDL	Low density lipoprotein
MUFA	Monounsaturated fatty acid
n-3 PUFA	Omega-3 polyunsaturated fatty acid
n-6 PUFA	Omega-3 polyunsaturated fatty acid
PDE	Pure direct effect
PM	Proportion mediated
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
SAT	Subcutaneous adipose tissue
SFA	Saturated fatty acid
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TIE	Total indirect effect
UN	United Nations
WC	Waist circumference
WHO	World Health Organization
VAT	Visceral adipose tissue

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Chapter 1

Introduction

Epidemiology and aetiology of diabetes

Diabetes mellitus is one of the most prevalent chronic metabolic disorders, characterised by elevated blood glucose levels due to pancreatic β-cell dysfunction and insulin resistance (1, 2). The International Diabetes Federation (IDF) estimated that the global prevalence of diabetes in individuals aged 20-79 years was around 10.5 % in 2021, affecting approximately 537 million people (3). In addition, the 10th edition of the IDF Diabetes Atlas estimated that the same number of individuals (~541 million) additionally lived with impaired glucose tolerance (4). These estimates also predict that the prevalence of diabetes will increase worldwide in the coming decades, particularly in middle-income countries in Africa, the Middle East and South-East Asia (Figure 1). In numerical terms, it is predicted that approximately 643 million people will be affected by diabetes by 2030, rising to approximately 783 million by 2045. This represents an increase in the prevalence of diabetes to 12.2 % (4). As a result, diabetes has become of the most rapidly growing global health emergencies of the 21st century, imposing a substantial economic burden on healthcare systems and governments worldwide. In 2021, total health expenditures due to diabetes reached 966 billion US dollars (4). According to the German Health Report Diabetes 2024 by the German Diabetes Society (DDG), at least 8.9 million people in Germany were living with diabetes in 2023 (5).

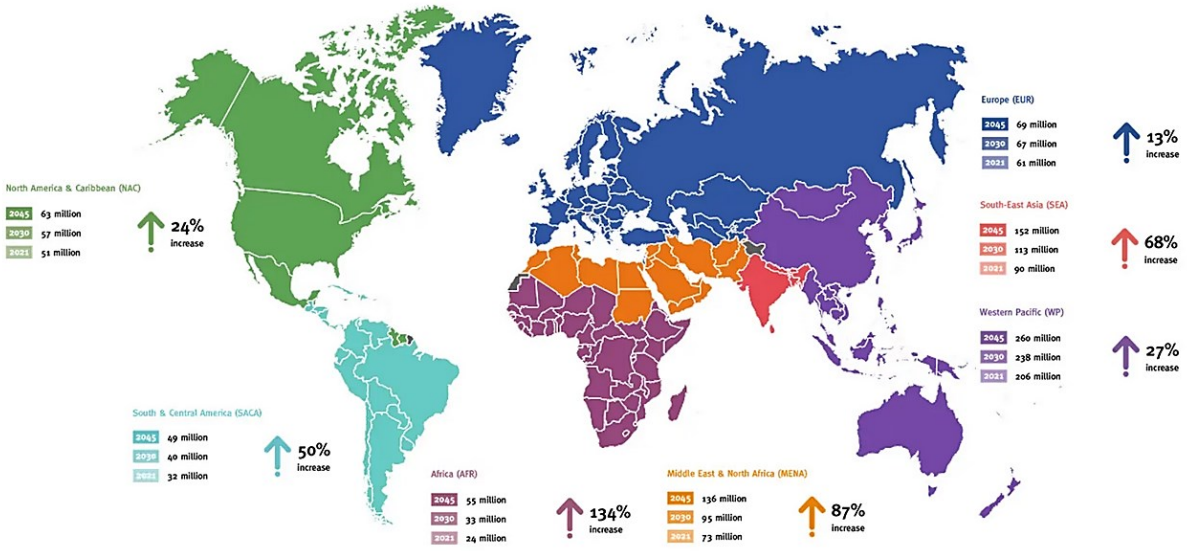

Figure 1: Number of adults aged 20-79 years living with diabetes worldwide and per IDF Region in 2021 and estimates for the years 2030 and 2045 (4)

The American Diabetes Association (ADA) classifies diabetes mellitus into four subtypes: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus and specific types of diabetes (e.g., neonatal diabetes or maturity-onset diabetes in the young) (2). As the latter two subtypes are not prominent in the data used in this dissertation, the focus will be on people with T1D and, in particular, T2D. Individuals with T1D suffer from autoimmune destruction of the insulin-producing β-cells in the pancreas, resulting in an absolute deficiency of insulin

secretion. In contrast, T2D is characterised by progressive loss of β-cell function and advanced insulin resistance, leading to elevated blood glucose levels and ultimately to relative insulin deficiency (2). The onset of T1D is strongly influenced by genetic predisposition, with a peak incidence in adolescence and early adulthood (6). Approximately 5-10 % of all cases of diabetes are T1D, while 90-95 % are consequently T2D (2). Although genetics also play a role in the aetiology of T2D, this type of diabetes is particularly associated with modifiable risk factors such as a sedentary lifestyle, poor diet and overweight (1, 7). According to the ADA, IDF and World Health Organization (WHO), people are diagnosed with T2D, if they have a fasting plasma glucose level of ≥126 mg/dL, a 2-hour plasma glucose level after an oral glucose tolerance test or a random plasma glucose level of ≥200 mg/dL, or a glycated haemoglobin (HbA1c) level of ≥6.5 % (2, 4, 8). In Germany, T2D is more commonly diagnosed in people over 50 years of age, with a peak incidence of 24 newly diagnosed cases per 1000 person-years observed in individuals aged 85 years (9).

Burden of diabetes

Due to the increasing prevalence of diabetes worldwide, healthcare systems are increasingly challenged with the responsibility of providing treatment for individuals with diabetes or preventing further comorbidities (4). Research indicates that a large proportion of individuals with T2D are overweight or obese, which represents a major risk factor for disease progression (10). However, there is also is an emerging trend in individuals with T1D towards being overweight and facing insulin resistance as a consequence of poor lifestyle choices and intensive insulin therapy (11). Insulin resistance and insulin deficiency not only affect glucose metabolism, but also trigger a cascade of pathophysiological changes throughout the body. Individuals with diabetes, especially T2D, are at increased risk of developing cardiometabolic comorbidities and complications, as well as experiencing impaired quality of life and premature death (12). Evidence from epidemiological studies has shown that there is a crucial link between diabetes and cardiovascular disease (CVD), with approximately one third of people living with T2D also affected by CVD (13). Moreover, findings from a meta-analysis of 102 prospective studies revealed that individuals with diabetes had a twofold higher relative risk of developing coronary heart disease (CHD) or ischemic stroke compared to individuals without diabetes (14). As a consequence, individuals with T2D also have a more than threefold higher risk of CVD mortality compared to people without diabetes (15). In particular, women with T2D appear to have a higher risk of CVD incidence and mortality (14, 15).

In addition, diabetes is associated with a spectrum of further complications and comorbidities, including diabetic retinopathy (16), lower-extremity amputations (17), chronic kidney disease (CKD) and end-stage renal disease (18, 19). In this context, previous studies have

demonstrated that metabolic dysfunction-associated steatotic liver disease (MASLD) is also associated with an increased incidence of T2D (20), indicating that there appears to exist a bidirectional relationship between liver fat accumulation and T2D due to induced insulin resistance and hepatic steatosis (21, 22). Furthermore, individuals with diabetes are at higher risk of developing depression or experiencing a lower quality of life than the general population (23, 24). Additionally, diabetes is associated with an increased risk of cancer and higher mortality rates (25, 26). In 2021, approximately 6.7 million deaths that were attributed to diabetes and its complications, making it one of the leading causes of premature death worldwide (4). In Germany, it is estimated that 21 % of all deaths are related to diabetes, with 16 % of these deaths attributable to T2D alone (27). In conclusion, diabetes represents an enormous public health burden with broad implications for individuals, families, and societies both in Germany and worldwide.

Risk factors of diabetes onset and progression

In order to address the diabetes epidemic and its serious complications, it is essential to identify the underlying risk factors that contribute to the onset and progression of T2D. Epidemiological studies have demonstrated that fundamental factors, including advanced age, a family history of diabetes, ethnicity and lower socioeconomic status, are associated with the onset of T2D (4, 28-30). However, as previously stated, behavioural, and thus modifiable, risk factors also play a substantial role in the prevention of T2D (1, 7). In this context, epidemiological evidence indicated that the adherence to a more favourable lifestyle has the potential to prevent the onset and progression of T2D (31). Consequently, several organisations, including the ADA and the IDF, recommend lifestyle modification as a cornerstone of diabetes prevention and management (32, 33). Studies have shown that non-smokers have a reduced risk of developing T2D in comparison to those who are current or former smokers (34). Similarly, in individuals with diabetes, non-smoking was associated with a lower risk of all-cause mortality, as well as CVD incidence and mortality (35). Moreover, comparable relationships were identified with regard to physical activity. Higher levels of physical activity were found to be associated with a reduced risk of T2D, regardless of the intensity and type of exercise (36). In addition, a recent systematic and meta-analysis found with moderate certainty of evidence that higher levels of physical activity in individuals with diabetes were inversely associated with the incidence and mortality of CVD, as well as microvascular complications, even at lower levels of activity (37). A moderate certainty of evidence means that we are moderately confident in the effect estimate, but further research is likely to have an important impact on our confidence and may result in a change of the estimate (38). Following this assessment, findings with a moderate or high (further research is very unlikely to change the confidence in the effect estimate) certainty of evidence are

considered for recommendations and guidelines (39). Beyond that, there has been a growing body of evidence published in recent decades on the influence of a favourable diet on the prevention and progression of diabetes.

In a recent umbrella review, a systematic overview of the associations between dietary food and nutrient intake and the T2D incidence was provided (40). The results indicated with high or moderate certainty of evidence that the intake of total meat, red and processed meat, bacon, white rice, French fries and hot dogs was associated with a higher relative risk of developing T2D. Conversely, the consumption of other foods, including whole grains, wheat bran, yoghurt, and dairy products, was associated with a lower risk of T2D. Furthermore, on a nutrient basis, the results demonstrated protective associations between the intake of cereal fibre, vegetable fat, and total fibre intake and T2D. In contrast, total protein, animal protein and a higher animal protein-to-potassium ratio were associated with a higher risk of T2D (40). In this context, there is an increasing body of epidemiological evidence that replacing animal-based foods with plant-based foods may be beneficial for metabolic health. Findings of a recent systematic review and meta-analysis indicated with moderate certainty of evidence that replacing butter with olive oil, as well as replacing red and processed meat, poultry or eggs with nuts, whole grains or cereals was associated with a lower risk of T2D (41).

Beyond that, diet can potentially also play an important role in diabetes management. In this context, several dietary guidelines have been published in recent years by professional organisations and societies with the objective of preventing the progression of diabetes. For instance, the IDF recommends that overweight and obese individuals with T2D reduce their daily calorie intake by 500-600 kilocalories (kcal), increase their intake of fibre-rich and low glycaemic index (GI) foods, and avoid sugar, sweets and sweetened beverages (32). In addition, the ADA and the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) have published comprehensive guidelines based on several specific food groups and dietary patterns to prevent the progression of diabetes (33, 42). According to these associations, it is recommended to increase the intake of minimally processed plant foods, such as fruit and vegetables, whole grains, legumes, nuts and seeds, as well as foods rich in fibre and omega-3 polyunsaturated fatty acids (n-3 PUFA). On the other hand, experts emphasise limiting the intake of processed or ultra-processed foods containing red and processed meat, refined grains, sugar and sodium, reducing overall carbohydrate intake and replacing sugar-sweetened beverages (SSBs) and fruit juices with preferably water (33, 42). In Germany, the German Diabetes Society (DDG) recommends that the consumption of non-starchy vegetables and low-processed foods should be preferred to refined sugars and highly-processed grains, which may be accessible by following a Mediterranean, vegetarian or vegan diet (43). Overall, the aforementioned guidelines are largely consistent with one another. However, the majority of these recommendations are based on evidence derived from the

general population, and systematic evidence of associations between dietary intake and progression of diabetes carried out in individuals with diabetes is still limited. Findings of a recent systematic review and meta-analysis indicated that a higher intake of whole grains, fibre, fish and n-3 PUFA was associated with a lower risk of all-cause mortality in individuals with T2D, with a moderate certainty of evidence (44). Moreover, an umbrella review of randomised controlled trials (RCTs) revealed that in addition to restricting total energy intake, certain diets, including the Mediterranean diet, a plant-based diet or a high-protein diet, may be beneficial for cardiometabolic health in individuals with T2D (45).

Carbohydrates in the context of diabetes prevention and progression

Previous studies have shown that the dietary carbohydrate intake may be an important factor in the context of diabetes. Although there is no evidence that a carbohydrate restriction is associated with the risk of T2D (40), findings from RCTs have indicated that a diet low in carbohydrates may be beneficial for the management of T2D (45). In this context, evidence has demonstrated that low-carbohydrate diets have been linked to reduced body weight, HbA1c and triglyceride levels, along with elevated high-density lipoprotein (HDL) cholesterol levels a decreased reliance on medication in individuals with T2D. These findings are supported by moderate to high certainty of evidence (45, 46). However, the source and quality of carbohydrate intake may be of particular importance in this context.

In recent years, there has been a growing recognition of the role of carbohydrate quality in the prevention of T2D and the management of both T1D and T2D (47, 48). In this context, the GI is the most commonly used method for evaluating the quality of carbohydrates. The GI is a measure on a scale of 0-100 that quantifies the extent to which carbohydrates in foods affect postprandial blood glucose levels after their consumption, relative to the same amount of a reference carbohydrate (typically a glucose solution or white bread) (49). Subsequently, carbohydrate-containing foods can be categorised on the GI scale according to how rapidly or slowly they are digested, absorbed and metabolised, resulting in high (≥70), medium (56-69) and low GI (≤55) foods (47, 49). The highest average GIs are observed in potatoes, rice, white wheat bread and cornflakes, while the lowest are found in dairy products, legumes, sports energy bars and nuts (50, 51). While the GI does not take into account the quantity of carbohydrate consumed, the glycaemic load (GL) is calculated as the product of the GI multiplied by the amount of carbohydrate in a typical portion divided by the given amount of food. Consequently, the GL is a more comprehensive measure in practice and a better predictor of glycaemic response than the amounts of macronutrients alone (47, 49).

In general, a lower the GI or GL value indicates a slower is the postprandial glycaemic response, which is considered more beneficial for glycaemic control (47, 49). In this context,

findings of a systematic review and meta-analysis of large cohort studies have provided evidence that diets with a high GI or GL are associated with an increased risk of T2D (52-54). Beyond that, an umbrella review of systematic reviews and meta-analyses of RCTs with a duration of >12 weeks has indicated that GI and GL may also have the potential to play an important role in the management of T2D. The findings showed that a low GI or GL was associated with reduced low-density lipoprotein (LDL) cholesterol (55, 56), which was rated with moderate certainty of evidence (45). Moreover, additional meta-evidence indicated that adherence to a low GI/GL diet improved glycaemic control, body weight, body mass index (BMI) and inflammation in individuals with diabetes (57, 58). Consequently, the dietary guidelines of the IDF and the EASD recommend following diets with low GI/GL for the management of T2D (32, 42).

Although diets containing low GI carbohydrates appear to be beneficial for individuals with diabetes, the evidence on the relationship between dietary sugar intake and incident diabetes is inconsistent and findings are partially inconclusive. However, this issue should be highlighted in research, as children and adolescents consume approximately 12-14 energy percent (En%) of their total energy intake from free sugars, and adults 8 En% (59). Dietary sugar intake has risen dramatically in recent decades, particularly in developing and emerging countries, due to population growth, higher incomes and increased demand for sugary confectionery and soft drinks, and it is anticipated that this trend will continue (59-61). In contrast, dietary sugar intake has remained stable or declined slightly in developed countries due to health concerns, but remains high in Western civilisations (60, 61). Figure 2, derived from data provided by the Food and Agriculture Organization of the United Nations (FAO), illustrates the global per capita consumption of sugar in 2021. The highest levels of per capita sugar consumption were observed in Guatemala (538 kcal/day), Cuba (506 kcal/day) and Barbados (480 kcal/day), while the lowest intakes were observed in the Democratic Republic of the Congo (23 kcal/day), Guinea-Bissau (24 kcal/day) and Myanmar (29 kcal/day).The daily per capita sugar consumption was approximately 380 kcal/day in Germany and 296 kcal/day in Europe as a whole in 2021 (62). Due to its negative impact on weight gain and dental caries, the WHO has strongly recommended a reduction in the intake of free sugars to less than 10 En% throughout the life course (63). In a consensus paper, professional German societies also adopted this recommendation for Germany, which corresponds to a daily maximum intake of 50 g free sugars, given a total energy intake of 2000 kcal per day (64). Conditionally, a further reduction of free sugar intake to less than 5 En% may be appropriate according to the WHO, particularly for children (63).

Nevertheless, there is an ongoing debate about the influence of dietary sugar intake on the onset and progression of diabetes. In 2018, in an essay published in the *BMJ*, it is argued that sugar may not only be a source of excess calories, but also a fundamental cause of T2D, and

research has primarily focused on the impact of fat and total energy intake (65). There is convincing meta-evidence that the consumption of SSBs is associated with an increased risk of T2D (66). This association has been evaluated as high certainty of evidence, indicating that further research is unlikely to change the confidence in this association (40). In contrast, the evidence for an association between dietary sugar intake as mono- and disaccharides and the incidence of T2D is insufficient and findings point in the opposite direction. In this context, the results of a systematic review and meta-analysis demonstrated that a higher total sugar intake was inversely associated with the incidence of T2D, but the results were imprecisely estimated (67). This meta-analysis also showed that a higher dietary sucrose intake was linked to a lower risk of T2D. However, the findings of the included primary studies were heterogeneous and the certainty of evidence was rated as very low or low, respectively (40). This indicates that there is limited (low) or very little (very low) confidence in the effect estimates and that it's very likely that further research will change the effect estimates (38). Moreover, the associations between fructose, glucose, lactose and maltose with T2D incidence were inconclusive (67, 68), all of which were rated with very low certainty of evidence (40).

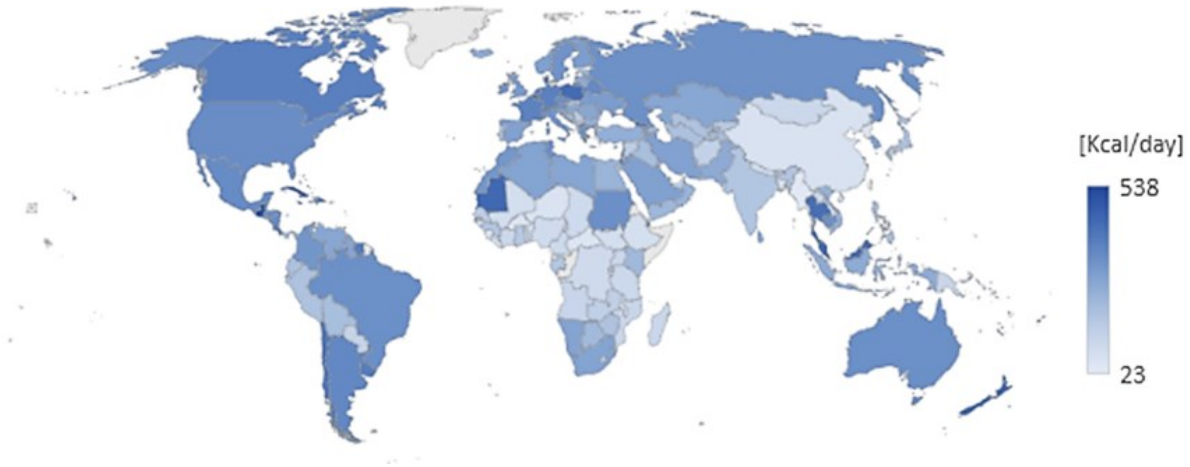

Figure 2: Global per capita sugar consumption per day in 2021 using food supply data of sugar (raw equivalent) of the Food and Agriculture Organization of the United Nations (62)
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These inconclusive epidemiological observations may be explained by measurement errors due to reporting bias, which is often accompanied by the common methods for assessing nutritional behaviour. Dietary intake is mostly retrieved with self-reports using different diet assessment approaches, such as 24-hour recalls, diet records or food frequency questionnaires (FFQ) (69). However, studies have shown that these tools are eventually prone to bias, which finally affects the accuracy of dietary assessment (70). The findings of these studies indicated that participants tend to underreport their true food intake, especially for generally known unhealthy food items, such as cakes and cookies (71). This pattern was particularly evident in overweight individuals, suggesting that social desirability and reporting

bias might be present (72). Therefore, the inconsistent findings of dietary sugar intake in relation to health outcomes might be induced due to misreporting.

Urinary sugar biomarkers

Since values of dietary sugar intake assessed by self-reports might vary from real values, presumably due to measurement errors, different approaches to measure dietary sugar intake should be taken into account. In this context, the use of objective sugar biomarkers may be a more accurate method to measure the true dietary sugar intake than assessment methods based on self-reports. One method for objectively assessing dietary sugar intake is the measurement of sucrose and fructose in urine samples.

The first time urinary sucrose and fructose were measured in urine was in 1996, when scientists discovered that the excretion of sucrose and fructose was correlated with sucrose intake after following a low-sucrose diet for three days (73). Subsequently, the urinary sucrose and fructose biomarkers have been investigated in numerous studies and in 2005, the first results of a validation study using 24-hour urinary sucrose and fructose (24uSF) biomarkers was published by Tasevska et al. (74). This validation involved two distinct studies conducted in healthy adult populations within highly controlled settings. The first study was a randomised crossover trial in 12 healthy males including three dietary regimens, each containing different levels of total sugars: low (63 g/d), medium (143 g/d) and high (264 g/d). Each dietary regimen was followed for a period of 10 days. On days four and seven of each diet, 24-hour urine samples were collected, and a high correlation of 0.89 was found between dietary sugar intake and urinary excretion of sucrose and fructose. In the second study, the habitual intake of 13 healthy subjects was assessed and participants' meals within the study were based on dietary information assessed with a detailed 7-day diet diary (7DD) for four consecutive weeks prior to the study. Over the course of 30 days, 24-hour urine samples were collected on a daily basis, demonstrating again a high correlation ($r = 0.84$) between dietary sugar intake and urinary excretion (74). Subsequently, further validation studies have confirmed the reliability of 24uSF, demonstrating that the correlation between dietary sugar intake and the urinary biomarker was also high in adolescents (75), across larger study samples (76, 77), over long-term consumption (77), and independent of BMI (78).

Following the validation of the 24uSF biomarker, Tasevska and colleagues compared it with self-reported dietary sugar intake in cohort studies by employing a prediction equation derived from the aforementioned validation study to estimate "true" sugar intake from the biomarker data (74). In this context, data from the Nutrition and Physical Activity Assessment study revealed a comparable correlation between the biomarker-predicted and self-reported dietary sugar intake when using an FFQ ($r = 0.22$), a 4-day food record ($r = 0.26$) and an average of

three 24-hour recalls (r = 0.26) (79). Moreover, data from the Observing Protein and Energy Nutrition (OPEN) study indicated that the correlation coefficients between biomarker-predicted and self-reported dietary sugar intake were higher in men (FFQ: r = 0.43; two 24-hour recalls: r = 0.58) than in women (FFQ: r = 0.16; two 24-hour recalls: r = 0.25) (80).

In addition, some studies have looked at urinary sugar biomarkers that were not measured in 24-hour urine samples. For instance, sucrose and fructose were quantified from spot urine samples in a subsample of the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) cohort. Studies carried out in the EPIC-Norfolk demonstrated a positive association between urinary sucrose and overweight or obesity, but inverse or null associations between self-reported dietary sugar intake and overweight or obesity (81, 82). Beyond that, a Swedish study reported correlation coefficients of approximately r = 0.2-0.3 between overnight urinary sucrose and fructose biomarker with total sugars, added sugars and sucrose in both men and women (83). These findings were similar to the correlations between morning urine samples and self-reported dietary sugar intake in children from the I.Family study (84). However, urinary biomarkers in any form other than 24-hour urine samples have not yet been shown to be objective biomarkers in validation studies.

Obesity on the pathway between sugar intake and diabetes

As previously stated, the question of whether dietary sugar intake directly influences the development of diabetes remains a topic of debate. One hypothesis suggests that a high-sugar diet leads to an overload in calorie intake, and thus to obesity (85, 86), which is the real risk factor for diabetes (87, 88). In this case, dietary sugar intake would exert an indirect influence on the development of T2D. In previous studies that investigated the association between dietary sugar intake and diabetes incidence, researchers conducted an additional model, in which they also controlled for BMI and revealed an indication that BMI may bias this relationship (89-91). As a result of this additional adjustment for BMI, the inverse findings were attenuated, indicating that BMI may influence this association. However, in order to ascertain the extent to which the relationship between dietary sugar intake and diabetes can be attributed to overweight and to identify the extent to which other pathophysiological mechanisms may influence this association, the methodological approach of mediation analysis can be applied.

In mediation analysis, the objective is to decompose the total effect of an exposure-outcome association into a direct and an indirect effect. The indirect effect describes the effect of the exposure on the outcome that operates via the causal pathway through a third variable (the mediator). In contrast, the direct effect represents the effect of the exposure on the outcome independent of the mediator (92, 93). To provide a more detailed clarification of the concept of mediation analysis, it is necessary to employ a counterfactual approach suggested by

VanderWeele (94). In a counterfactual framework, the total indirect effect (TIE) is defined as the difference in the counterfactual outcome if the mediator was set to the level it would have been when the person was exposed (M_1) versus the level it would have been when the same person was not exposed (M_0), assuming that the exposure was present (Y_1). Moreover, the pure direct effect (PDE) represents the difference in the counterfactual outcome, if a person was exposed (Y_1) in contrast to the same person was not exposed (Y_0) to the independent variable, assuming that the mediator is held constant at the value it would have been in the absence of exposure (M_0) (94). The formula for decomposing the total effect into TIE and PDE is as follows:

$$\underbrace{Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0}}_{\text{Total effect}} = \underbrace{(Y_{1M_1} - Y_{1M_0})}_{\text{TIE}} + \underbrace{(Y_{1M_0} - Y_{0M_0})}_{\text{PDE}}$$

Additionally, the proportion mediated (PM) can be calculated as the quotient of the TIE and the total effect. The PM quantifies the extent to which the total effect is explained by the mediator, expressed as a percentage. Higher values indicate a stronger impact of the mediator on the exposure-outcome association (92).

In order to perform mediation analysis, certain criteria must be met. First, there must be an association between exposure and outcome. Second, the exposure must be related to the mediator. Third, the mediator must be related to the outcome, indicating that the mediator lies on the causal pathway between exposure and outcome. In light of this causal inference, it is recommended that exposure, mediator and outcome should ideally be measured at three different time points, if applicable (92).

Substitution of carbohydrates with other macronutrients

To gain further insight into the relationship between carbohydrate intake and diabetes progression, the approach of substitution analysis was employed. As previously stated, there is evidence indicating that diets high in carbohydrates high in GI and SSBs are detrimental to health in terms of T2D (40, 53). Consequently, a number of international organisations have advised a reduction in the consumption of high GI carbohydrates (32, 42), as well as free and added sugars (51, 95). However, reducing carbohydrates without restricting total energy intake leads to compensatory increased intake of protein and fat, which may subsequently affect metabolic health. In order to investigate this effect, isocaloric substitution analysis, a well-established tool in nutritional epidemiology, can be conducted (96, 97).

In isocaloric substitution analysis, the impact of replacing one dietary component with another on a specific outcome is investigated, while the overall caloric intake is kept constant. This statistical approach allows the results of feeding studies to be mimicked with epidemiological data, thus identifying the most beneficial diet (97). Two different methods can be applied, which ultimately lead to the same results: the leave-one-out and the partition method (Table 1). In this section, both methods will be briefly outlined for the scenario in which the food component A (e.g., protein) is replacing the food component C (e.g., carbohydrates), while the remaining food component B (e.g., fat) remains constant. The leave-one-out method involves the inclusion of the replacing variable A, variable B, and the total intake of A, B, and C combined, but not variable C alone. However, the partition method allows the inclusion of all three food components in the model on an individual basis. In substitution analyses based on linear regression models, the substituting effect would then be represented by the beta-coefficient for variable A (α_1) in the leave-one-out method and the difference in beta-coefficients of the replacing variable A minus the replaced variable C in the partition method (β_1-β_3) (97). Consequently, the substitution effect can be interpreted as the change in outcome resulting from the replacement of variable C with variable A.

Table 1: Depiction of the two most common models used for substitution analysis - modified version of Song (97)

Model name	**Model expression**	**Substitution parameter** (substituting A for C)	**Variance estimates**
Leave-one-out model	$f(Y) = \alpha_1 A + \alpha_2 B + \alpha_3 (A+B+C)$	α_1	$var(\alpha_1)$
Partition model	$f(Y) = \beta_1 A + \beta_2 B + \beta_3 C$	$\beta_1 - \beta_3$	$var(\beta_1 - \beta_3) = var(\beta_1) + var(\beta_3) - 2cov(\beta_1 - \beta_3)$

Furthermore, it is crucial to account for potential important confounding variables, when conducting substitution analyses with dietary data. First of all, it is essential to control the models for total dietary energy intake in order to ensure that the substitution is performed in an isocaloric setting. Moreover, the models must be adjusted for a priori-defined covariates based on existing knowledge in the literature or directed acyclic graphs (e.g., age, sex, physical activity). In addition, it is necessary to control for all the other food components besides the replacing and the replaced food component (96). In analyses based on nutrient intake, where carbohydrates are replaced with total fat, the remaining food component protein must be maintained at a constant level. However, if monounsaturated fatty acids (MUFA) are replaced at the expense of carbohydrates, it is necessary to adjust for protein again, but also for polyunsaturated fatty acids (PUFA) and saturated fatty acids (SFA), in order to complete the macronutrient intake (96).

Aims of this doctoral thesis

The objective of the publication-based doctoral thesis was to investigate the relationship between dietary carbohydrate and sugar intake and diabetes prevention and management in three major research projects.

First, we hypothesised that the relationship between dietary sugar intake and diabetes, particularly T2D, is not solely attributable to the impact of obesity. Thus, there may be additional direct sugar-related mechanisms that contribute to the relationship between dietary sugar intake and diabetes. In order to examine this hypothesis, two causal mediation analyses were conducted. The first one was based on aggregated ecological data, in which we aimed to investigate the direct effect of per capita sugar consumption on diabetes prevalence, as well as the indirect effect and accordingly the PM of BMI on this association on a global scale (project 1).

Second, we sought to examine the association between dietary sugar intake and incidence of T2D on an individual level, using a sucrose biomarker from spot urine sample, as well as dietary sucrose intake from a FFQ or 7DD assessed in a subsample of the EPIC-Norfolk. In our second mediation analysis, we then examined the impact of BMI and waist circumference (WC) on the association between urinary sucrose and T2D incidence in order to calculate the indirect effect and PM through the influence of BMI or WC and the direct effect that could be explained by urinary sucrose (project 2).

Third, we hypothesized that the dietary carbohydrate intake in general plays a crucial role in the management of T1D and T2D, with a lower intake potentially being associated with more favourable body fat distribution and liver fat accumulation. However, to maintain the energy intake at a constant level, carbohydrates must be substituted with fat or protein, which may affect the aforementioned outcomes. In order to investigate the impact of replacing carbohydrates on magnetic resonance imaging (MRI)-derived subcutaneous (SAT) and visceral fat tissue (VAT), as well as liver proton magnetic resonance spectroscopy (^{1}H-MRS)-derived hepatic liver (HL) content, we conducted cross-sectional substitution analyses, using data from the German Diabetes Study (GDS) including individuals with recent-onset T1D and T2D: First, carbohydrates were replaced with total fat, MUFA, PUFA, SFA and protein; Second, higher GI carbohydrates were replaced with low GI carbohydrates, animal-based and plant-based MUFA, omega-3 (n-3) and omega-6 (n-6) PUFA, even-chain, very-long-chain and odd-chain SFA, as well as animal-based protein and plant-based protein (project 3)

Chapter 2

Association between per capita sugar consumption and diabetes prevalence mediated by the body mass index: results of a global mediation analysis

(doi: 10.1007/s00394-020-02401-2)

Summary

There is an ongoing debate, whether dietary sugar intake is influencing the onset of T2D. Previous studies have demonstrated that a higher intake of SSBs is associated with an increased T2D risk. However, the evidence on the relation between the intake of mono- and disaccharides and T2D is heterogeneous and inconclusive. Furthermore, it is generally hypothesised that a higher sugar intake leads to overweight or obesity, which might be the true risk factor for diabetes. In order to investigate, whether dietary sugar intake may potentially have a direct influence on diabetes, the aim of this study was to examine the mediation effect of BMI on the association between per capita sugar consumption and diabetes prevalence based on aggregated ecological data.

This ecological study included aggregated freely accessible data of 192 countries collected from reliable global organisations. The data on per capita sugar consumption was obtained from the FAO, the data on BMI from the WHO, the data on diabetes prevalence from the IDF, and the data on demographic and economic covariates from the Central Intelligence Agency (CIA), the United Nations (UN) and the FAO. In order to simulate a prospective sequence between per capita sugar consumption (from 2007), BMI (from 2012) and diabetes prevalence (from 2017), lead time intervals were taken into account. Missing values were imputed using multiple imputation and the association between per capita sugar consumption and diabetes prevalence was investigated with multivariable linear regression analysis. Mediation analysis was performed to examine the potential mediating role of BMI on this association.

Globally, the mean per capita sugar consumption was 191 ± 122 kcal/day, the mean BMI was 24.0 ± 2.3 kg/m^2, and the mean diabetes prevalence was 8.5 ± 2.8 %. The findings of the multivariable linear regression analysis indicated that an increase in per capita sugar consumption per 100 kcal/day was associated with a 1.6 % higher prevalence of diabetes [β (95 % CI): 1.62 (0.71, 2.53)]. The mediation analysis indicated that the influence of BMI on this association was 66 % [PM (95 % CI): 66 % (34 %, 100 %)].

In conclusion, these findings demonstrated that per capita sugar consumption was associated with a higher diabetes prevalence on a global level. Approximately two thirds of this association was mediated by the BMI. Nevertheless, up to one third of the association between per capita sugar consumption and diabetes could be explained by other, potentially direct, mechanisms. Further studies using individual data are warranted to confirm these results.

Chapter 3

The mediating role of obesity on the prospective association between urinary sucrose and diabetes incidence in a sub-cohort of the EPIC-Norfolk

(doi: 10.1038/s41387-023-00243-5)

Summary

Findings from epidemiological studies have yielded inconclusive results regarding the association between dietary sugar intake in the form of mono- and disaccharides and the development of diabetes. This may be explained by the fact that most of these studies assessed dietary sugar intake through self-report which may be prone to reporting bias. In order to avoid these measurement errors, objective biomarkers, such as urinary sucrose, may be a more reliable choice for examining the association between dietary sugar intake and diabetes onset. Thus, the objective of this study was to investigate the associations between sucrose intake, both measured via self-report and urinary sucrose, with T2D incidence. Furthermore, we aimed to examine the influence of overweight on an individual level on the association between urinary sucrose and incident diabetes.

In this study, 2996 participants from the prospective EPIC-Norfolk cohort with available data on urinary sucrose within the detection limit were included. Urinary sucrose biomarker was measured in spot urine samples and dietary sucrose intake was assessed with a FFQ and a 7DD. The associations between dietary and urinary sucrose and diabetes incidence were investigated in multivariable Cox proportional hazard models. The PM of BMI and WC on this association was calculated in a causal mediation analysis.

During a mean follow-up period of 11.2 ± 2.9 years 97 of the 2996 participants (53 % women, mean age: 60.6 ± 9.5 years) developed T2D. The results of the multivariable Cox regression indicated that an increase in self-reported dietary sucrose intake per 50 g/d was associated with a 37 % lower risk of T2D based on data from 7DD [HR (95 % CI): 0.63 (0.43, 0.91)]. Using the FFQ data showed similar, but imprecisely estimated, results [HR (95 % CI): 0.81 (0.46, 1.42)]. Conversely, higher levels of urinary sucrose were associated with an increased risk of T2D, both in continuous analysis [HR (95 % CI) per 100 µM: 1.14 (0.95, 1.36)] and in the comparison of highest versus lowest intake [HR (95 % CI): 1.36 (0.77, 2.41)]. However, the findings were imprecisely estimated. The results of the mediation analysis demonstrated that the PM of BMI or WC was 16 % or 22 %, respectively, indicating that approximately one fifth of the association between urinary sucrose and the incidence of T2D can be explained through overweight.

In conclusion, these findings demonstrated that objectively measured sugar intake via urinary sucrose biomarker was associated with an increased incidence of T2D. It appears that this association is only partly influenced by BMI and WC, suggesting that other pathomechanisms may play an essential role in the development of T2D.

Chapter 4

Cross-sectional association between the isocaloric replacement of carbohydrates with protein and fat in relation to fat compartments distribution and hepatic lipid content in recent-onset type 1 and type 2 diabetes

Summary

Diet does not only play a role in T2D prevention, but also in the management of both, T1D and T2D. Especially a carbohydrate restriction is recommended in this context. However, reducing the carbohydrate intake while keeping the total energy at a constant level leads to compensatory increased intake of fat and protein. In this context, it is crucial to consider the quality of these nutrients, as it can affect the fat compartments distribution. Thus, the aim of this study was to investigate the isocaloric substitutions of carbohydrates with fat and protein in individuals with recent-onset T1D and T2D in relation to SAT, VAT and HL content.

In this cross-sectional analysis, participants with recent-onset T1D (n=137) and T2D (n=170) from the ongoing GDS were included. Macronutrient intake was assessed using a validated FFQ and calculated based on reported frequencies in combination with assigned portion sizes for each food item. SAT and VAT volumes were quantified using a whole-body MRI and HL content via ^{1}H-MRS. Isocaloric substitution analyses based on multivariable linear regression models were conducted to investigate the substitution of carbohydrates with total fat, MUFA, PUFA, SFA and protein in regard to SAT, VAT and HL content. In more detail, to consider the quality of macronutrients, also the replacement of higher GI carbohydrates with low GI carbohydrates, plant- and animal-based protein and MUFA, n-3 and n-6 PUFA, as well as even-chain, odd-chain and very-long-chain SFA was examined.

The macronutrient intake was comparable between diabetes types, both reporting moderate-low carbohydrate (36-37 En%) and high fat intake (45-46 En%). In individuals with T1D, the replacement of carbohydrates with total fat was not associated with SAT, while substituting carbohydrates with protein was associated with higher SAT [β (95 % CI) per 5 En%: 3100 cm³ (25, 6200)]. Beyond that, the substitution of carbohydrates with fat or protein was not associated with VAT or HL content in individuals with T1D. In individuals with T2D, replacing carbohydrates with total fat or protein did not result in any association with SAT or VAT, respectively. However, substituting carbohydrates with MUFA was linked to higher VAT volume [per 5 En%: 1200 cm³ (230, 2200)], while the substitution with PUFA was associated with lower VAT volume in T2D [per 5 En%: -970 cm³ (-1900, -40)]. For HL content, similar findings were observed in T2D when carbohydrates were replaced with PUFA [per 5 En%: -3.3 % (-6.9, 0.4)]. Conversely, replacing carbohydrates with SFA was associated with higher HL content [per 5 En%: 2.4 % (-0.6, 5.4)]. More detailed analyses revealed that replacing higher GI carbohydrates with even-chain SFA was associated with higher HL content [per 1 En%: 1.4 % (-0.1, 3.4)], whereas a replacement with very-long-chain SFA or odd-chain SFA was linked to lower HL content [both per 0.1 En%: -3.6 % (-7.4, 0.3) and -2.7 % (-5.4, 0.0)]. Similarly, replacing carbohydrates with protein was associated with lower HL in T2D [per 5 En%: -2.4 % (-4.9, 0.0)], particularly due to plant-based protein [per 1 En%: -2.8 % (-4.8, -0.8)].

These findings indicate that not solely a restriction in carbohydrates, but also the quality of nutrients replaced for those carbohydrates may be essential for the accumulation of adipose tissue and HL content, particularly in individuals with T2D. Therefore, the integration of PUFAs, very-long-chain and odd-chain SFAs, as well as particularly plant-based proteins, seems to be beneficial in regard to VAT and HL content.

Chapter 5

Discussion

Key findings of this doctoral thesis

The projects included in this dissertation were designed to address three research aims, with the objective of providing further insights into the relationship between dietary intake of carbohydrates and sugar and diabetes prevention and management (see Chapter 1).

The key findings of this dissertation are as follows:

1) Per capita sugar consumption was found to be globally associated with a higher prevalence of diabetes on an ecological level. This association can be explained to a large extent (approximately 66 %) by the indirect pathway via the BMI. Nevertheless, up to one-third of the association of the relationship between dietary sugar intake and diabetes can be attributed to other, potentially direct, mechanisms (98).
2) On an individual level, dietary sucrose intake assessed with questionnaires showed inverse, thus protective, associations, supporting the hypothesis that dietary sugar intake is underreported in self-reports. However, higher urinary sucrose levels were associated with a higher risk of T2D incidence. In mediation analysis, we found that approximately one-fifth of the association between urinary sucrose and diabetes incidence can be explained through overweight (BMI: 16 %, WC: 22 %). These findings align with our initial results and suggest that other mechanisms may influence the sugar-diabetes relationship (99).
3) The substitution analyses revealed that replacing carbohydrates with PUFA (both n-3 and n-6) was associated with lower VAT volumes and HL content, especially in individuals with T2D. Additionally in T2D, the substitution of higher GI carbohydrates with odd-chain and very-long-chain SFA, as well as plant-based protein, demonstrated an association with lower HL content. Consequently, it appears that not merely the restriction of carbohydrate intake is crucial for diabetes management, but rather the quality of the nutrients that are substituted for carbohydrates. The findings suggest that this is particularly essential in individuals with T2D (Lang et al. 2024, submitted).

Association between dietary sugar intake and risk of type 2 diabetes

As previously stated, the existing literature on the relationship between dietary sugar intake and the incidence of T2D is inconsistent. While the evidence from previous epidemiological studies is inconclusive in terms of the association between dietary sugar intake as mono- and disaccharides and the incidence of T2D (67), the impact of SSBs on T2D onset appears to be convincing. In this context, there is evidence that a higher intake of SSBs is linked to a 26 % higher risk of T2D per serving (66), which was rated with a high certainty of evidence (40). In contrast, a higher intake of total sugars, sucrose, fructose, glucose, maltose and lactose was

not or even inversely associated with the incidence of T2D (67, 68). However, these findings were rated with a low or very low certainty of evidence (40), and thus, it is very likely that future studies will change the effect estimates.

Nevertheless, there are potential explanations for the discrepancy in findings on SSBs and other sources of dietary sugar intake in the context of T2D development. Due to their liquid form, the consumption of SSBs results in a lower level of satiety than solid sugar-containing foods (100). In addition, the results of a feeding trial demonstrated that the intake of sugars consumed in a liquid state does not result in as much compensation in energy during subsequent meals as the intake of sugars consumed in a solid state, which may ultimately lead to an increase in energy intake and body weight (101). Moreover, the digestive process of liquids is more rapid than that of solid foods, as they do not require the mechanical digestion that occurs with solid foods. This results in a faster gastric emptying (102). Consequently, a higher intake of SSBs is associated with rapidly increased spikes of postprandial blood glucose and insulin levels (103). Beyond that, the consumption of SSBs has been demonstrated to have an addictive effect due to the activation of the dopaminergic reward systems (104). Additionally, evidence suggests that the addition of caffeine, which is a component of several common SSBs (e.g., soft drinks, energy drinks, sweetened coffee), can reinforce the consumption of SSBs in a manner that resembles addiction (105). Furthermore, a higher consumption of SSBs is typically associated with an overall less healthy lifestyle, including poor dietary choices and a sedentary lifestyle, particularly in adolescents (106, 107). Eventually, SSBs are often consumed in large quantities and thus contribute to a high dietary GL (108). Given that the majority of common SSBs are consumed in standardised portion sizes, SSB consumption may be less susceptible to reporting bias than other sugar sources that are typically assessed using dietary assessment methods based on self-reports.

In this context, previous studies have evaluated that particularly overweight participants tend to underreport their self-reported dietary sugar intake, especially for unhealthy foods (71, 72). Consequently, it is likely that that the aforementioned associations between dietary sugar intake and the incidence of T2D are significantly influenced by misreporting. In order to prevent reporting bias, it would be advisable to employ objectively measured dietary sugar intake when investigating this relationship. One potential approach would be to use aggregated data based on estimations and extrapolations. Upon consideration of aggregated supply data, the findings of our first project indicated that a daily increase of 100 kcal per capita sugar consumption was globally associated with a 1.6 % higher diabetes prevalence (98). These findings were similar to previous ecological studies that have investigated the association between per capita sugar consumption and diabetes prevalence (109, 110). However, it should be noted that the data quality of the aggregated data may vary between countries due to differences in surveillance

infrastructure, and thus, may not accurately reflect the actual dietary sugar intake on an individual level (111, 112).

In order to examine objectively measured dietary sugar intake on an individual level, biomarkers for sugar intake can be employed. Previous studies have demonstrated that using 24uSF is an appropriate approach to objectively measure dietary sugar intake, since there was a high correlation between the biomarker and the true dietary sugar intake in feeding trials (74-78). Consequently, the biomarker was validated considering specific biases (80). In a calibration study, self-reported dietary sugar intake was linked to a decreased risk of T2D; however, after applying an equation derived from the aforementioned validation study (80), the findings attenuated and this association no longer existed (113). The findings of our second project demonstrated comparable results. While dietary sucrose intake assessed with self-reports was associated with a lower risk of T2D, higher urinary sucrose levels pointed to a 14 % increased incidence of T2D per 100 µM (99). These findings are consistent with previous research investigating the relationship between dietary and urinary sugar and obesity, which has demonstrated a positive association between urinary biomarkers and obesity, whereas no association was observed for self-reported dietary sugar intake (81, 82). However, these findings are based on urinary sucrose biomarkers from spot urine samples, which have not yet been validated, and thus, may not be as reliable as 24uSF. Nevertheless, the findings on the association between urinary biomarker and obesity has been confirmed with similar findings in a study using the 24uSF (114).

Beyond that, there are further approaches besides urinary biomarkers to objectively measure dietary sugar intake. Previous studies have, for instance, also considered stable isotope ratios of carbon-13 and carbon-12 (δ13C) as well as nitrogen-15 and nitrogen-14 (δ15N) as potential dietary biomarkers measured in hair, capillary finger stick blood or blood serum (115). Findings from the multicentre PREMIER trial demonstrated that a reduction in self-reported SSB intake was associated with lower δ13C over 18 months, suggesting that δ13C may be a predictor for SSB intake (116). Moreover, there were found correlations between δ13C levels and intake of SSBs and added sugar in cross-sectional studies with adult populations (117-120). Particularly in children δ13C appears to be a promising objective biomarker for dietary sugar intake (121, 122). However, findings on δ15N were inconclusive, showing a high correlation between δ15N and dietary sugar intake in a native study population in Alaska (119), but no such association in another study population (118). In terms of T2D, a study conducted in the EPIC-Norfolk demonstrated that higher δ15N levels were associated with a 23 % increased risk of T2D, while δ13C showed an inverse association with T2D incidence (123). However, the reliability of these biomarkers as a predictor of dietary sugar intake is uncertain, as the authors observed a stronger correlation between the biomarkers and dietary fish and fish protein intakes than between the biomarkers and dietary sugars or SSBs (123). Therefore, further controlled

feeding studies are required to ascertain the validity of δ13C and δ15N as reliable biomarkers for dietary sugar intake.

Influence of the BMI on the association between sugar intake and type 2 diabetes

The question of whether dietary sugar intake represents a significant factor in the aetiology of T2D remains a topic of discussion in current research. While a substantial body of research has focused on dietary fat intake and total energy balance as the primary risk factors for obesity and T2D, some researchers have proposed alternative perspectives. In this context, statements have been published indicating that dietary sugar consumption has a greater impact on human health than merely providing empty calories (65), and that it has the potential to be toxic for human health, comparable with the impact of alcohol (124). In order to ascertain whether dietary sugars are more than just an excess of calories, it is necessary to investigate the influence of overweight and obesity on the pathway between dietary sugar intake and T2D onset.

In this context, previous studies investigated this association and added statistical models, in which they further adjusted for BMI. In the absence of BMI adjustment, previous studies have identified inverse or null associations between total sugar intake and the incidence of T2D (89-91, 125, 126). However, with the additional adjustment for BMI, inverse associations were no longer observed, and findings were attenuated (89-91), suggesting that particularly overweight and obese participants tended to underreport their dietary sugar intake. Moreover, a possible explanation would be that BMI may influence the association between dietary sugar intake and diabetes onset. However, this adjustment does not allow for the quantification of the influence of the BMI on this association. One approach to detect the influence of overweight and obesity on this association is the implementation of causal mediation analysis, which was previously described in detail in Chapter 1. Briefly, the total effect between dietary sugar intake and T2D onset is decomposed into the TIE via the causal pathway of overweight and obesity and the PDE, which represents the direct association independent of the influence of this pathway (94). As a result, the parameters provide information about the magnitude the association is driven by the mediator and the extent to which dietary sugar intake may directly influence the development of T2D.

In this context, the results of our ecological mediation analysis demonstrated that the proportion of the total effect of BMI on the association between per capita sugar consumption and diabetes prevalence that could be attributed to the indirect pathway was 66 % on a global level (Figure 3A) (98). According to these findings, this association is influenced by the BMI via the indirect pathway to a large extent. In this context, there is evidence that a higher dietary

sugar intake is leading to weight gain (85, 86), which is a risk factor for the development of T2D (87, 88). Nevertheless, up to 34 % of the association between per capita sugar consumption and diabetes prevalence can be attributed to other mechanisms. Beyond that, we found that the PM of the BMI and WC on the association between urinary sucrose and diabetes was found to be only 16 % and 22 % on an individual level (Figure 3B) (99). To the best of our knowledge, there is only one further study that recently has examined the mediation effect of BMI on the relationship between dietary sugar intake and diabetes in a Chinese population. In this study, the PM of BMI was 12 % (127), which is comparable with the findings of our prospective study. Although the authors reported that these findings were statistically significant, the reported effect sizes were very small (PDE: β = 0.0004 (95 % CI: 0.0001, 0.0006)). Nevertheless, these findings indicate that potentially direct sugar-related mechanisms are likely to play an essential role in the development of T2D. Therefore, it is important to elucidate which mechanisms may contribute to the relationship between dietary sugar and T2D.

In the first two projects included in this dissertation, the methodological approach of mediation analysis was applied. When conducting mediation analysis, some potential challenges must be taken into account. The required criteria for conducting a mediation analysis are presented in detail in Chapter 1. In summary, the exposure (e.g., dietary sugar intake) must be associated with both the mediator (e.g., BMI) and the outcome (e.g., incidence of T2D), and the mediator must be associated with the outcome. In order to simulate the causal pathways between exposure, mediator and outcome, data from three different time points should be incorporated (92). However, this aspect may be challenging depending on the data availability. Interestingly, the results of our mediation analyses demonstrated similar results, when using a time sequence of five years or the most recent available ecological data (project 1) or mediator assessed at baseline or a health check after three years (project 2).

One major challenge in the context of mediation analysis is confounding. In conventional effect estimations, it is necessary to adjust for confounding by all characteristics that exert an influence on both the exposure and the outcome (dietary sugar intake → incidence of T2D). However, as the mediator is included as a third variable in addition to exposure and outcome, confounding can also occur in the relations between exposure and mediator (dietary sugar intake → BMI) and mediator and outcome (BMI → incidence of T2D) (93, 128). Therefore, it is particularly essential to adjust for potential confounding variables to avoid that the calculated mediated effect is biased by any confounders on the causal pathway. Nevertheless, unmeasured confounders are a potential risk of bias that should be considered in the implementation of mediation analyses and in the interpretation of their results (92, 128).

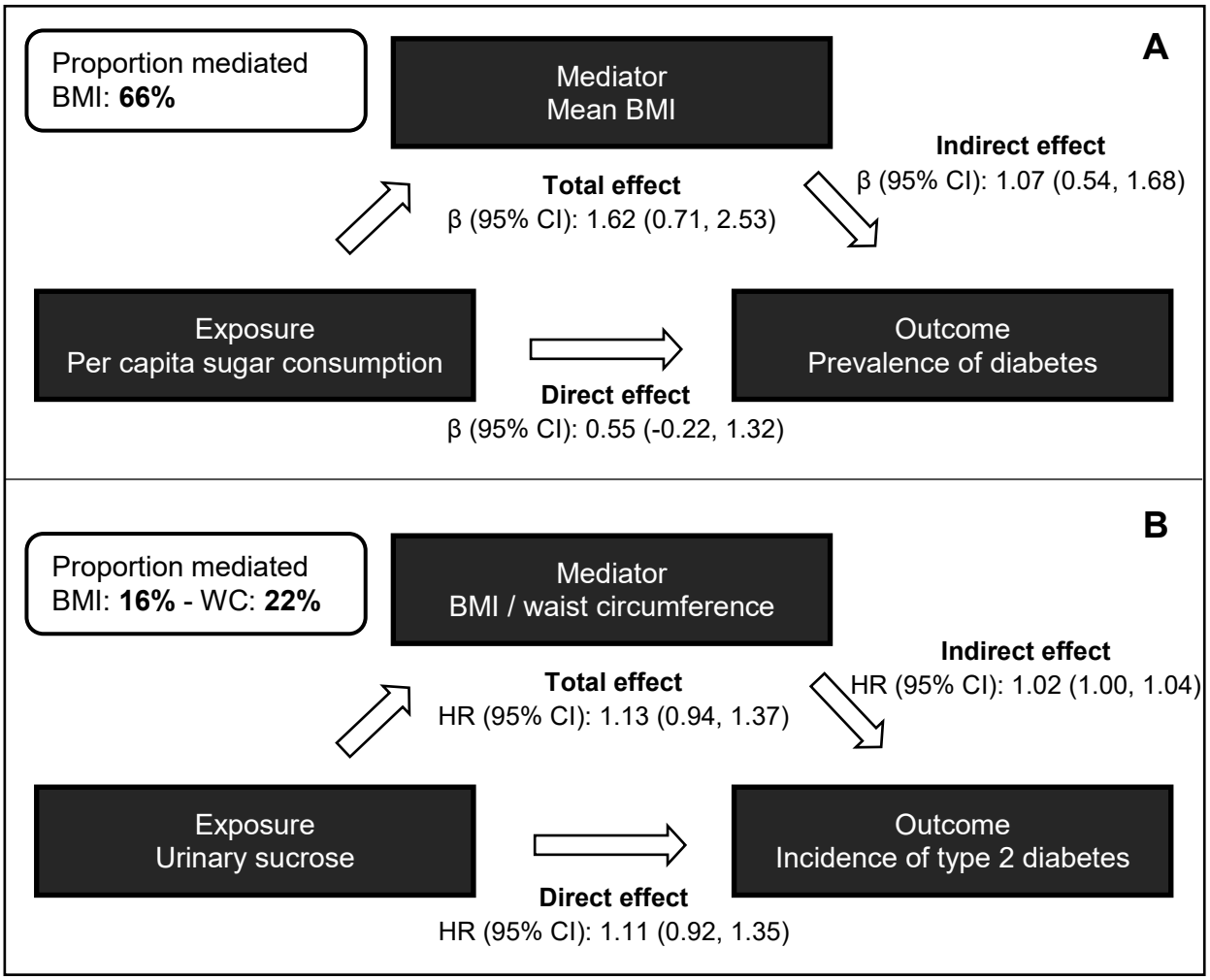

Figure 3: Summary of the findings of the mediation analyses (project 1 and 2) investigating the influence of BMI on the association between per capita sugar consumption and diabetes prevalence (A) and the influence of BMI and WC on the association between urinary sucrose and incidence of type 2 diabetes (B).
95 % CI, 95 % confidence interval, β, beta coefficient; BMI, body mass index; HR, hazard ratio; WC, waist circumference;
The figure illustrates the associations between objectively assessed dietary sugar intake and diabetes prevalence or incidence (98, 99), which are decomposed into an indirect effect via the causal pathway of BMI/WC and a direct effect of sugar on diabetes prevalence or incidence. The proportion mediated is calculated as the quotient of the indirect effect and the total effect, indicating the extent to which the association is mediated by the indirect effect. Higher values (β>0, HR>1) indicate a higher diabetes prevalence or incidence.

Furthermore, it is important to mention that the use of mediation analyses is not only restricted to the research questions that were investigated in the presented studies. Mediation analysis can be applied to any associations, in which a third variable is influencing the examined relation in order to decompose the total effect into an indirect and direct effect. For example, it would be interesting to perform mediation analyses also in persons with diabetes to evaluate the relationship between the dietary intake and outcomes of diabetes progression (e.g., liver fat or CVD incidence) that may be mediated by a third variable (e.g., weight change, insulin resistance or inflammatory biomarkers). Consequently, the application of mediation analysis should be considered in forthcoming research.

Potential direct sugar-related mechanisms

In addition to the aforementioned indirect causal pathway via overweight and obesity resulting from solely an excess of energy intake, several other mechanisms may explain the association between dietary sugar intake and the onset of diabetes (Figure 4).

First of all, a higher intake of dietary sugar has the potential to exert a direct impact on glucose metabolism, as studies have shown that foods containing added sugar, or particularly SSBs, induce rapid spikes in blood glucose levels and consequently lead to increased insulin secretion (108, 129). A sustained intake of foods containing added sugars can result in a reduction in insulin sensitivity (130), which may ultimately lead to the development of T2D (131). Furthermore, foods containing added sugars typically have a medium to high GI value (50, 132), and due to their large quantities, which they are often ingested in, they can contribute to a high GL (108). In this context, a recent systematic review and meta-analysis of large prospective cohort studies has demonstrated that foods with a high GI and GL are associated with a 27 % and 15 % increased risk of T2D, respectively (53). Moreover, these results indicated that higher GI foods are risk factors for CVD, mortality and cancer.

In addition, dietary sugar intake has an impact on the liver due to the metabolism of fructose (108). Sucrose, the commercially available form of sugar typically referred to as "table sugar", consists the two components sucrose and fructose. Particularly the latter can play an essential role in the development of liver fat. In general, fructose is metabolised by the liver into glucose, lactate and fatty acids for use as metabolic substrates, when consumed at moderate quantities (133). However, excessive fructose intake causes an increased hepatic de novo lipogenesis, which can subsequently lead to dyslipidaemia and insulin resistance (134, 135). As a result of this, triglyceride and cholesterol levels may increase, which can result in an elevated accumulation of VAT and ectopic lipids, and ultimately, the development of MASLD (108, 135). In this context, it has been shown that there is a bidirectional association between MASLD and T2D (21, 131). On the one hand, higher accumulations of liver fat can contribute to the development of T2D by inducing insulin resistance, metabolic dysfunction, and releasing pro-inflammatory cytokines and hepatokines (20, 136). On the other hand, diabetes can also lead to an enlargement of liver fat content due to hyperglycaemia and dyslipidaemia (21, 136). The reality is likely to be a complex interplay of both mechanisms, occurring simultaneously (136).

Furthermore, an excess of fructose intake has been demonstrated to promote hepatic uric acid production, which has been linked to the development of gout (137). Previous research has identified that both gout and hyperuricemia are risk factors for T2D, CVD, and hypertension (138, 139).

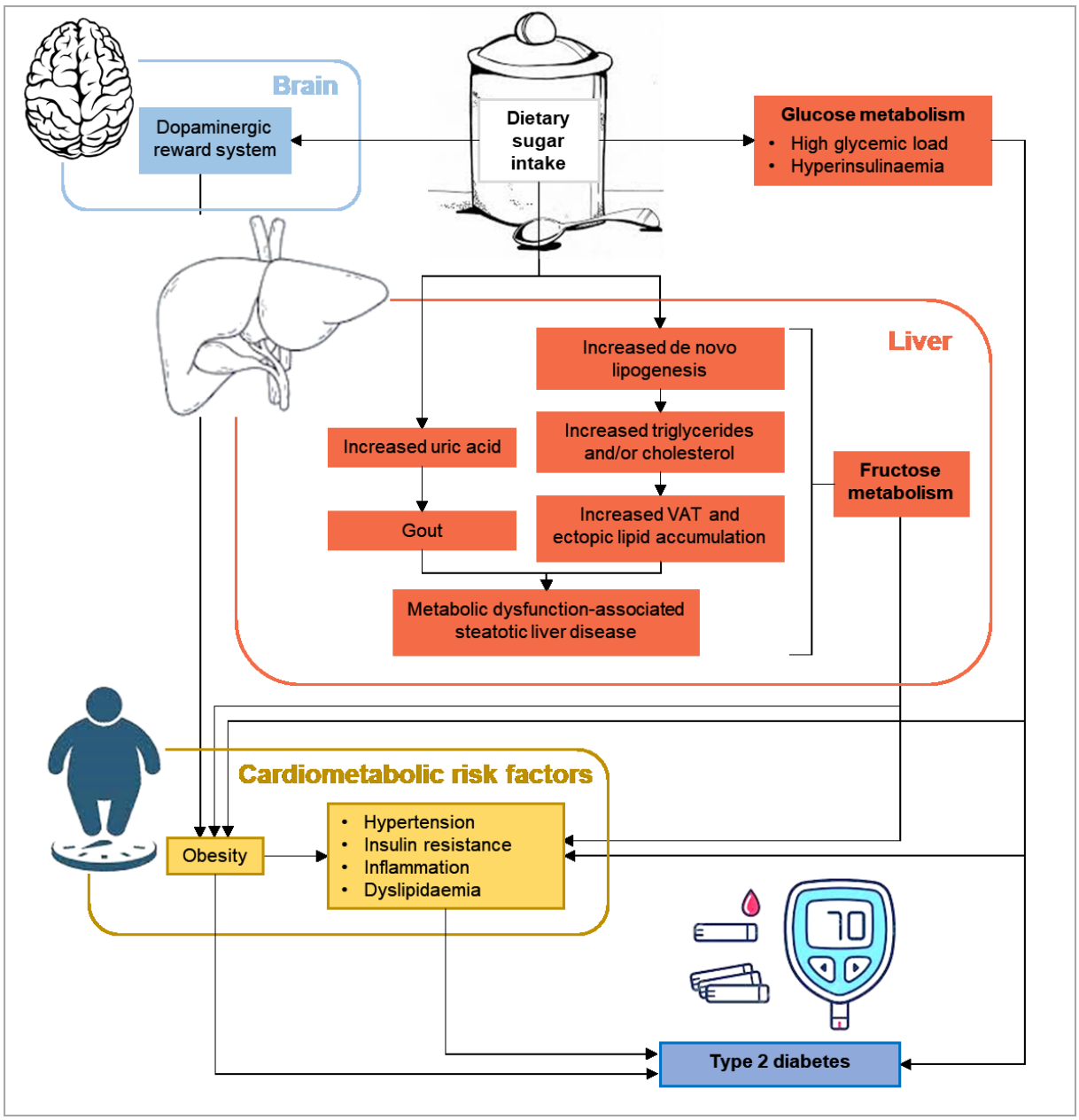

Figure 4: Pathophysiological mechanisms for dietary sugar intake and the development of type 2 diabetes. Reused with permission and modified after Malik 2022 (108)

Ultimately, the consumption of sugar-containing products has the potential to induce addictive effects due to the intense release of opioids and the activation of the dopaminergic reward system in the brain (104). This can trigger addictive-like behaviours, including cravings, bingeing and withdrawal, which may ultimately lead to excessive consumption of sugar (104, 140). As a consequence, an overconsumption of sugar containing products may occur, which may eventually result in overweight and obesity (108).

Carbohydrate substitution in diabetes management

The aforementioned findings demonstrated that objectively measured dietary sugar intake can play a crucial role in the prevention of T2D onset. Beyond that, dietary modifications have also

the potential to prevent the progression of diabetes, and thus, represent a cornerstone in the management of both T1D and T2D. In general, it is recommended that overweight and obese individuals with T2D reduce their daily total energy intake by 500-600 kcal (32), which is thought to result in weight loss (42). In addition to energy restriction, the nutrient composition of the diet may also be an important factor in managing diabetes. Recent guidelines have emphasized the potential benefits of a diet rich in MUFAs and PUFAs, particularly n-3 PUFAs, for individuals with diabetes (33, 42). Moreover, it is recommended that the consumption of simple and refined carbohydrates (e.g., sugar-containing products) should be minimized, with a greater emphasis placed on the intake of high-fibre and low GI foods (32, 33, 42). In this context, findings from previous RCTs demonstrated that a restriction of carbohydrates may be an effective approach to prevent diabetes progression, as it was associated with the reduction of body weight, HbA1c levels, and a more beneficial blood lipid profile (45). However, when carbohydrate intake is reduced without simultaneously restricting total energy intake, there is an increase of the compensatory intake of fat and protein. This may have consequences for the body fat distribution, which was investigated in the third project (Lang 2024, submitted).

In examining the role of dietary carbohydrates, it is crucial to consider not only the quantity but also the quality of the consumed carbohydrates. This can be achieved by differentiating between higher and low GI carbohydrates, as described in detail in chapter 1. In summary, foods with a higher GI induce the postprandial glycaemic response and, as a result, represent a potential risk factor for the development of comorbidities (49). Surprisingly, we observed no association when replacing higher GI carbohydrates with low GI carbohydrates in regard to SAT and VAT volumes in our study, for both individuals with T1D and T2D. However, the intake of higher GI carbohydrates was relatively high in this cohort, and it is possible that reporting bias may have occurred, particularly for unhealthy foods (e.g., sweets), which are typically often underreported (71, 72).

A reduction in carbohydrate intake may result in an increase in fat or protein intake, which could subsequently affect metabolic health. To date, only one previous cross-sectional study has investigated the substitution of carbohydrates with fat in relation to body fat composition in the general population. In this study, the replacement of carbohydrates with total fat was associated with higher VAT volumes and hepatic fat content (141). In contrast to these findings, no association was identified in our study between the replacement of carbohydrates with total fat and any of the outcomes, in both individuals with T1D or T2D. However, our findings indicated that the substitution of (higher GI) carbohydrates with MUFA (both animal- and plant-based) was linked to higher VAT volumes, while the substitution with (even-chain) SFA was associated with higher HL content in individuals with T2D. In contrast, we observed lower VAT volumes and HL content when replacing (higher GI) carbohydrates with PUFAs (both n-3 and n-6), odd-chain and very-long-chain SFAs and (plant-based) protein, particularly in individuals

with T2D (Table 2). A comprehensive comparison with existing evidence on macronutrient intake was previously described in detail in Chapter 4.

Table 2: Summary of the substitution analysis (project 3) investigating the replacement of carbohydrates with fat and protein and higher glycemic index carbohydrates with subtypes of fat and protein in association with SAT, VAT and HL content individuals with T1D and T2D

Isocaloric replacement of	with	Type 1 diabetes			Type 2 diabetes		
		SAT	VAT	HL	SAT	VAT	HL
Carbohydrates	total fat	→	→	→	→	→	→
	MUFA	→	→	→	→	↑	→
	PUFA	→	→	→	↘	↓	↓
	SFA	↗	→	→	→	↘	↗
	protein	↑	→	→	↗	→	↓
Higher GI carbohydrates	low GI carbohydrates	→	→	→	→	→	→
	animal-based MUFA	↗	→	→	→	↑	→
	plant-based MUFA	↘	→	→	→	↗	→
	n-6 PUFA	→	→	→	→	↘	↘
	n-3 PUFA	→	↘	→	↘	↘	↘
	even-chain SFA	↗	→	→	↗	→	↑
	very-long-chain SFA	↓	↘	→	→	↘	↓
	odd-chain SFA	→	↘	→	→	↘	↓
	animal-based protein	↗	→	→	↑	→	↘
	plant-based protein	↘	↘	→	↑	→	↓

GI, glycaemic index; HL, hepatic lipid; MUFA, monounsaturated fatty acid ;n-3, omega-3; n-6, omega-6; PUFA, polyunsaturated fatty acid; SAT, subcutaneous adipose tissue; SFA, saturated fatty acid; T1D, type 1 diabetes; T2D, type 2 diabetes; VAT, visceral adipose tissue;

These findings indicate that not solely the reduction of carbohydrates, but also the quality of the substitutes may play an important role for body fat distribution in individuals with diabetes. In this context, differences in macronutrient quality are also dependent on the food sources from which they are derived. The sources of the identified beneficial nutrients are as follows: PUFAs are primarily found in vegetable oils, fish, nuts and seeds (142, 143), very-long-chain SFAs in nuts, peanut butter and canola oil (144, 145), odd-chain SFAs in milk and dairy products (146), and common sources of plant-based proteins are grains, legumes, nuts and seeds, and soy products (147). In this context, it would also be feasible to implement food substitution models based on the quantity of food intake, which can be measured in terms of weight, volume, or servings (e.g., replacing 50 g of sweets with 50 g of nuts). However, like any method, food substitution models (both based on energy and quantity) also have their challenges and limitations that should be taken into account when applied.

Food substitution models based on food groups have the advantage of modelling the data as it is reported, thereby reflecting the quantities in which the food is generally consumed. In an isocaloric context (e.g., replacing 5 En% carbohydrates with 5 En% total fat), a substitution may result in discrepancies in the quantity of the substituted nutrient components, whereas

substitutions based on the quantities of foods with different energy contents (e.g., replacing 150 g of processed red meat with 150 g of poultry) are accompanied by a residual difference in energy intake. In this case, the substitution of processed red meat would result in a difference in energy intake of 170 kcal (96). Such discrepancies can impact the findings and thus need to be considered when determining the appropriate method for addressing the respective research question. In addition, potential reporting bias may be present due to measurement errors in the assessment of dietary intake, which can also influence the results (96, 97).

Furthermore, the choice of confounders in food substitution models can also be challenging. Potential socioeconomic and health-related confounding variables should be selected a priori based on the literature or using directed acyclic graphs (96). Additionally, food substitution models need to be adjusted for total energy intake and isocaloric substitutions need to be further controlled for all the other food components besides the two substitutes (96, 97). In substitutions based on food groups, it may be advisable to select additional dietary confounders that are associated with the consumption of the examined substitutes, as they are frequently consumed with the substituted foods. In this example, an additional adjustment for potatoes (often consumed with red meat) and rice (often consumed with poultry) may provide a more accurate representation of the dietary changes (96). However, at this point it should be noted that certain food selections are associated with specific health behaviours. For example, the consumption of poultry is generally associated with a healthier lifestyle than the consumption of red meat (97). Consequently, the substitution effect may not be fully explained by the replacement of red meat with poultry, but may also reflect an overall healthy lifestyle. It is therefore recommended to show both effect estimates with and without additional adjustment for other food groups (96).

Moreover, it is important to note that these food substitution models are based on observational data and therefore do not involve actual food replacements in the study participants (96, 97). It is therefore important to distinguish the results of epidemiological food substitution models from the findings of RCTs. Epidemiological food substitution models are a theoretical approach to mimic the replacement in feeding studies using observational data, while in actual feeding trials one food component is in fact replaced by another component as part of an intervention (148, 149). Nevertheless, investigating long-term clinically relevant outcomes (e.g., T2D incidence or mortality) is very difficult to accomplish in RCTs, as they are costly, time-intensive and do not investigate these associations in real-world conditions (150, 151). Consequently, substitution analyses using observational data have increasingly become a well-established approach in nutrition epidemiology (96, 97), with a growing number of studies published in recent years (152-154).

Nevertheless, the number of substitution analyses carried out in individuals with diabetes is still limited. Therefore, future research could undertake comprehensive substitution analyses using prospective data from large cohort studies comprising participants with diabetes. In this context, two prospective studies using data from 15 EPIC centres investigated the isocaloric substitution of carbohydrates with fat (total fat, MUFA, PUFA and SFA) or protein (total protein, animal-based, plant-based) with regard to all-cause and CVD mortality risk and 5-year weight change in individuals with T2D (155, 156). However, it would also be of interest to examine these associations in other large cohorts outside of Europe and additionally with a more detailed consideration of macronutrient quality. Beyond that, future studies should investigate the replacement of carbohydrates with fat and protein (and their subtypes) in relation to HbA1c or diabetes-related complications and comorbidities, such as the incidence of CVD, nephropathy, depression, cognitive disorders, and cancer.

Beyond that, it is also possible to combine both approaches of mediation and substitution analysis. As with all observational analyses, food substitution models may not only include potential confounders, but also variables that are potentially mediating the investigated association, since they are on the causal pathway between exposure (food substitution) and outcome (96). For example, the substitution of animal-based foods with plant-based foods may result in weight loss or a reduction of inflammation, which is associated with a lower risk of CVD in individuals with diabetes. In this case, it would be of interest to ascertain the extent to which the association between the replacement of animal-based foods with plant-based foods may be explained through the change in weight or inflammation (indirect effect), or if the substitution itself led to a risk reduction (direct effect). To address this question, it would be advisable to include data from three different time points (dietary data – mediator – outcome). However, no mediation analysis of food substitution models has yet been conducted. Therefore, future research should consider performing such analyses to gain further insight into diet-disease relations.

Strengths and limitations

A comprehensive discussion of the specific strengths and limitations of each project has already been carried out in the chapters 2-4. Within this section, the general strengths and limitations of this dissertation will be addressed.

There are several strengths of the studies that were included in this dissertation. Within all three projects, innovative methodological approaches in nutritional epidemiology, such as mediation and substitution analysis, have been applied to investigate the relation between dietary carbohydrates or sugar intake and diabetes. This was the first time that causal mediation analyses were conducted to investigate the indirect impact of obesity on the

association between per capita sugar consumption and diabetes using aggregated ecological data and on an individual level using data from a prospective cohort study. Moreover, an objective biomarker for sugar intake was employed in the latter study. Furthermore, this was to our knowledge the first investigation, in which the substitution of carbohydrates with other macronutrients in regard to body fat distribution and liver fat was examined in individuals with recently diagnosed T1D and T2D. Here, the outcomes were comprehensively measured using MRI or ^{1}H-MRS, and the quality of macronutrient intake was also taken into account.

However, it should be noted that these studies have certain limitations. First, since findings of the studies are based on ecological and aggregated data (project 1) or observational data (projects 2 and 3), it is not possible to draw any conclusions about causality. Therefore, it is possible that bias due to confounding may have occurred and influenced the direction and magnitude of the observed associations. However, in all of these three studies, analyses were adjusted for a comprehensive set of potential a priori defined confounders that were obtained from reliable global organisations (project 1) or established cohort studies using validated assessment methods (projects 2 and 3). The adjustment for socioeconomic and health-related covariates was intended to minimise the risk of confounding. Nevertheless, it is possible that residual confounding due to unmeasured or imperfectly measured covariates may still affect the results. Consequently, further prospective studies are required to confirm the results of our studies. Second, since the studies investigated data on dietary intake, reporting bias cannot be ruled out. In our first project per capita sugar consumption was based on food supply data from the FAO, which are mainly based on estimations of national statistical offices. Consequently, they may not reflect the actual intake of an individual (111). However, these data were adjusted for exports and any kind of non-human consumption. In the observational studies (project 2 and 3), dietary intake was assessed with questionnaires based on self-reports (FFQ or 7DD), which can lead to measurement errors, particularly in overweight and obese individuals (71, 72). Nevertheless, these questionnaires are validated and in project 2, sucrose intake was also objectively assessed with urinary sucrose, which is less likely prone to reporting bias. Finally, it is possible that selection bias may be present in the observational studies. Both the EPIC-Norfolk and the GDS include participants who adhere to a healthy lifestyle to a large extent (157, 158). Moreover, the EPIC-Norfolk study population is comprised of individuals of advanced age. Additionally, due to the comprehensive GDS study protocol, certain population groups (e.g., individuals with poor glycaemic control or psychiatric disorders) were excluded from study participation (159). In conclusion, it must be acknowledged that the findings may not be fully transferable to the general population (project 2) and to all individuals with diabetes (project 3), respectively.

Implications for public health and future research

The findings of this dissertation indicated that dietary intake of carbohydrates and sugars may play an essential role in the prevention and management of diabetes.

Previous research has shown that dietary sugar intake was not or even inversely associated with the risk of T2D (67). However, the findings of the studies included in this dissertation demonstrated that an objectively measured sugar intake, assessed via aggregated data or urinary sucrose biomarker, was positively associated with the onset of diabetes (98, 99). These findings support the hypothesis that dietary sugar intake assessed by self-reports is prone to reporting bias, particularly in the underreporting of sugar-containing foods (71, 72). It is therefore recommended that future studies account for objectively measured sugar biomarkers in order to expand the existing body of research on the association between unbiased dietary sugar intake and the incidence of T2D. In this context, the reliability of urinary sucrose from spot urine samples has not yet been validated, and thus, feeding studies are required to prove the validity of urinary biomarkers from spot urine samples in comparison to 24uSF. Nevertheless, our findings suggest that a reduction in dietary sugar intake may be beneficial in preventing the development of T2D. To date, several societies and associations, such as the WHO, have recommended a reduction of free sugars to <10 En % for both adults and children due to its adverse effects on weight gain and dental caries (63, 64). Future studies relying on objectively measured sugar intake should investigate whether a reduction of free and added sugars also prevents the onset of T2D. In addition, further research is needed to investigate direct mechanisms of dietary sugar intake in relation to the development of T2D.

Furthermore, macronutrient intake and its quality have been identified as important factors in the management of diabetes (Lang 2024, *submitted*). In this context, previous findings have indicated that a reduction in carbohydrate intake may be a promising approach for individuals with diabetes to prevent disease progression (45). On the one hand, this may result in a reduction in total energy intake, which is recommended for obese individuals with T2D (32). On the other hand, this may lead to a compensatory higher intake of fat or protein, which can be investigated through substitution analysis. In this context, the findings of our study indicated that the implementation of PUFAs, odd-chain and very-long-chain SFAs, as well as plant-based proteins into the diet of individuals with diabetes appears to be beneficial for the body fat distribution, particularly for individuals with T2D. However, evidence on the substitution of carbohydrates with other macronutrients in regard to markers of diabetes management and progression (e.g., HbA1c, blood glucose, CVD, nephropathy) is still limited in both individuals with T1D and T2D. Consequently, further evidence from both RCTs and observational studies in individuals with diabetes is required in order to gain further insight into this relationship. In order to ultimately draw conclusions for public health recommendations, systematic reviews

and meta-analyses of substitution analysis in individuals with diabetes are needed. Furthermore, future research should consider combining substitution and mediation analysis, to evaluate to what extent the relationship between replacing carbohydrates and health outcomes can be explained by substitution effect (direct effect) or by the influence of a third, mediating variable (indirect effect).

Conclusions

In conclusion, this dissertation provides insights into the relationship between dietary sugar intake and T2D onset, both on a global and on an individual level. The findings of this dissertation indicated that objectively measured sugar intake was associated with higher prevalence and incidence of diabetes. Moreover, it has been demonstrated that overweight and obesity partially influence the association between dietary sugar intake and diabetes, but other potentially direct sugar-related mechanisms may also play an essential role in the development of T2D.

Furthermore, this dissertation emphasises the importance of macronutrient quality in diabetes management. It is not solely a restriction in carbohydrate intake, but also a change towards a higher consumption of PUFAs, odd-chain and very-long-chain SFAs, as well as plant-based protein instead of high GI carbohydrates that appears to be beneficial for body and liver fat accumulation, particularly in individuals with T2D.

In conclusion, this dissertation highlights the importance of dietary carbohydrate and sugar intake in the context of diabetes prevention and management. However, conclusions regarding causality are limited due to the observational study designs, and thus, further prospective studies are required to confirm these findings. Ultimately, in order to publish public health recommendations in evidence-based guidelines, meta-analyses based on these prospective studies need to be conducted.

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Appendix

Online supplemental material – Project 1

Association between per capita sugar consumption and diabetes prevalence mediated by the body mass index: results of a global mediation analysis

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Online supplemental material – Project 2

The mediating role of BMI on the prospective association between dietary and urinary sucrose with diabetes incidence in a sub-cohort of the EPIC-Norfolk

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Online supplemental material – Project 3

Cross-sectional association between the isocaloric replacement of carbohydrates with protein and fat in relation to fat compartments distribution and hepatic lipid content in recent-onset type 1 and type 2 diabetes

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