Deutsches Diabetes-Zentrum
Leibniz-Zentrum für Diabetes-Forschung
an der Heinrich-Heine-Universität Düsseldorf
Institut für Biometrie und Epidemiologie

The role of dietary biomarkers, nutritional interventions, and eating patterns in diabetes prevention and management

Dissertation

zur Erlangung des Grades eines „Doctor of Philosophy“ (PhD) in Medical Sciences der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von
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2025

Als Inauguraldissertation gedruckt mit Genehmigung der
Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

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For Thea

Teile dieser Arbeit wurden veröffentlicht:

Schaefer E, Neuenschwander M., Schiemann T., Iser N., Baechle C., Shokri-Mashhadi N., Schwingshackl L., Schulze M. B., Schlesinger S., (2025), Fatty acids biomarkers and incidence of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective observational studies. Advances in Nutrition, 2025, 17 (1), doi: 10.1016/j.advnut.2025.100565

Szczerba E., Barbaresko J., Schiemann T., Stahl-Pehe A., Schwingshackl L., Schlesinger S., (2023), Diet in the management of type 2 diabetes: umbrella review of systematic reviews with meta-analyses of randomized controlled trials. BMJ Med. 2 (1), doi: 10.1136/bmjmed-2023-000664

Barbaresko J., Lang A., **Szczerba E.,** Baechle C., Beckhaus J., Schwingshackl L., Neuenschwander M., Schlesinger S., (2023), Dietary Factors and All-Cause Mortality in Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Prospective Observational Studies. Diabetes Care. 46 (2): 469-477, doi: 10.2337/dc22-1018

Schaefer E., Lang A., Kupriyanova Y., Bódis K. B., Weber K. S., Buyken A. E., Barbaresko J., Kössler T., Kahl S., Zaharia O. P., Szendroedi J., Herder C., Schrauwen-Hinderling V. B., Wagner R., Kuss O., Roden M., Schlesinger S., (2024), Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet is associated with lower visceral and hepatic lipid content in recent-onset type 1 diabetes and type 2 diabetes. Diabetes Obes Metab. 26 (10): 4281-4292, doi: 10.1111/dom.15772.

Zusammenfassung

Der Einfluss von Nahrungsfetten auf das Risiko für Typ-2-Diabetes (T2D) ist unklar. Fettsäure (FA)-Biomarker könnten die Bioverfügbarkeit besser abbilden, da sie sowohl die Aufnahme als auch den Stoffwechsel erfassen. Ernährung ist ein zentraler Bestandteil des Diabetesmanagements. Doch da aktuelle Empfehlungen meist auf der Allgemeinbevölkerung basieren, ist ihre Übertragbarkeit auf Personen mit T2D fraglich. Auch die Evidenz zu Ernährungsmustern wie die DASH-Ernährungsweise (Dietery Approaches to Stop Hypertension) bei Typ-1-Diabetes (T1D) und T2D ist begrenzt, insbesondere hinsichtlich der Körperfettverteilung. Die Ziele dieser Arbeit waren, die Evidenz zu FA-Biomarkern und T2D-Risiko, zur Effektivität von Ernährungstherapien sowie zu Zusammenhängen zwischen verschiedenen Ernährungsfaktoren und der Gesamtmortalität bei T2D zusammenzufassen. Darüber hinaus sollten neue Daten zur DASH-Ernährungsweise bei neu diagnostiziertem T1D und T2D bereitgestellt werden.

Zur Beantwortung dieser Fragestellungen haben wir systematische Literaturrecherchen, lineare Dosis-Wirkungs-Metaanalysen, einen Umbrella-Review sowie eine Beobachtungsstudie mit linearen und nichtlinearen Regressions- und Mediationsanalysen durchgeführt.

Wir haben robuste inverse Assoziationen zwischen bestimmten gesättigten (15:0, 17:0), n-3 (20:5, 22:5, 22:6) und n-6 (18:2) mehrfach ungesättigten FAs (PUFAs) und dem T2D-Risiko festgestellt. Höhere Spiegel von einfach ungesättigten FAs (16:1n-7, 18:1n-9) und bestimmten n-6 PUFAs (γ-20:3, γ-18:3, 20:4) waren dagegen mit einem erhöhten Risiko assoziiert. Die Ergebnisse waren über alle Bioproben hinweg konsistent, mit den stärksten Assoziationen in Plasma-Phospholipiden und Erythrozyten. Bei der Ernährungstherapie von T2D zeigte sich eine robuste Evidenz für den Nutzen von Energierestriktion sowie von pflanzenbasierten, mediterranen, kohlenhydratarmen und eiweißreichen Ernährungsformen hinsichtlich kardiometabolischer Parameter. Eine höhere Aufnahme von Fisch, Vollkorn, Ballaststoffen und n-3 PUFAs war mit einem geringeren Risiko der Gesamtmortalität assoziiert. Darüber hinaus, war die Einhaltung einer DASH-Ernährungsweise bei Personen mit T1D und T2D mit einem geringeren Anteil an viszeralem Fett, bei T2D auch Leberfett, assoziiert. Diese Assoziationen wurden teilweise durch Veränderungen des BMIs und des Taillenumfangs erklärt; bei T2D spielte zudem eine verbesserte Insulinresistenz des Fettgewebes eine zentrale Rolle.

Zusammenfassend verdeutlichen die Ergebnisse die wichtige Rolle von FA-Biomarkern im Zusammenhang mit dem Risiko für T2D und liefern neue Einblicke in die unterschiedlichen Funktionen einzelner FAs. Mehrere Ernährungsansätze - pflanzenbasierte, mediterrane, DASH, kohlenhydratarme und eiweißreiche Ernährung - sowie höhere Aufnahme von Fisch, Vollkorn, Ballaststoffen und n-3 PUFAs verbesserten kardiometabolische Marker oder verringerten das Mortalitätsrisiko. Schließlich können die Vorteile einer gesunden Ernährung bei Personen mit Diabetes über den Gewichtsverlust hinaus auch Verbesserungen der Insulinsensitivität des Fettgewebes umfassen.

Summary

The role of dietary fat in the development of type 2 diabetes (T2D) risk remains uncertain, with inconsistent findings across studies. Fatty acid (FA) biomarkers may better reflect bioavailability by capturing both intake and metabolism. While diet is a cornerstone in diabetes management, current recommendations are mainly based on general population studies, and their applicability to people with T2D remains unclear. Furthermore, evidence on dietary patterns like the Dietary Approaches to Stop Hypertension (DASH) diet among people with type 1 diabetes (T1D) and T2D is limited, especially regarding association with adipose tissue distribution. We therefore aimed to summarize the current evidence on FA biomarkers and T2D risk, synthesize evidence on dietary treatment of T2D and associations between dietary factors and all-cause mortality risk in people with T2D, as well as to provide novel data on the DASH dietary pattern in individuals with newly diagnosed T1D and T2D.

We applied various methods, including systematic literature searches, linear dose-response meta-analyses, an umbrella review, and an observational study using linear and non-linear regression analyses and mediation analysis.

We found robust inverse associations between certain saturated FAs (15:0, 17:0), n-3 (20:5, 22:5, 22:6), and n-6 (18:2) polyunsaturated FAs and T2D risk, whereas higher concentrations of specific monounsaturated FAs (16:1n-7, 18:1n-9) and n-6 polyunsaturated FAs (γ-20:3, γ-18:3, 20:4) were linked to increased risk. Findings were consistent across biospecimens but strongest associations were found in plasma phospholipids and red blood cells. As for dietary treatment of T2D, we identified high to moderate certainty of evidence that, beyond energy restriction, plant-based, Mediterranean, low-carbohydrate, as well as high-protein diet are beneficial for cardiometabolic health, including anthropometric measures, glycaemic control and blood lipids. Furthermore, higher intake of fish, whole grain, fiber, and n-3 polyunsaturated FAs were inversely associated with all-cause mortality in individuals with T2D. Additionally, persons with T1D and T2D can derive benefits from a shift to DASH-style diet experiencing improvements in visceral adipose tissue; additionally, those with T2D may derive benefits in relation to hepatic lipid content. Changes in BMI and waist circumference partly explained these associations, with improved adipose tissue insulin resistance in T2D playing a key role in the link between DASH diet changes and hepatic lipid content.

In summary, the findings highlight the relevance of FA biomarkers in the association with T2D risk and enhance our understanding of the distinct role of individual FAs. Several dietary approaches, including energy-restricted, plant-based, Mediterranean, DASH, low-carbohydrate, and high-protein diets, as well as higher fish, whole grain, fiber and n-3 polyunsaturated FAs intake consistently improved cardiometabolic markers or decreased mortality risk in people with diabetes. Finally, the benefits of following a healthy diet can extend beyond weight loss to improvements in adipose tissue insulin sensitivity.

List of abbreviations

Adipo-IR – Adipose Tissue Insulin Resistance Index

AMSTAR 2 - A MeaSurement Tool to Assess systematic Reviews

BMI – Body Mass Index

CI – Confidence interval

CoE – Certainty of Evidence

CVD – Cardiovascular disease

DALYs – Disability-Adjusted Life Years

DASH – Dietary Approaches to Stop Hypertension

DNL – De-Novo Lipogenesis

DNSG - The Diabetes and Nutrition Study Group

EPIC - European Prospective Investigation into Cancer and Nutrition

FA – Fatty acid

GBD – Global Burden of Disease Study

GDS – German Diabetes Study

GLP-1 RA – Glucagon-Like Peptide-1 Receptor Agonist

GRADE – Grading of Recommendations, Assessment, Development and Evaluations

HLC – Hepatic lipid content

Look AHEAD - Action for Health in Diabetes

MASLD - Metabolic dysfunction-associated steatotic liver disease

MUFA – Monounsaturated fatty acid

PLIS - The Prediabetes Lifestyle Intervention Study

PPL – Plasma phospholipids

PUFA – Polyunsaturated fatty acid

RBC – Red blood cells

RCT – Randomized controlled trial

ROBINS-I – Risk Of Bias In Non-randomized Studies - of Interventions

RoB 2 tool – Risk-of-Bias 2 tool

SAT – Subcutaneous adipose tissue

SFA – Saturated fatty acid

T1D – Type 1 diabetes

T2D – Type 2 diabetes

VAT – Visceral adipose tissue

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Chapter 1

Introduction

1.1 Epidemiology and aetiology of diabetes

Type 2 diabetes (T2D) is fourth most prevalent non-communicable diseases, with its prevalence steadily rising over the past decades, reaching pandemic levels (1). In 2021, approximately 589 million adults aged 20 to 79 were estimated to live with diabetes (2). This number is projected to grow to 853 million by 2050, with the most significant increase in the African and Middle Eastern regions (Figure 1).

Figure 1. Number of people with diabetes worldwide and by International Diabetes Federation Region in 2034-2050 (20-79 years). Modified after IDF Diabetes Atlas, 11th edn. (2).

Additionally, an estimated 251.7 million people worldwide are believed to have undiagnosed diabetes, meaning over four in ten adults with diabetes are unaware they have the condition (2). The rising prevalence of diabetes is most probably driven by the improved detection, better treatment, and longer life expectancy of people with diabetes (3). At the same time, stabilization or even a decrease in the incidence of T2D in some high-income countries since 2010 was observed (4). Authors speculate that this decline may reflect the impact of prevention efforts such as increased awareness, changes to the physical environment like bike tracks and exercise parks, and, as observed in the United States, improvements in diet and related behaviours (5).

Similar trend has been detected in Germany; however, an annual increase in incidence rate by 3% was noted in younger age groups, specifically in the age group 20 to 39 years (6). Data from Denmark showed a decrease in T2D incidence rates between 2011 and 2014, followed by increasing incidence rates between 2014 and 2016, demonstrating that the trends can reverse quickly (7).

T2D is primarily driven by the body's inability to respond adequately to insulin, known as insulin resistance, resulting in elevated blood glucose levels. In response, a compensatory mechanism occurs and the body produces even more insulin. At the same time, endogenous glucose production by the liver increases and glucose uptake from muscle and fat tissue decreases at a constant insulin level. Over time, ß-cell function may deteriorate and insulin production may cease (8).

1.2 Burden of diabetes

Diabetes imposes a considerable burden on healthcare systems. The global health expenditure due to diabetes grew from 232 billion USD in 2007 to more than a trillion USD in 2024, representing a 338% increase over 17 years (2). The population-based Maastricht Study revealed that the average total societal costs per 6 months for individuals with T2D amounted to €3,006, which was 2.2 times greater than for those with normal glucose tolerance (€1,377) (9). According to the Global Burden of Disease (GBD) Study 2021, diabetes accounted for 37.8 million total diabetes related years of life lost and 41.4 million years lived with disability (10). Diabetes also increases the risk of further complications, notably serving as a key risk factor for ischemic heart disease and stroke (11), which were the first and second leading contributors to the 2019 GBD Study (12). Moreover, individuals with T2D tend to develop cardiovascular disease (CVD) an average of 14.6 years earlier, and with greater severity, than those without T2D (13). In the United States, T2D is responsible for 44% of new cases of end-stage renal disease (14). The relative risk of retinopathy, nephropathy and neuropathy in people with T2D is at least 10-20 times higher, while the risk of CVD is two to four times greater compared to those without the condition (15). Consequently, an increased risk of numerous diabetes related complications is leading to an increased risk of premature death. It is the world's eighth leading cause of death and disability, as per estimates from the GBD Study 2019 (12). In addition, a comprehensive systematic review with meta-analysis of 35 studies over a mean 10.7-year follow-up period revealed an 85% higher relative risk of all-cause mortality among populations with existing T2D, compared to those without the condition (16). In Germany alone,

approximately 140,000 deaths in 2010 were attributed to elevated mortality rates in individuals with T2D (17).

1.3 Modifiable risk factors for diabetes onset and progression

The risk of developing T2D is influenced by both non-modifiable and modifiable factors. Non-modifiable factors include age, family history, genetics, and ethnicity. Modifiable factors encompass, for example, dietary habits, body weight, physical activity, socio-economic status, smoking, alcohol intake, and stress (2, 18-21). Regarding genetic factors, between 30% and 70% of T2D risk can be attributed to genetic factors (22). However, the inclusion of polygenic risk scores into a prediction model consisting of risk factors - such as age, body mass index (BMI), smoking status, physical activity, high-density lipoprotein cholesterol, triglycerides, and systolic blood pressure - demonstrated only marginal improvements in predicting disease onset (23). This underscores the crucial role of modifiable lifestyle factors in T2D prevention. In this context, excessive alcohol intake and smoking are known to significantly increase the risk of T2D (24, 25). Globally, tobacco use accounted for 12% (95% confidence interval (CI) 4.5; 20.9) and alcohol use for 1.8% (95% CI 0.3; 3.9) of T2D Disability-Adjusted Life Years (DALYs) (10). Furthermore, transitioning from inactivity to meeting recommended physical activity levels reduced the risk of T2D by 24% (0.76 (95% CI 0.71; 0.84) (26). An increase in BMI, in waist circumference and in visceral adiposity pointed to a 72%, 61% and 205% higher relative risk of T2D, respectively (27). Globally, high BMI was shown to be the primary risk factor for T2D, accounting for 52% (95% CI 26; 72) of DALYs (10).

Besides their role in prevention, lifestyle factors also play an important role for the treatment of diagnosed diabetes (28). Smoking was associated with 55% and 48% higher relative risk of all-cause and CVD mortality respectively, as well as with 43% increased risk of CVD incidence in persons with type 1 diabetes (T1D) and T2D (29). The adverse impact of smoking appeared to be larger in persons with diabetes than in persons without diabetes in terms of CVD risk (30). Among individuals with existing T2D, higher levels of physical activity were associated with reduced risks of both CVD incidence and mortality (31), even when the activity level was below World Health Organisation recommendations. Physical activity level determines individuals' body weight and fat distribution, which are also critical in T2D management. Also in T1D, a higher prevalence of retinopathy and neuropathy has been observed in overweight people compared with normal-weight people (32). Importantly, interventions aimed at weight reduction through lifestyle changes, such as increased physical activity and healthy diet, have

shown considerable benefits. For instance, participants of the Look AHEAD (Action for Health in Diabetes) trial with existing T2D who achieved a 10% reduction in body weight experienced a 21% reduction in the risk of a composite CVD outcome (33).

Obesity is a key risk factor targeted in diabetes management and is closely associated with the disease progression (33-35). It is accompanied by an accumulation of subcutaneous adipose tissue (SAT), the largest adipose tissue depot, which accounts for up to 80% of total adipose tissue and serves as a physiological buffer for excess energy (36). In obesity, white adipose tissue also accumulates ectopically within the visceral cavity, surrounding organs with fat (37). Visceral adipose tissue (VAT) is highly metabolically active and becomes increasingly dysfunctional as obesity develops. It continuously releases free fatty acids (FAs) into the portal circulation, directly affecting the liver and contributing to insulin resistance, systemic inflammation, dyslipidaemia, and atherosclerosis (37, 38). As VAT content increases, hepatic lipid content (HLC) also rises, further exacerbating cardiovascular risk and insulin resistance. Higher VAT and HLC have been associated with increased risk of retinopathy, nephropathy and neuropathy, and CVD in people with diabetes mellitus (34, 35). Interestingly, an increased VAT volume alone was not associated with greater metabolic dysfunction unless HLC was also elevated, highlighting HLC as an even more critical risk factor for metabolic diseases (39). Reducing the HLC is particularly important, as approximately 60% of persons with T2D (40) and 9-44% of those with T1D (41, 42) have metabolic dysfunction-associated steatotic liver disease (MASLD). The coexistence of MASLD and diabetes is associated with a two times higher risk of CVD, compared to diabetes alone (40). Finally, a decrease in HLC was associated with diabetes remission (43).

1.4 Diet in the prevention of diabetes

Among different modifiable risk factors, diet constitutes another cornerstone of T2D prevention. Insufficient intake of whole grains, yogurt, fruit, nuts and seeds, and non-starchy vegetables and excess intake of refined rice and wheat, processed meats, unprocessed red meat, sugar sweetened beverages, potatoes and fruit juice was estimated to be attributable to 14.1 million incident T2D cases in 2018, accounting for 70% of global incident cases (44). Over the decades numerous dietary patterns reflecting healthy diet, like Alternative Healthy Eating Index, vegetarian, Dietary Approaches to Stop Hypertension (DASH), Mediterranean, and plant-based diets have been linked to lower T2D risk (45, 46). Furthermore, an umbrella review on the prevention of T2D through diet pointed to robust evidence for the associations between

whole grain, fibre, processed and red meat intake, sugar sweetened beverages and T2D risk (45). Additionally, inverse associations were observed for yogurt, total dairy, coffee, and vegetable fat intake, while positive associations were observed for higher artificially sweetened beverages, total protein and animal protein intake with T2D risk. Interestingly no precise association was observed for total fat intake, as well as saturated (SFAs), mono- (MUFAs) and poly-unsaturated fatty acids (PUFAs) (45).

1.4.1 Dietary fat intake in the prevention of T2D

In the context of dietary fat intake, current dietary guidelines for prevention of T2D recommend lowering the intake of total fat, especially through lowering the intake of SFAs and trans-FAs (47). At the same time, other guidelines stress that the type of fat consumed is more important than the absolute amount and recommend increasing the intake of foods rich in long-chain n-3 PUFAs, such as fish, nuts and seeds (28), as well as increasing the intake of vegetable fat and decreasing the intake of animal fat (47). Evidence from observational studies indicate that following dietary patterns, like Mediterranean or DASH diet, rich in MUFAs and PUFAs dietary sources, were associated with lower risk of T2D (48, 49). However, evidence from a meta-analysis of randomised-controlled trials (RCTs) did not show any effect of n-3 PUFAs supplementation on T2D risk (50), as well as no effects of n-3 and n-6 PUFAs on glycaemic control (51) or on secondary CVD prevention in persons with existing T2D (52, 53). In agreement with current guidelines, a systematic review and meta-analysis by Neuenschwander and colleges pointed to 3% higher risk of T2D with higher animal fat intake per 10g/d, with moderate certainty of evidence (CoE); however, no precise association was observed between total and vegetable fat intake. In addition, a harmful association for SFAs and beneficial association for MUFAs were not confirmed, while when considering specific FAs separately, a 6% higher risk of T2D was observed per 250 mg/d higher intake of eicosapentaenoic (20:5) and docosahexaenoic acids (22:6). Furthermore, specific FAs within the whole group (e.g., SFAs) can have varying association with T2D; thus, leading to no association for the whole group. However, those results rely on self-reported dietary data which are prone to misclassification, recall and underreporting bias (54).

1.4.2 FA biomarkers and risk of T2D

One possibility to overcome the limitations of self-reported dietary fat intake is the measurement of FA concentrations in biological specimens. Biomarkers of FA provide more accurate measurements of dietary intake, allowing differentiation between specific FAs.

Additionally, they reflect the internal dose, accounting for variations in absorption and metabolism, to which tissues are exposed. As a result, they may be more strongly associated with the physiological effects of nutrients than measures that only reflect dietary intakes (55). By definition, dietary biomarkers should be sensitive to intake, well-integrated over time, and specific (54). In terms of sensitivity, dietary intake of a given FAs should correlate with its measured concentration. Correlations between FA biomarkers and dietary intake vary by specific FA. FAs that cannot be synthesized endogenously are considered most sensitive to dietary intake. These include α-linolenic acid (α-18:3), linoleic acid (18:2), the long-chain PUFAs derived from α-linolenic acid (α-18:3) and linoleic acid (18:2), as well as trans-FAs (56). A recent study from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported low to moderately high correlations between FA intakes and broad range of circulating FA levels, with correlations ranging from -0.23 to 0.55 (56). Furthermore, with regard to the time integration, a biomarker should reflect the cumulative effect of diet over an extended period rather than day to day differences in nutrient intake (54). FAs biomarkers can be measured as free FAs in serum, components of circulating triglycerides, red blood cell (RBC) membranes, phospholipids, cholesterol esters, or adipose tissue from various sites (57). Triglycerides and cholesterol ester reflect dietary intake over past few hours to few days. Plasma phospholipids (PPL) and RBC reflect slightly longer period of time, with RBC believed to reflect dietary intake of even last three months due to RBC lifespan (57). However, studies showed similar course of changes in the FAs concentration in PPL and RBC after dietary interventions (58, 59). Lastly, to be specific, a dietary biomarker should not be influenced by the intake of other foods or nutrients, or by genetic, environmental, or lifestyle factors (54). However, previous studies have shown that concentrations of many FAs can be influenced by genetic background, smoking habits, alcohol intake and sex (60, 61). Additionally, some FAs can be synthetized endogenously via de-novo lipogenesis (DNL) - a metabolic pathway that enables the endogenous synthesis of triglycerides and other lipids from dietary starch, sugar, and protein (62). The primary FA produced through DNL is palmitic acid (16:0), which can be elongated to stearic acid (18:0) or desaturated to form palmitoleic acid (16:1n7). Additionally, stearic acid (18:0) can undergo further desaturation to generate oleic acid (18:1). Therefore, FAs biomarkers should be considered as both, a reflection of dietary intake and endogenous metabolic processes.

Although in the past, several systematic reviews and meta-analyses have summarized the evidence on the association between circulating FAs and the risk of T2D and pointed to different associations between specific FAs and T2D risk (63-67), most of the previous meta-

analyses only conducted high versus low comparisons (63, 65). By doing so, different levels of concentrations are being compared, what may lead to wrong conclusions about differences between studies (68). Furthermore, none of the previously published meta-analyses assessed the CoE of the findings and did not consider differences between specific biospecimens of FAs measurement (i.e., total plasma, PPL, or RBC membrane). Given that the concentration of specific FAs varies across biospecimens, and each biospecimen has a different ability to reflect dietary FAs intake, it is reasonable to expect that the association with T2D may vary depending on the biospecimen used for FA measurement (69). Finally, new studies have been published and thus an updated systematic review with meta-analyses is warranted (70-73).

1.5 Diet in management of T2D

Once T2D has manifested, diet continues to play a crucial role in the management of the disease and results of studies published over the last decades clearly point to an important role of diet. Systematic reviews and meta-analyses summarizing the results of RCTs in people with T2D, pointed to beneficial effects of diets with low-fat and low glycaemic index on fasting blood glucose, HbA1c, and low-density lipoprotein cholesterol levels (74, 75). Furthermore, decreasing carbohydrate intake to less than 26% of total energy was shown to improve not only glycaemic measures but also reduce body weight (76), while increasing protein intake to more than 25% of total energy led to improvements in blood pressure and blood lipids (77). However, no clear benefit could be shown in another two meta-analyses of RCTs for intermittent fasting in terms of HbA1c levels (78) and for long-chain n-3 PUFAs supplementation on insulin and glucose levels (50).

In terms of diabetes complications, evidence from observational studies on diet-health associations in people with T2D remains limited. Single prospective observational studies showed an inverse, but imprecise association between vegetarian diet and higher plant-based protein intake and the risk of cataract, heart failure, nephropathy, and neuropathy in people with T2D (79-81). Other studies indicated inverse associations between higher adherence to a Mediterranean diet, DASH, plant-based diet, or low carbohydrate diet with all-cause mortality risk in this population (82-85). Similarly, higher intake of vegetables or nuts was associated with lower all-cause mortality risk (86, 87), while no association was found for dairy or meat intake (87, 88). However, only a few systematic-reviews with meta-analyses summarized evidence on diet and all-cause mortality risk in people with T2D, showing beneficial association for higher coffee and fish intake (89, 90).

In 2023, Evidence-based European recommendations for the dietary management of diabetes have been published by the The Diabetes and Nutrition Study Group (DNSG) (91). The guideline stress importance of body weight reduction via reduced energy intake and increased physical activity among overweight and obese persons with T2D. In addition, increasing the dietary fiber intake to minimum of 35g/d, lowering the intake of free or added sugars, SFAs and trans-FAs, and replacing them with n-6 and n-3 PUFAs is being recommended. Furthermore, dietary patterns like Mediterranean, Nordic or vegetarian diets, emphasising the consumption of whole grains, whole vegetables and fruit, legumes, nuts, seeds and vegetable oils, while reducing the consumption of red and processed meat, sugar-sweetened beverages, sweets and refined grains, are recommended for improvement of glycaemia and body weight, CVD and all-cause mortality risk reduction. However, the dietary guidelines often refer to surrogate marker, such as glycemic control or lipids, and, as authors of the guideline acknowledge, many recommendations are derived from studies on the general population (91). This raises concerns about the applicability of these findings to population with T2D and about translating improvements in surrogate markers into recommendations for the prevention of complications. Although hyperglycaemia is a common issue among individuals with T2D, the disease is multifaceted, with significant variations in adipose tissue distribution, insulin sensitivity and secretion pathways. Additionally, previous research suggests variations in responses to foods or dietary interventions due to differences in clinical profiles, genetics, gut microbiota, and lifestyle factors (92-94). Therefore, a “one-size-fits-all” dietary approach may be unrealistic, considering the broad clinical spectrum of people with T2D, their diverse cultural backgrounds, and personal preferences (95). Consequently, it is necessary to summarize and evaluate the existing evidence on the effects of dietary intervention exclusively in persons with T2D at highest available evidence level, by conducting an umbrella review of systematic reviews and meta-analyses of RCTs. However, RCTs are typically short-term and rarely powered to assess long-term outcomes, such as all-cause mortality (96). To address this gap, it is also important to synthesize evidence from prospective observational studies through a systematic review and meta-analysis, providing complementary insights into the associations between various dietary factors and all-cause mortality risk in people with T2D.

1.6 Diet and adipose tissue distribution in diabetes management

Lifestyle modifications, particularly dietary interventions, have been shown to effectively reduce SAT, VAT or HLC. Hypocaloric diet, time-restricted fasting and Mediterranean diet

have demonstrated benefits in reducing total body fat, VAT and HLC among general populations or individuals with prediabetes (97-100). Only few studies investigated the association between diet and adipose tissue distribution in persons with T2D, while evidence for those with T1D is even scarcer (91). In T1D, factors such as ß-cell dysfunction, intensive insulin therapy, blood glucose fluctuations, and impaired lipid metabolism create unique metabolic challenges and further highlight the need for dietary strategies to support metabolic health in this population (101). As for individuals with T2D, an isocaloric MUFA-enriched diet, compared to a high-carbohydrate and fiber-rich diet, reduced HLC (-26% vs -6%) (102). Another RCT in participants with obesity or T2D found that a high-fiber, isocaloric diet lowered VAT by 1114 mm^2 (95% CI: -1777 to -451) and HLC by 2.5% (95% CI: -3.6 to -1.4) compared to controls (103). Additionally, a calorie-restricted vegetarian diet led to greater VAT reduction and improvements in adipokine levels and oxidative stress markers than a conventional calorie-restricted diet over 24 weeks in individuals with T2D (104).

Given that the DASH dietary pattern, originally developed for hypertension management, emphasizes higher MUFA intake (e.g., from nuts and seeds), increased fiber intake (e.g., from whole grains, vegetables and legumes), and reduced red meat and processed meat consumption (105), it may exert similar beneficial effects on adipose tissue distribution, as observed in the trials described above. The DASH diet additionally recommends lower intake of sugar sweetened beverages, higher intake of which is considered one of the main drivers of weight gain (106). It has also been linked to a lower visceral adiposity index in older adults (107) and has been shown to improve hepatic fibrosis and promote weight loss in individuals with MASLD (108-110).

Importantly, when investigating the association between diet and health outcomes in persons with diabetes, one has to keep in mind that the diabetes diagnosis is often a teachable moment that can lead to significant changes in dietary behaviour, particularly in the first years following diagnosis. Therefore, assessing diet based on a single measurement may overlook important dietary adaptations over time. So far, no study has investigated the association between changes in the adherence to the DASH diet and changes in SAT, VAT and HLC distribution in persons with T1D and T2D.

1.6.1 Changes in BMI, waist circumference and adipose tissue insulin resistance index on the pathway between DASH diet and adipose tissue distribution

Another crucial point when investigating the association between changes in adherence to a healthy diet and alterations in adipose tissue distribution is whether dietary changes directly

influence the changes in adipose tissue distribution or is it merely a consequence of weight loss. For example, the NutriAct trial analyzed the effect of a high-protein and high-PUFA diet on HLC and found that the beneficial effect of increased protein intake was modified by BMI changes. In contrast, higher PUFA intake lowered HLC independently of weight loss (111). Similarly, replacing dietary carbohydrate with protein and fat improved HLC independently of changes in body weight in persons with T2D (112). Another mechanism could be through adipose tissue or whole-body insulin sensitivity, as dysfunctional and insulin resistant tissues can cause ectopic lipid deposition and drive hepatic steatosis (113, 114). Additionally, intervention based on diet and physical activity showed to enhance adipose tissue insulin and whole-body sensitivity (115).

In the scenarios described above, the DASH diet would exert an indirect influence, promoting weight loss or improvements in adipose tissue and whole-body sensitivity, and consequently leading to changes in VAT or HLC. Adjusting for variables that lie on the pathway between the DASH diet and adipose tissue distribution may help clarify whether these variables bias the relationship. If the association weakens after adjusting for a potential mediator, it suggests potential mediation. However, to assess the extent to which BMI, waist circumference or adipose tissue insulin resistance index (Adipo-IR) influence the association between adherence to the DASH diet and adipose tissue distribution, mediation analysis can be applied. So far, no study has quantified the extent to which changes in BMI, waist circumference and Adipo-IR modify the association between DASH diet and anthropometric changes in people with T1D and T2D.

1.7 Methodology of evidence synthesis

The goal of evidence synthesis is to summarize existing evidence from primary studies in order to provide highest level of evidence. Study designs for evidence synthesis include systematic reviews, meta-analyses and umbrella reviews.

As for the identification of relevant literature, several methods are available. In order to assure that all studies on the topic of interest are being identified, a systematic literature review is the gold standard (116). It involves defining a clear research question, setting inclusion and exclusion criteria, developing a search strategy, and screening studies independently by two reviewers - ensuring transparency, reproducibility, and reduced selection bias. Literature reviews are often combined with meta-analyses, which enhance evidence synthesis by quantifying results and offering the highest level of evidence (Figure 2.a). By pooling data from

multiple primary studies, meta-analyses yield more precise estimates with narrower confidence intervals and help to identify heterogeneity. Although systematic reviews with meta-analyses are placed at the top of the evidence pyramid, the revised version (Figure 2.b) highlights the importance of critically appraising included studies (117). It suggests that systematic reviews and meta-analyses should serve as a lens through which other types of studies are interpreted, as their conclusions are only as reliable as the quality of the underlying studies. Furthermore, even lines have been replaced with wavy lines. It indicates that, depending on the study question and the quality of the study in question, evidence from, for example, RCTs may not always be stronger than evidence from an observational cohort study. Additionally, a meta-analysis of well-conducted RCTs at low risk of bias cannot be equated with a meta-analysis of RCTs or observational studies at higher risk of bias (117).

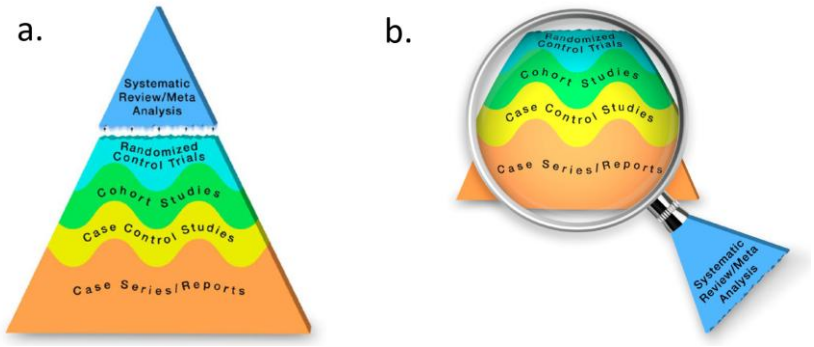

Figure 2.a. The proposed new evidence-based medicine pyramid, b. The revised pyramid: systematic reviews are a lens through which evidence is viewed (and applied). Modified after Murad et al. (117).

Due to this limitation, risk of bias assessment is a crucial step in a systematic review, conducted by two authors independently. It aims to evaluate the risk of bias of the included studies and the extent to which results may deviate systematically from the truth (118). The evidence pyramid illustrates a hierarchy of internal validity based on the risk of bias, indicating, for example, that case reports provide less robust evidence than cohort studies, and cohort studies less than RCTs (Figure 2.a). However, variations in risk of bias also exist within the same level of evidence - that is, among studies with the same design - which can influence the results of a meta-analysis. To evaluate this, different tools are available. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (118) aim to assess the risk of bias in observational epidemiologic studies, while Risk-of-Bias (RoB) 2 tool in RCTs (119). Both tools are domain specific. For ROBINS-I, domains include bias due to confounding selection of

participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. ROBINS-I treats each non-randomized study as an attempt to emulate a "target trial". Due to the inherent risk of residual confounding, observational studies typically receive a "Moderate" risk rating at best, even when major confounders are well accounted for. The RoB 2 tool assesses bias in RCTs across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Importantly, the results of risk of bias assessment should be considered during synthesis of findings across studies through systematic reviews with meta-analysis, either by conducting subgroup analyses separating studies according to risk of bias or by excluding studies at "Critical risk" or "Serious risk" from the beginning.

Furthermore, since evidence coming for example from a RCTs may not always be stronger than evidence coming from an observational cohort study, aspects beyond study design and risk of bias should be considered in the step of CoE assessment (120). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system is currently the gold standard for grading evidence, aiming to assess the quality of the evidence supporting the study findings and strength of recommendations in healthcare through a systematic, transparent, and rigorous approach. The GRADE approach encompasses five domains, which can lower the evidence; risk of bias, inconsistency, indirectness, imprecision, publication bias. According to the older approach, evidence from observational studies always starts the assessment at "Low Certainty of evidence", a downgrading by default of two levels, however, four domains can upgrade the evidence: large effects, dose-response effects, all-plausible residual confounding (121, 122) (Figure 3).

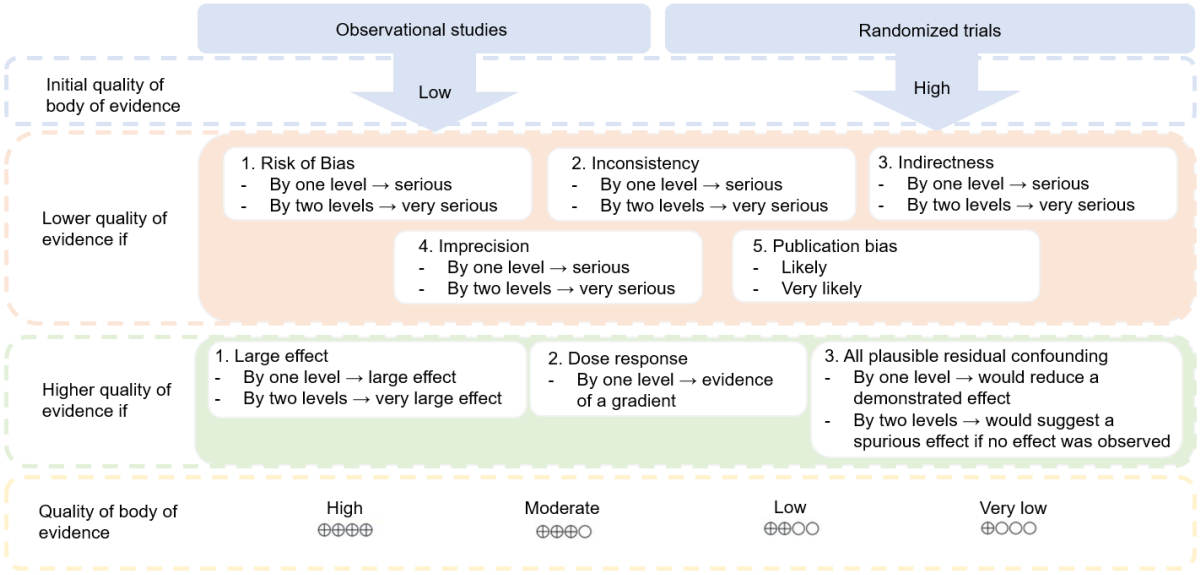

Figure 3. A summary of GRADE's approach to rate quality of evidence (121).

However, the Cochrane risk of bias assessment tools (i.e., ROBINS-I) provide a thorough assessment of risk of bias in relation to a hypothetical randomized trial, and "Low risk" of bias corresponds to the risk of bias in a high-quality randomized trial. This opens up the possibility of using the risk of bias assessment, rather than the lack of randomization per se, to determine the degree of downgrading of a study result from the starting point, and means that evidence from results of observational studies and RCTs can be compared. Therefore, the current approach suggests, that if Cochrane tools were used for risk of bias assessment of observational studies, studies will be assigned a starting rating of "High Certainty of evidence". However, even with "Moderate" risk of bias as a result of ROBINS-I evaluation, evidence should be downgraded by one level in the Risk of bias domain in the GRADE tool, due to the residual confounding (123). Therefore, evidence from observational studies can be maximally rated with moderate CoE.

As for the other domains in the GRADE approach: inconsistency refers to heterogeneity in results across studies included in a meta-analysis, especially when effect estimates vary in direction or size; indirectness considers whether the evidence directly applies to the research question in terms of population, intervention, comparator, and outcome; imprecision assesses whether the effect estimates are sufficiently precise, typically based on the width of CIs and the number of events or participants; and publication bias refers to the possibility that studies with negative or null results are less likely to be published, potentially leading to an overestimation of the true effect. Each domain can be downgraded by two levels leading to a final CoE assessment of "High", "Moderate", "Low" or "Very low". Table 1 lists the meaning and interpretation of each of the CoE levels.

Table 1. Interpretation of Certainty of Evidence (CoE) levels.

CoE level	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Finally, when multiple systematic reviews and meta-analyses are already available on a broader topic, evidence can be summarized in an umbrella review (124). Umbrella review helps identify the gaps in a specific research field and can inform recommendations for further research, and thus are considered to have higher level of evidence than systematic reviews with meta-analyses (Figure 4). If several studies are available on exactly the same study question, systematic review with meta-analysis with highest quality or number of studies should be included in an umbrella review (125). Furthermore, methods are available to assess the methodological quality of included studies, for example AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) - a tool for critical appraisal of systematic reviews and meta-analyses (126). Taken together, umbrella reviews provide a comprehensive overview of study quality, effect sizes, uncertainty, heterogeneity, and potential biases across a well-defined but broad research field, while providing crucial insights into guideline development (127).

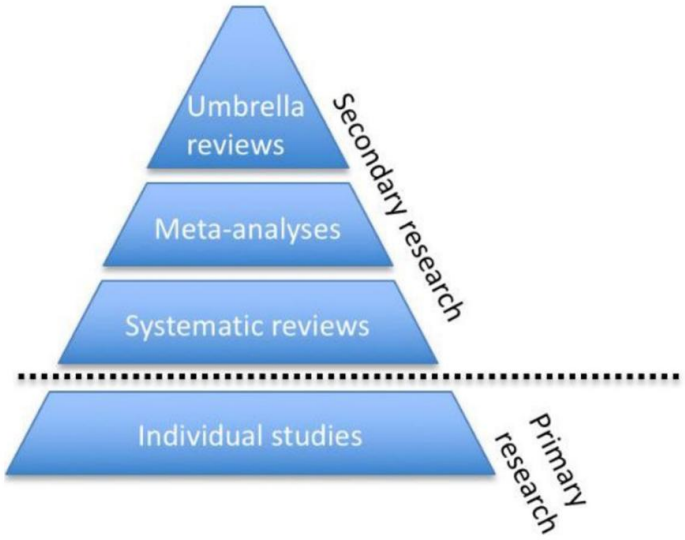

Figure 4. Hierarchy of evidence synthesis methods (124).

1.8 Mediation analysis

Mediation analysis is used to explore how an exposure influences an outcome by decomposing the total effect into direct and indirect pathways (Figure 5).

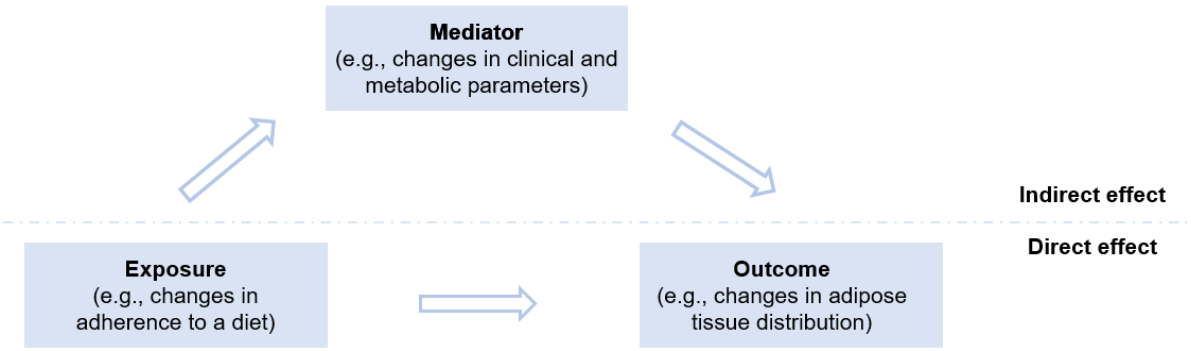

Figure 5. Chart of causal pathways regarding the association between changes in the adherence to a diet and changes in adipose tissue distribution.

The indirect effect captures the portion of the association that operates through a third variable which lies along the causal pathway, known as the mediator. In contrast, the direct effect reflects the influence of the exposure on the outcome that occurs independently of the mediator (128). Vander Weele introduced mediation analysis within a counterfactual framework, breaking down the total effect of an exposure on an outcome into two components: the total indirect effect and the pure direct effect (129). The formula for decomposing the total effect into total indirect effect and pure direct effect is as follows:

$$\underbrace{Y_1 - Y_0 = Y_{1M_1} - Y_{0M_0}}_{\text{Total effect}} = \underbrace{(Y_{1M_1} - Y_{1M_0})}_{\text{total indirect effect}} + \underbrace{(Y_{1M_0} - Y_{0M_0})}_{\text{pure direct effect}}$$

The total indirect effect represents the difference in the outcome when the mediator is set to the level it would naturally take if the person were exposed (M_1) versus when they were not (M_0), while assuming the exposure is present (Y_1). The pure direct effect reflects the difference in the outcome when a person is exposed (Y_1) compared to when they are not (Y_0), while holding the mediator constant at the level it would have under no exposure (M_0) (129). Additionally, the proportion mediated can be calculated as the ratio of the total indirect effect to the total effect

and quantifies how much of the exposure-outcome relationship is explained by the mediator. A higher proportion mediated indicates a stronger role of the mediator in the association (128).

To conduct a mediation analysis, several criteria should be met. First, the exposure must be associated with the outcome. Second, the exposure should be related to the mediator. Third, the mediator must be associated with the outcome, indicating that it lies on the causal pathway between the exposure and the outcome. Finally, if applicable, it is recommended that the exposure, mediator, and outcome are measured at different time points (128).

1.9 Aims of this doctoral thesis

Given the identified gaps, the objective of this publication-based doctoral thesis was to investigate the role of dietary aspects in prevention as well as in management of diabetes mellitus in four major research topics.

First, we conducted a systematic review with dose-response meta-analysis including prospective cohort studies on the association between FAs biomarkers and relative risk of T2D. Additionally, the CoE was evaluated in order to assess the reliability of the observed associations. We hypothesised that biomarkers of specific FAs, reflecting both dietary intake and metabolic processes, are differently associated with T2D risk, as well as that biospecimen of FA measurement can be determinant in terms of the strength of observed associations.

Second, we conducted an umbrella review to summarize all evidence coming from meta-analyses of RCTs published over the last years on the effectiveness of various dietary interventions on health outcomes among persons with existing T2D. As described above, current guidelines for diabetes management are based on results of studies, which did not focus on persons with existing T2D exclusively. Therefore, it is crucial to summarize existing evidence and assess the CoE and the methodological quality of the included meta-analyses using state of the art methods to inform guidelines and enhance diabetes management.

Third, we conducted a systematic review with meta-analysis to comprehensively evaluate evidence from prospective cohort studies on diet, including dietary patterns, food groups, individual foods, macro- and micronutrients, and secondary plant compounds, and their associations with all-cause mortality risk in people with T2D. To date, evidence on diet and long-term health outcomes in this population is limited, and the impact of different dietary factors on mortality has not been systematically summarized. To assess the reliability of the observed associations and support translation into guidelines, the CoE was evaluated.

Fourth, we investigated the relationship between DASH diet and SAT, VAT and HLC distribution in persons with newly diagnosed T1D and T2D from the German Diabetes Study (GDS). Additionally, since dietary habits assessed recently after diabetes diagnosis may not reflect the long-term dietary habits, we also investigated the associations between changes in DASH diet adherence and changes in the SAT, VAT and HLC over 5-year follow-up period. Finally, we hypothesised that associations observed cannot be solely explained by body weight loss but also by metabolic changes such as whole-body insulin sensitivity, Adipo-IR and non-esterified fatty acids. To quantify the extent to which these factors could explain the association between changes in DASH diet adherence and SAT, VAT and HLC distribution, a mediation analysis was conducted.

Chapter 2

Fatty acids biomarkers and incidence of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective observational studies

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Advances in Nutrition, 2025, 17 (1), doi: 10.1016/j.advnut.2025.100565

Summary

Previous studies on dietary fat intake and T2D risk have yielded contradictory results. This may, in part, be explained by the differential associations of specific FAs, such as palmitic acid (16:0) and pentadecanoic acid (15:0), within the broader category of total SFAs with T2D risk. Another contributing factor could be the limitations of self-reported dietary intake data, which are prone to misclassification, underreporting, and recall bias. In contrast, FA concentrations measured in biospecimens more accurately reflect dietary intake and metabolic processes, avoiding self-reporting bias. Therefore, in our study we aimed to conduct a systematic review and dose-response meta-analysis of prospective cohort studies on the association between biomarker of FAs, stratified by biospecimen type, and relative risk of T2D.

In total we screened 19,946 titles and abstracts, assessed full text of 329 articles, and finally included 27 prospective cohort studies and conducted 34 dose-response meta-analyses in all biospecimens combined and 94 biospecimen-specific dose-response meta-analyses on the association between the concentrations of 33 specific FAs or their groups (SFAs, MUFAs, n-6 and n-3 PUFAs) with the relative risk of T2D. A total of 19 studies had moderate and eight serious risk of bias. Our results were consistent across biospecimens, with stronger associations in PPL and RBC. We found moderate CoE for a 3-36% lower relative risk of T2D with higher concentrations of certain SFAs (pentadecane acid (15:0): summarized relative risk 0.68 (95% CI 0.56; 0.81); margaric acid (17:0): 0.64 (0.41; 0.78)), as well as n-3 PUFAs (eicosapentaenoic acid (20:5): 0.97 (0.95; 0.99), docosahexaenoic acid (22:6): 0.92 (0.88; 0.96)), and n-6 PUFAs (LA (18:2): 0.93 (0.91; 0.95)) measured in PPL or RBC. In contrast, higher levels of MUFAs (palmitoleic (16:1n-7): 1.06 (1.03; 1.10), oleic (18:1n-9): 1.04 (1.01; 1.06)) as well as n-6 PUFAss (dihomo-γ-linoleic (γ-20:3): 1.07 (1.03; 1.11), γ-linoleic (γ-18:3): 2.23 (1.42; 3.50), and arachidonic (20:4): 1.02 (1.01; 1.04)) measured in PPL or RBC were linked to a higher relative risk of T2D.

To summarize, our findings underline the role of FA biomarkers in T2D prevention. Furthermore, stronger associations observed in PPL and RBC highlight the critical role of biospecimen selection. Future research should investigate underlying causal mechanisms and the complex interrelationships between FAs to enhance our understanding of their role in T2D development.

Advances in Nutrition 17 (2026) 100565

Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL
journal homepage: https://advances.nutrition.org/

Review

Fatty Acid Biomarkers and Incidence of Type 2 diabetes: A Systematic Review and Dose–Response Meta-analysis of Prospective Observational Studies

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A B S T R A C T

The role of dietary fat in type 2 diabetes (T2D) development remains debated. Fatty acid (FA) biomarkers may better reflect bioavailable FAs than self-reported dietary intake. We conducted a systematic review and dose–response meta-analysis investigating associations between FA biomarkers and risk of T2D, considering different biospecimens of FA measurement. PubMed and Web of Science were searched until 9 November, 2022, and a search alert was followed until 17 February, 2025. Prospective cohort studies investigating FA biomarkers and T2D risk were included. Summary relative risks (SRR) and 95% confidence intervals (CIs) for all biospecimens combined and separately were estimated using a random-effects model. Risk of bias was assessed with the Risk Of Bias In Non-randomized Studies of Interventions tool, and the certainty of evidence (CoE) was rated with the Grades of Recommendations, Assessment, Development, and Evaluation approach. We included 27 articles. Analyses of plasma phospholipids (PPL) and red blood cells (RBC) provided inverse associations between higher concentrations of specific saturated FAs (SFAs) [15:0: SRR 0.68 (95% CI: 0.56, 0.81); 17:0: 0.64 (0.41, 0.78)], n−3 polyunsaturated FAs (PUFAs) [20:5: 0.97 (0.95, 0.99), 22:6: 0.92 (0.88, 0.96)], and n−6 PUFA [18:2: 0.93 (0.91, 0.95)] and risk of T2D, with moderate CoE. In the same biospecimens, higher levels of specific monounsaturated FAs (MUFAs) [16:1n−7: 1.06 (1.03, 1.10), 18:1n−9: 1.04 (1.01, 1.06)], and n−6 PUFAs [γ−20:3: 1.07 (1.03, 1.11), γ−18:3: 2.23 (1.42, 3.50), and 20:4: 1.02 (1.01, 1.04)] were associated with higher risk of T2D. Although combined analyses across biospecimens were consistent, stronger associations were observed in PPL and RBC. Associations of specific FAs within the same class (SFAs, MUFAs, PUFAs) varied in direction regarding risk of T2D. Certain SFAs, n−3 PUFAs, and 18:2 were inversely associated with T2D risk, whereas certain MUFAs and n−6 PUFAs were positively associated. Stronger associations in PPL and RBC highlight the importance of biospecimen selection. The protocol of this study was registered a priori in PROSPERO (CRD42020184575).

Keywords: biomarkers, fatty acids, type 2 diabetes, meta-analysis, prevention

Statements of Significance

This systematic review and meta-analysis is the first to investigate dose–response associations between FA biomarkers and risk of T2D across different biospecimens, and the first to assess the CoE for these associations.

Abbreviations: CI, confidence interval; CoE, certainty of evidence; FA, fatty acid; PPL, plasma phospholipids; RBC, red blood cells; RoB, risk of bias; RR, relative risk; SRR, summary relative risk; T2D, type 2 diabetes.

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https://doi.org/10.1016/j.advnut.2025.100565
Received 11 June 2025; Received in revised form 1 October 2025; Accepted 26 November 2025; Available online 3 December 2025

Introduction

Guidelines for type 2 diabetes (T2D) prevention recommend increasing vegetable fats, lowering animal fats, replacing SFAs with MUFAs and PUFAs, and lowering *trans*-fatty acid (FAs) intake [1]. However, a recent systematic review with meta-analysis of randomized controlled trials suggested that higher intake of omega-3 (n−3), omega-6 (n−6) FAs, or total PUFA has little effect on T2D prevention [2]. Our recent systematic review and dose–response meta-analysis also did not find an increased risk of T2D with higher SFA intake [3], possibly because of differing associations for specific FAs within the SFA group. A large body of literature indicates that circulating SFAs, such as palmitic acid (16:0) and stearic acid (18:0) [4], exert lipotoxic effects by promoting ceramide and diacylglycerol accumulation in pancreatic ß-cells, impairing insulin signaling, and triggering inflammation [5]. In contrast, circulating MUFAs appear less harmful [6], and PUFAs may enhance insulin secretion by increasing membrane fluidity, facilitating glucose transporter (GLUT4) translocation, and reducing inflammation [7–9]. Together, these findings highlight the pivotal role of FAs in T2D development.

Circulating FAs measured in red blood cells (RBCs) or plasma show moderate-to-strong correlations with corresponding intake assessed via food frequency questionnaire [10]. These biomarkers reflect both diet and endogenous metabolism, offering a more objective measure of bioavailable FAs than self-reported dietary information alone [11]. Previous systematic reviews with meta-analyses combining studies that measured FAs in different biospecimens found that circulating odd-chain SFAs were linked to lower risk of T2D, whereas even-chain SFAs and palmitoleic acid (16:1n−7) concentrations were associated with higher risk of T2D [12–14]. No associations were observed for total MUFAs and oleic acid (18:1n−9) [14]. Higher concentrations of α-linolenic (α−18:3), linoleic acid (18:2), and total n−6 PUFA were associated with lower risk of T2D [14–16], whereas the association with total n−3 PUFA was imprecisely estimated, as indicated by wide 95% confidence intervals (CIs) [14]. However, not all of the existing systematic reviews and meta-analyses quantified dose–response associations [12,14] or covered the whole spectrum of FA [13,15,17]. Importantly, prior studies suggested that the biospecimen used for FA measurement may influence its association with the risk of T2D. Findings of the pooling project "Fatty Acids and Outcomes Research Consortium" suggest the strongest associations for odd-chain FAs, *trans*-FAs, and n−3 PUFAs measured in plasma phospholipids (PPL) compared with total plasma or cholesteryl ester [18–20]. Therefore, the influence of the biospecimen type on the associations between FA biomarkers and risk of T2D should be comprehensively evaluated at the highest available evidence level. However, none of the systematic reviews with meta-analyses published to date have captured the role of biospecimen type [12–17,21], nor have they assessed the confidence in the findings, expressed as the certainty of evidence (CoE) [12–17,21]. Moreover, several new studies on this topic have been published since the publication of the most recent systematic reviews and meta-analyses [19,20,22,23].

Therefore, our study aimed to examine the association between all FA biomarkers, stratified by the type of biospecimen, with the risk of T2D in a systematic review and dose–response meta-analysis of prospective observational studies.

Methods

The present systematic review and meta-analysis was planned, conducted, and reported according to the PRISMA 2020 statement (Supplemental Table 1). The protocol of this study was registered a priori with PROSPERO (CRD42020184575).

Search strategy and study selection process

We included studies if the following criteria were met: *1*) adult participants (≥18 y) were free of T2D at the study begin, *2*) FA concentrations were measured in blood (total plasma, PPL, RBC, cholesteryl ester, and triacylglycerol measured in plasma or serum, total serum, whole blood, without further differentiation between more detailed fractions, e.g., PPL subfractions) or in adipose tissue as exposure, *3*) the outcome of interest was T2D incidence, and *4*) the study design was a prospective observational study (including cohort, nested case-control, case-cohort studies, and follow-up of intervention studies) published in a peer-reviewed journal.

The systematic literature search was performed in PubMed and Web of Science using predetermined search terms, from inception to 9 November, 2022. We continued screening articles from the PubMed search alert until 17 February, 2025 to identify newly published studies. No restrictions regarding publication language or filters were applied. Two researchers independently conducted the entire study selection process. Initially, titles and abstracts of all identified articles were screened, followed by retrieval and examination of the full-texts of potentially relevant studies based on the inclusion criteria. Disagreements between the 2 researchers were resolved through consensus or consultation with a third researcher. Additionally, reference lists of all eligible articles were reviewed to identify any additional relevant studies. The full search strategy is provided in Supplemental Table 2.

In the meta-analysis combining specific FAs measured in various biospecimens, we selected results based on the ability of the biospecimen to reflect long-term dietary intake in the case of duplicate cohorts. Biospecimens of FAs measurement were ranked according to their ability to reflect long-term intake as follows: *1*) adipose tissue, *2*) RBC membrane phospholipids, *3*) serum phospholipids or PPL, *4*) whole blood, *5*) total plasma/serum, and *6*) cholesteryl esters [24]. For the meta-analyses stratified by biospecimen type, when duplicate cohorts were available for a particular FA, we included the most recent result based on the largest sample size. If 2 reports from the same cohort were available for the same FA but used different units of measurement, we prioritized the measurement expressed as a % of total FA concentration. If only absolute concentration values were available, we converted them to % of total FA concentration. Studies with insufficient data for the calculation of dose–response meta-analyses were excluded.

Data extraction

One reviewer extracted the data from all identified studies using a predefined data extraction form, and a second reviewer checked the data for accuracy. The following characteristics

were extracted from each study: last name of the first author, year of publication, country where the study was conducted, cohort name, duration of follow-up, baseline participant characteristics (sex, age), total number of participants, number of T2D cases, outcome assessment (self-report of diabetes with or without objective medical details, use of diabetes medication, blood test, medical records), exposure (group of FAs, single FA), biospecimen type (RBC, PPL, total serum, total plasma, cholesteryl ester, whole blood, adipose tissue), categories of exposure with measured concentration of a given FA, and maximally adjusted risk estimates expressed as hazard ratio, relative risk (RR) or odds ratio with their corresponding 95% CI and the adjustment factors. For 7 studies, relevant data were missing, and the authors were contacted; 5 of them provided the necessary information [22, 25–28].

Risk of bias and CoE

We evaluated the risk of bias (RoB) using the RoB in nonrandomized studies of interventions tool [29]. Supplemental Table 3 contains detailed information on the rating. RoB was assessed by 2 reviewers independently, and any discrepancies were discussed with a third researcher to reach a consensus.

The CoE for each meta-analysis outcome was assessed using the Grades of Recommendations, Assessment, Development, and Evaluation approach [30]. Supplemental Table 4 contains the description of the instrument and rating judgments. Two reviewers independently rated the CoE, and any disagreements were resolved by consensus or consultation with a third researcher.

Statistical analysis

Summary relative risks (SRR) and corresponding 95% CI were calculated by conducting dose–response meta-analyses with a random-effects model, applying the method of DerSimonian and Laird [31]. First, we performed dose–response meta-analyses for FA concentrations and risk of T2D, combining all biospecimens. Next, we conducted dose–response meta-analyses for specific FA concentrations measured in the same biospecimen (e.g., RBC or PPL) and risk of T2D, when 2 or more studies were available. To conduct dose–response meta-analyses, for studies that did not report linear estimates, we applied the method described by Greenland and Longnecker [32] and computed study-specific slopes (linear trends) and 95% CIs based on the natural logarithm of the RRs and 95% CIs across categories of each FA. The following data were required for ≥3 exposure categories: the quantified exposure value (e.g., % of total FAs), the risk ratio with the corresponding 95% CI, and the number of cases and person-years. If the number of cases in single categories was not provided in a study, information on the total number of cases and total person-years or the number of total persons plus follow-up period was used to equally distribute the number of cases across the quantiles or categories as described previously [33]. If a range of FA concentration were presented, the midpoint value was assigned as the exposure level for the respective category. For open categories, we assumed the same width as the adjacent category. Because circulating FAs concentrations vary widely [34], we harmonized the dose–response estimates to specific FAs or their groups to make RRs directly comparable across specific FAs with differing abundances. Specifically, groups of FAs, such as total SFAs, total MUFAs, or total n−3 and n−6 PUFAs, were analyzed per 3.0% higher concentration in total FA. Specific FAs, with large relative concentrations, including 16:0, 18:0, 18:1n−9, 18:2, arachidonic acid (20:4), and DHA (22:6), were analyzed per 1.0% higher concentration in total FAs. For the remaining FAs, the calculations were conducted per 0.1% of total FAs concentration [34,35]. A nonlinear dose–response meta-analysis could not be conducted because the data from the original studies were insufficient and only available from very few cohorts. We calculated the I^2 statistic to assess the heterogeneity among the observed RRs in the meta-analyses. Potential publication bias was evaluated using funnel plots and Egger's test ($P < 0.1$) when ≥10 studies were available.

For meta-analyses including ≥10 cohorts, we conducted subgroup analysis in the biospecimen-specific meta-analyses by continent of the study origin. A P value <0.05 was considered statistically significant. To assess the robustness of our findings, we excluded studies with high RoB and omitted 1 study at a time to investigate the influence of individual studies on the results.

All analyses were performed using Stata (Version 14.2, StataCorp).

Patient and public involvement

No patients or members of the public were involved in setting the research question, designing the study, interpreting the results, or writing the manuscript. The results of this study will be spread to the public via social media or a press release.

Results

In total, we identified 19,946 articles after removing duplicates (Figure 1), of which 329 articles were assessed at the full-text level. Out of these, 25 articles met our inclusion criteria. In addition, we identified 2 articles through reference screening [36,37], whereas no eligible articles were identified via the PubMed alert. Thus, 27 articles were included in the present systematic review and meta-analyses. Articles excluded after full-text reviewing, with corresponding reasons for exclusion, are listed in Supplemental Table 5.

Supplemental Table 6 presents the characteristics of the included studies. The mean follow-up time ranged from 2.5 to 42.3 y, and the number of participants ranged from 187 to 95,854. The number of incidents T2D cases ranged from 28 to 12,132, and the mean age of participants ranged from 49 to 82 y. A total of 16 cohorts were conducted in Europe, 9 in the United States, 4 in Asia, and 2 in Australia. Six cohorts included only men, and 2 only women. FA biomarkers were measured in total plasma, total serum, PPL, RBC, plasma cholesteryl ester, whole blood, and adipose tissue. Quantification of FAs was conducted mainly by gas chromatography, whereas in 2 cohorts a targeted nuclear magnetic resonance metabolomics platform was used [22,23].

RoB was moderate in $n = 19$ studies and serious in $n = 8$ studies (Supplemental Figure 1). In the confounder domain, 6 studies were evaluated with a serious RoB, indicating that most of the studies adjusted for important confounding factors such as age, sex, smoking, alcohol intake, and education/socioeconomic status. Additionally, 4 studies were evaluated with a serious RoB because of exposure assessment and potential exposure misclassification during follow-up.

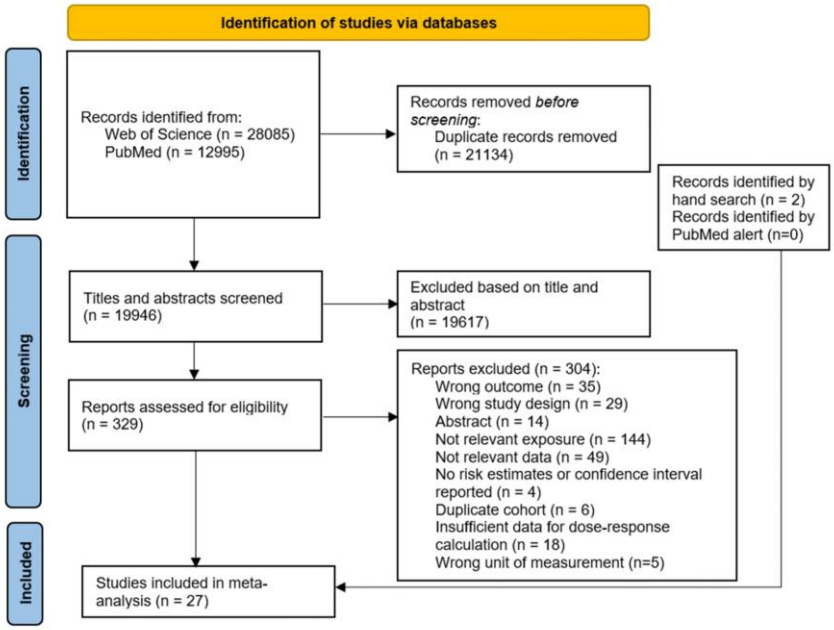

FIGURE 1. Flow-chart of the systematic literature search.

FA biomarkers and incidence of T2D

We conducted 34 dose–response meta-analyses in all biospecimens combined and 93 biospecimen-specific dose–response meta-analyses on the association between the concentrations of 27 specific FAs and their groups (SFAs, MUFAs, *trans*-FAs, n−6, and n−3 PUFAs) with the risk of T2D (Supplemental Table 7). Figures 2–4 summarize the results of the meta-analyses for all biospecimens combined and for specific biospecimens. Supplemental Figures 2.1–2.34 present forest plots of each separate meta-analysis. The assessment of the CoE for each meta-analysis is summarized in the supplement (Supplemental Tables 8–11).

SFAs

The associations for total SFAs pointed to an increased risk of T2D when measured in all biospecimens combined, as well as in specific biospecimens; however, the 95% CI included the null value (Figure 2). The association was strongest when SFAs were measured in PPL (per 3.0% higher concentration: [SRR (95% CI)] 1.68 (1.24, 2.27), $n_{\text{cohorts}} = 2$, $I^2 = 0\%$); however, the CoE was rated very low.

The meta-analyses on specific SFAs revealed strongest inverse associations with risk of T2D for pentadecanoic (15:0) and margaric (17:0) acids when measured in PPL [per 0.1% higher concentration: 15:0: 0.68 (0.57, 0.82), $n_{\text{cohorts}} = 7$, $I^2 = 58\%$; and 17:0: 0.64 (0.52, 0.78), $n_{\text{cohorts}} = 5$, $I^2 = 67\%$, both moderate CoE]. On the other hand, the risk of T2D was increased with higher concentrations of 16:0 in the meta-analysis of all biospecimens combined, as well as in PPL, RBC, cholesteryl ester, or total plasma, but the CoE was low to very low.

For the remaining SFAs, the associations were weak or inconsistent, with a CoE rated mainly as low to very low.

MUFAs and *trans*-FAs

For total MUFAs measured in all biospecimens combined, a positive association with risk of T2D was observed [per 3.0% higher concentration: 1.16 (1.02, 1.31), $n_{\text{cohorts}} = 6$, $I^2 = 53\%$], but the CoE was low (Figure 3). The association persisted in measurements from total plasma but not from RBC and PPL, as the null value was included in the 95% CI (low to very low CoE).

For 16:1n−7, a weak but positive association with risk of T2D was observed in the meta-analysis on all biospecimens combined, with strongest associations observed in meta-analyses on RBC and PPL measurements [per 0.1% higher concentration, RBC: 16:1n−7: 1.06 (1.03, 1.10), $n_{\text{cohorts}} = 8$, $I^2 = 82\%$; PPL 1.07 (1.02, 1.12), $n_{\text{cohorts}} = 7$, $I^2 = 83\%$, both moderate CoE]. For 18:1n−9, the meta-analysis combining all biospecimens and the meta-analysis including only RBC measurements indicated a weak positive association with risk of T2D [per 1% higher concentration, all biospecimens combined: 1.04 (1.01, 1.07), $n_{\text{cohorts}} = 17$, $I^2 = 40\%$; RBC: 1.04 (1.01, 1.06), $n_{\text{cohorts}} = 8$, $I^2 = 5\%$, both moderate CoE]. In contrast, no association was observed for PPL (moderate CoE). There was an indication for an inverse association between higher concentration of *trans*-vaccenic acid (*t*−18:1n−7) in all biospecimens combined and risk of T2D [per 0.1% higher concentration: 0.93 (0.87, 1.00); $n_{\text{cohorts}} = 4$, $I^2 = 83\%$; moderate CoE]. Even stronger association was observed for PPL measurement; however, CoE was rated as very low. Similarly, for eicosenoic acid (20:1), and the *trans*-FAs—*trans*-palmitoleic acid (*t*−16:1n−7), *trans*-hypogeic acid

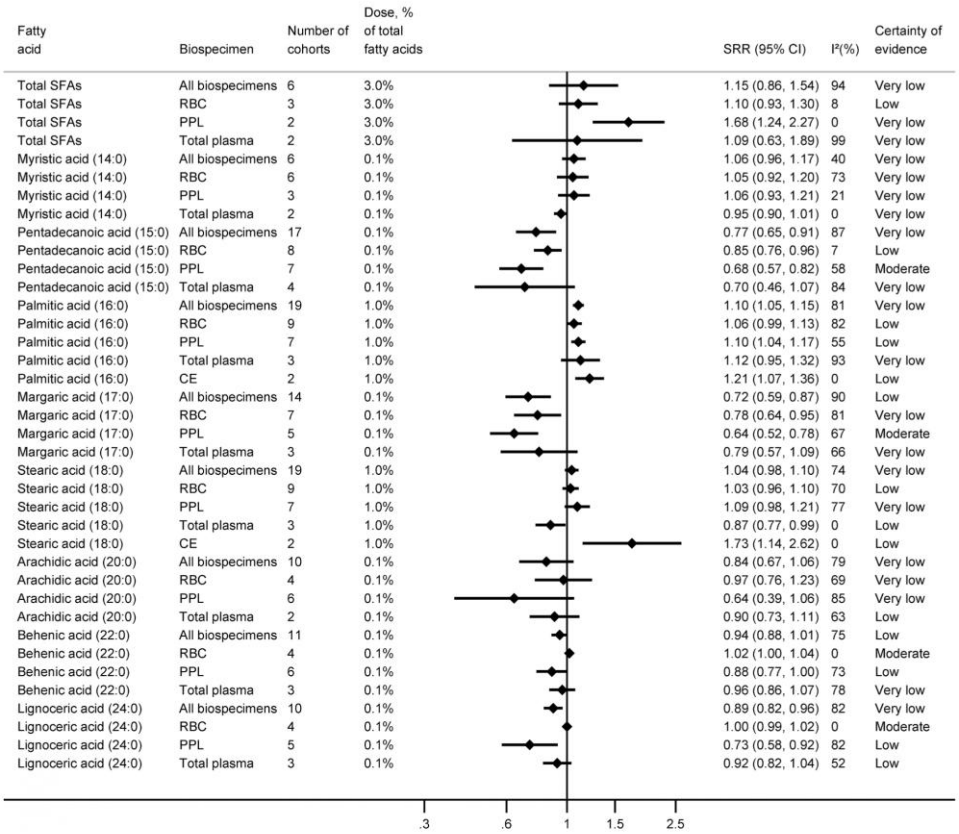

FIGURE 2. Summary results of linear dose–response meta-analyses for SFAs and risk of type 2 diabetes. CE, cholesteryl ester; CI, confidence interval; PPL, plasma phospholipids; RBC, red blood cells; SRR, summary relative risk.

(*t*−16:1n−9), and *trans*-linoleic acid (*t*−18:2)—findings pointed to inverse associations with the risk of T2D when measured in all biospecimens, PPL or RBC (low to very low CoE). For the remaining FAs [palmitelaidic acid (16:1n−9), nervonic acid (24:1), and *trans*-elaidic acid (*t*−18:1n−9)], no associations were observed (moderate to very low CoE).

PUFAs

Total PUFAs and total n−6 PUFAs pointed to an inverse association with risk of T2D when measured in all biospecimens combined, RBC, or total plasma (moderate to very low CoE). However, the 95% CI included the null value (Figure 4).

For specific n−6 PUFAs, there was a lower risk of T2D for higher 18:2 concentration in all biospecimens combined, but the CoE was low. The inverse association was also observed across specific biospecimens, and the CoE was moderate for the associations in PPL [0.93 (0.91, 0.95), $n_{cohorts} = 8$, $I^2 = 44\%$) and total plasma [0.96 (0.93, 0.99), $n_{cohorts} = 8$, $I^2 = 87\%$]. For higher concentrations of γ-linolenic acid (γ−18:3) and di-homo-γ-linolenic acid (γ−20:3), the risk of T2D was increased [γ−18:3 in RBC: 2.23 (1.42, 3.50), $n_{cohorts} = 3$, $I^2 = 32\%$; γ−20:3 in RBC: 1.07 (1.03, 1.11), $n_{cohorts} = 2$, $I^2 = 0\%$; γ−20:3 in PPL: 1.06 (1.05, 1.07), $n_{cohorts} = 2$, $I^2 = 0\%$, all with moderate CoE]. For 20:4, no association with risk of T2D was observed in all biospecimens combined, or when measured in RBC, whereas contrary directions of associations were observed for measurements in PPL and total plasma (moderate CoE). Docosatetraenoic acid (22:4) was positively associated with risk of T2D for all biospecimens combined and PPL, but no associations were observed for RBC, with low to very low CoE.

An inverse association for total n−3 PUFAs was observed for all biospecimens combined and for total plasma, but no association was evident for RBC (all rated as low CoE). For specific n−3 PUFAs, a clear inverse association was observed only for 22:6 in all biospecimens combined [per 0.1% higher concentration: 0.93 (0.90, 0.97), $n_{cohorts} = 26$, $I^2 = 82\%$), low CoE], with the association confirmed in PPL [per 0.1% higher concentration: 0.92 (0.88, 0.96), $n_{cohorts} = 9$, $I^2 = 0\%$], but not in RBC (both moderate CoE). An inverse association between the combination of EPA (20:5), docosapentaenoic acid (22:5), and 22:6 and risk of T2D was observed when measured in all biospecimens combined and in biospecimen-specific analyses (RBC,

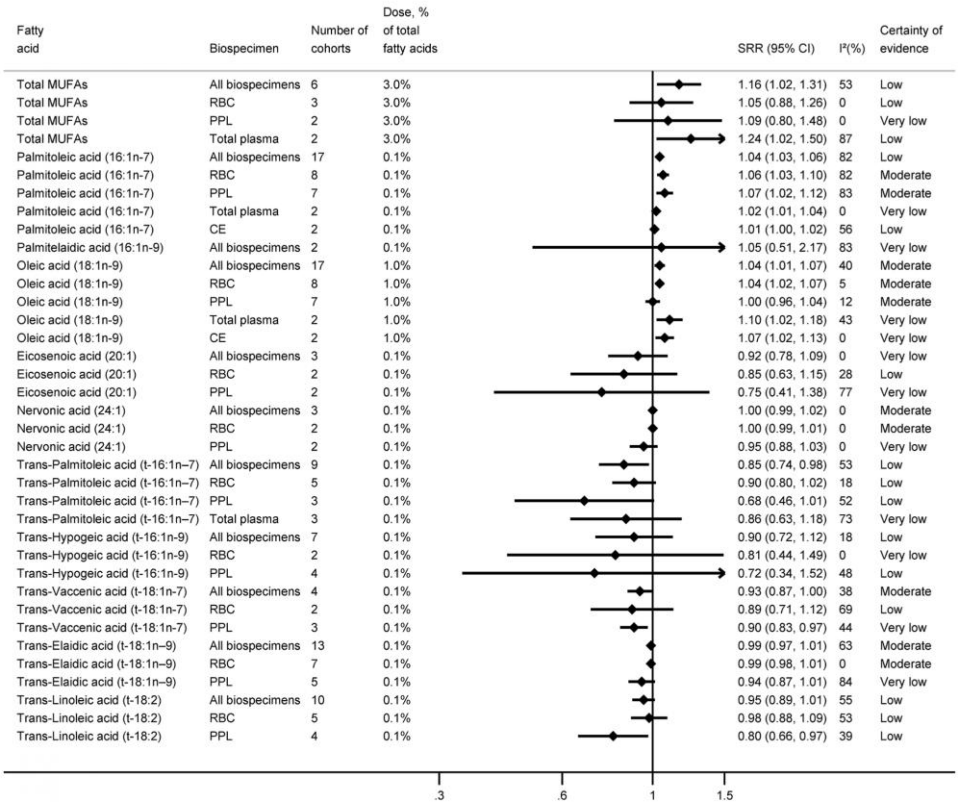

FIGURE 3. Summary results of linear dose–response meta-analyses for MUFAs and *trans*-fatty acids and risk of type 2 diabetes. CE, cholesteryl ester; CI, confidence interval; PPL, plasma phospholipids; RBC, red blood cells; SRR, summary relative risk.

PPL, total plasma, cholesteryl ester), with CoE ranging from low to moderate. However, when 20:5 and 22:5 were considered separately, as well as α−18:3, weak inverse or no associations were observed, regardless of the biospecimen (low to moderate CoE) (Figure 4).

Subgroups and sensitivity analyses

Geographic location explained some of the heterogeneity: I^2 decreased to 0% for α−18:3, 22:5, and 22:6 for studies conducted only in the United States, and for 20:5 and 22:6 for studies conducted only in Europe (Supplemental Table 12). Subgroup analyses stratified by geographic location further pointed to a positive association between α−18:3 and an inverse association between 20:4 and risk of T2D in the United States, whereas no precise association was found in Europe. Conversely, an inverse association between 20:5 and a positive association between 22:6 and risk of T2D was found in studies conducted in Europe, whereas no association was found in studies conducted in the United States (Supplemental Table 12). Furthermore, most of the results were robust (Supplemental Table 13), as excluding studies with high RoB from the meta-analyses only weakened the association for 17:0 measured in RBC but did not considerably affect the results. In contrast, a precise positive association was observed between α−18:3 measured in RBC and risk of T2D (Supplemental Table 13). In sensitivity analyses using the leave-one-out approach, the exclusion of any single study did not influence the overall results (Supplemental Figures 3.1–3.68).

Publication bias and small study effects

We detected asymmetry in the funnel plots for 15:0, 16:0, 22:0, 24:0, 18:2, and 22:6 measured in all biospecimens and 18:2 and 22:5 measured in RBC caused by the lack of small studies with positive associations between these FAs and risk of T2D (Supplemental Figures 4.1, 4.2, 4.6, 4.7, 4.13, and **4.22**). For 16:1n−7, the asymmetry was caused by the lack of small studies pointing to an inverse association between 16:1n−7 and risk of T2D (Supplemental Figure 4.8).

Discussion

Our systematic review with dose–response meta-analysis provides robust evidence for an association between higher concentrations of certain SFAs (15:0, 17:0), n−3 PUFAs (22:5,

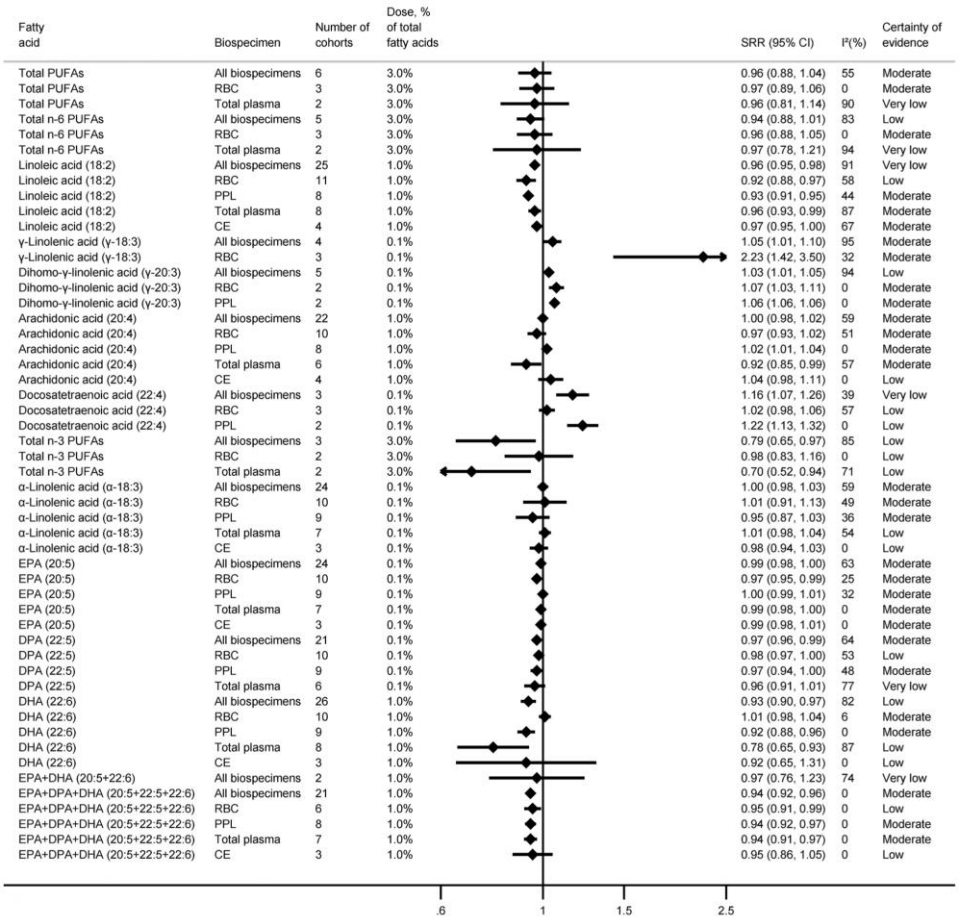

FIGURE 4. Summary results of linear dose–response meta-analyses for PUFAs and risk of type 2 diabetes. CE, cholesteryl ester; CI, confidence interval; DPA, docosapentaenoic acid; PPL, plasma phospholipids; RBC, red blood cells; SRR, summary relative risk.

22:5, 22:6), and n−6 PUFA (18:2) with a lower risk of T2D. In contrast, higher levels of MUFAs (16:1n−7, 18:1n−9) as well as n−6 PUFAs (γ−20:3, γ−18:3, and 20:4) were linked to a higher risk of T2D. We showed that concentrations of FAs measured in different biospecimens generally point in the same direction. However, the associations from PPL and RBC measurements were usually stronger, with higher confidence in these findings.

Comparison with other studies

In contrast to previous studies, we found moderate CoE for an inverse association for 22:5 and the combination of 22:5, 22:5, and 22:6 measured in PPL, and for a positive association for γ−18:3 measured in RBC [12–15]. The differences may stem from the fact that most previous meta-analyses only compared high compared with low FA concentrations and, crucially, combined different biospecimens. Also, in contrast to previous studies, we identified positive associations for 18:1n−9 measured in RBC, and an inverse association for n−3 PUFAs measured in total plasma. We did not confirm associations with *t*−16:1n−7 or α−18:3 regarding the risk of T2D [14]. Our results often pointed to stronger associations in PPL, suggesting that this biospecimen may better reflect long-term dietary intake of specific FAs and provide more accurate insights into metabolic processes linked to risk of T2D. In contrast, prior systematic reviews and meta-analyses tended to prioritize RBC because of its long-term stability, potentially diluting associations when different biospecimens were combined [10].

On the other hand, our results on 15:0, 17:0, 16:0, 16:1n−7, 18:2, and γ−20:3 measured in PPL or RBC, which were rated with low to moderate CoE, are in line with previous studies [13, 14,16]. Similarly, we found positive associations for total SFAs measured in PPL, 18:0 measured in cholesteryl esters, and total MUFAs measured in total plasma, as well as an inverse association for *t*−18:1n−7 measured in PPL. However, these findings

were graded with low to very low CoE, meaning that future studies may change the results [13,14].

Compared with previous systematic reviews and meta-analyses, our study assessed the CoE, showing that several findings were rated as low or very low CoE, primarily because of imprecision and wide 95% CIs that included the minimal important difference, which raises concerns about clinical relevance. However, although some findings rated with moderate CoE may show weak associations with T2D, it is crucial to emphasize their importance. For example, a 1% higher 18:2 concentration was associated with a 7% lower risk of T2D. Considering that 18:2 levels in PPL average around 20% and dietary interventions can shift this by ≤5% [35], the observed association is likely clinically significant.

Potential explanations

The stronger associations observed for FAs measured in PPL may reflect the physiological relevance of phospholipids in cell membrane structure and function. Membrane phospholipid saturation influences fluidity, which affects insulin receptor activity and signaling, and thus contributes to the pathology of T2D [38]. Additionally, n−3 PUFAs in phospholipids help stabilize membranes, modulate inflammation, and influence gene expression via receptor interactions [39].

The different associations between specific SFAs and risk of T2D in our study support the view that SFAs are not a uniform group [3]. Higher intakes of dairy products rich in 15:0 and 17:0, such as milk and yogurt, have been linked to a lower risk of T2D [40], and replacing low-fat milk with whole-fat yogurt appears to be beneficial [41]. However, a recent RCT-based study found that substituting dairy SFAs with unsaturated plant-derived FAs was associated with reduced risk of T2D, suggesting a more favorable role for plant-based fats [42]. Nonetheless, dairy SFAs could still offer advantages compared with other animal SFAs. Consistently, our results pointed to a positive association for 16:0, a predominant FA in meat [24]. Experimental studies further suggest that 16:0 and 18:1n−9 may impair insulin secretion by promoting inflammation in pancreatic cells [5]. However, interpretation is complicated by the fact that circulating FAs reflect both dietary intake and endogenous synthesis [24]. Odd-chain FAs can be synthetized endogenously from short-chain FAs produced by the gut microbiome because of higher fiber intake [43]. Similarly, even-chain SFAs like 16:0 and 18:0 are produced through de novo lipogenesis, typically driven by excess intake of sugar or alcohol, and can be desaturated into 16:1n−7 or 18:1n−9, respectively [44].

Although higher intake of plant-based MUFAs, like olive oil, nuts, and seeds, was inversely associated with risk of T2D [3,45,46], animal-based MUFAs were associated with an increased risk [47]. However, circulating MUFAs correlate poorly with dietary intake [24], suggesting that the positive associations observed for 18:1n−9 and 16:1n−7 in our study may be partly driven by endogenous synthesis via de novo lipogenesis.

Although previous studies linked higher intake of *trans*-FAs with a higher risk of T2D [46], we found no association for *t*−18:1n−9. This may be due to *trans*-FA biomarkers capturing both industrial (e.g., from margarine spreads, bakery foods, fried foods) and natural ruminant sources (e.g., dairy foods) [48]. In addition, strong intercorrelations between *trans*-FAs with other FAs exist, and a previous study demonstrated that adjusting for other *trans*-FAs considerably attenuated the association between *t*−16:1n−7 and risk of T2D [49]. Similarly, another study showed that adjusting for produced FAs via de novo lipogenesis attenuated the association for 18:2 and the risk of T2D [50]. However, most of the studies in our meta-analysis accounted for such confounding. Additionally, as FAs were measured as percentages of total FAs rather than absolute amounts, an increase in the relative percentage of 1 FA necessarily corresponds to a decrease in the percentage of another FA. This means that the observed associations might reflect a substitution effect, where the changes in 1 FA are indirectly driven by shifts in the levels of other FAs. Future research should consider FA interrelationships and apply substitution models to better isolate independent effects.

Long-chain PUFAs, particularly essential FAs like 18:2 and α−18:3 and their derivatives 20:5 and 22:6, are considered better dietary biomarkers [11,24,51]. However, 18:2 levels are also influenced by genetic variability in FA desaturase 1 and 2, which affects conversion to 20:4 [52]. Increased Δ-6 desaturase activity has been linked to risk of T2D, which is consistent with our observed positive associations for γ−18:3 and γ−20:3 [11]. For α−18:3, no clear inverse association was observed in our study. Previously, we showed a weak J-shaped association between dietary intakes of α−18:3 and risk of T2D [3]. This could explain the null association in the current study, as we only examined linear associations. In addition, α−18:3 rapid oxidation after consumption may explain low correlations with circulating levels [24]. In contrast, 20:5, 22:5, and 22:6 showed inverse associations, likely because of their roles in improving insulin sensitivity and glucose metabolism [17].

Strengths and limitations

This is the first systematic review with dose–response meta-analysis to comprehensively evaluate the associations between a broad range of FA biomarkers and the risk of T2D, examining both all biospecimens combined and specific biospecimens separately. For the first time, CoE has been assessed for the reported associations, offering an evaluation of the confidence in the findings. The objective exposure measurement in the included studies lowers the risk of misreporting and misclassification bias.

The limitation of this work is that 30% of the studies were rated as serious RoB because of insufficient confounder control (socioeconomic status, education, and alcohol intake), classification of intervention, or deviations from intended intervention. However, our findings did not change after excluding studies with high RoB. As with all observational studies, residual confounding cannot be completely ruled out. In this context, RoB was the most common reason for downgrading the CoE. Additionally, publication bias was detected for 2 meta-analyses and also contributed to lower CoE. Subgroup analyses could not be performed for all FAs because of the low number of included cohorts in biospecimen-specific meta-analyses. Furthermore, the FA concentrations were measured only once at baseline in most studies, and changes during follow-up could not be taken into account. In addition, the investigation of the nonlinearity of dose–response analyses was not feasible because of insufficient information provided from primary studies.

In conclusion, our results summarize the potential of circulating FAs, reflecting both dietary intake and endogenous metabolic processes, in the prevention of T2D. The findings show robust inverse associations between certain SFAs (15:0, 17:0), n−3 PUFAs (20:5, 22:5, 22:6), and n−6 PUFA (18:2) and risk of T2D. Conversely, a higher concentration of specific MUFAs (16:1n−7, 18:1n−9) and certain n−6 PUFAs (γ−20:3, γ−18:3, and 20:4) was associated with a higher risk of T2D. In general, findings from different biospecimens pointed in the same direction but were particularly pronounced in PPL and RBC. From a methodological perspective, our findings emphasize the importance of considering specific biospecimens for FA measurement when conducting meta-analyses.

Author contributions

The authors' responsibilities were as follows — MN, SS: designed the study question and developed the search term of the systematic review and meta-analysis; ES, MN, NS-M, TS, NI, SS: conducted the systematic literature search; ES, MN, TS, NI, SS: were involved in data acquisition; ES, MN, TS, NI, CB, SS: conducted the assessment of risk of bias; ES: conducted the statistical analyses; ES, MN, LS: rated the certainty of evidence; ES, SS: interpreted the results and drafted the first version of the manuscript; and all authors: critically reviewed and approved the submission of the final manuscript.

Conflict of interest

LS is an Editor for *Advances in Nutrition* and played no role in the journal's evaluation of the manuscript. The other authors report no conflicts of interest.

Funding

The German Diabetes Center is funded by the German Federal Ministry of Health (Berlin, Germany) and the Ministry of Culture and Science of the state North Rhine–Westphalia (Düsseldorf, Germany) and receives additional funding from the German Federal Ministry of Education and Research through the German Center for Diabetes Research (DZD e.V.). The funders had no role in the design, analysis, interpretation, or writing of this article.

Data availability

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data for this study were extracted from published meta-analyses, all of which are available and accessible.

Declaration of generative AI in scientific writing

During the preparation of this work, the author(s) used ChatGPT to improve the language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2025.100565.

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https://www.sciencedirect.com/science/article/pii/S2161831325002030

Chapter 3

Diet in the management of type 2 diabetes: umbrella review of systematic reviews with meta-analyses of randomised controlled trials

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BMJ Med, 2023, 2(1), doi: 10.1136/bmjmed-2023-000664

Summary

According to the International Diabetes Federation, diabetes complications can be prevented or delayed by maintaining blood glucose, blood pressure and cholesterol levels as close to normal as possible. Lifestyle factors, including diet, are considered as cornerstone of T2D management. Importantly, current diabetes management guidelines are based on evidence coming from studies that do not exclusively focus on T2D population, which questions their translation and applicability to this population. Over the last years, numerous RCTs investigated the effectiveness of various dietary interventions on health outcomes in people with T2D and their results have been summarized in meta-analyses. Thus, we aimed to conduct an umbrella review in order to summarize all evidence from systematic reviews and meta-analyses of RCTs on the effectiveness of any dietary interventions on health outcomes among persons with existing T2D.

Out of 25,221 articles identified, full texts of 764 were screened. We included 88 publications with 312 meta-analyses of RCTs. A vast majority (77%) of the included publications was assessed as very low to low, while 23% as moderate to high methodological quality. We identified robust evidence for beneficial effect of liquid meal replacement on body weight reduction (mean difference -2.37 kg (95% CI -3.30; -1.44) and BMI (-0.87 kg/m^2 (-1.32; -0.43)), as well as of low-carbohydrate diet on HbA1c (-0.47% (-0.60; -0.34)) and triglycerides levels (-0.30 mmol/l (-0.43; -0.17)). Beneficial effects of liquid meal replacement, plant-based, Mediterranean, high-protein, low glycaemic index, and low-carbohydrate diets (<26% total energy) in terms of various cardiometabolic measures were also identified with moderate CoE. Furthermore, omega-3 FAs supplementation led to lower risk of major cardiovascular events (summarized relative risk 0.94 (0.87; 1.02)). Remaining dietary interventions had low to very low certainty of evidence.

To summarize, our study showed that persons with T2D can implement various dietary strategies to improve health outcomes. As for body weight reduction, energy restriction, particularly through liquid meal replacement, appears to be the most effective approach. Beyond energy restriction, dietary approaches such as plant-based, Mediterranean, low-carbohydrate, or high-protein diets, and a higher intake of omega-3 FAs can be favourable for cardiometabolic health in individuals with T2D.

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Diet in the management of type 2 diabetes: umbrella review of systematic reviews with meta-analyses of randomised controlled trials

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2023-000664).

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Cite this as: *BMJMED* 2023;2:e000664. doi:10.1136/bmjmed-2023-000664

Received: 5 June 2023
Accepted: 29 September 2023

ABSTRACT

OBJECTIVE To systematically summarise and evaluate the existing evidence on the effect of diet on the management of type 2 diabetes and prevention of complications.

DESIGN Umbrella review of systematic reviews with meta-analyses of randomised controlled trials.

DATA SOURCES PubMed, Embase, Epistemonikos, and Cochrane, from inception up to 5 June 2022.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Systematic reviews with meta-analyses of randomised controlled trials reporting summary effect estimates on the effect of diet on any health outcome in populations with type 2 diabetes were included in the review. Only meta-analyses with randomised controlled trials with the duration of at least 12 weeks were eligible for inclusion. Summary data were extracted by two investigators independently. Summary effect estimates with 95% confidence intervals were recalculated with a random effects model if the information provided was insufficient. Methodological quality was assessed with the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 tool and the certainty of evidence with the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) approach.

RESULTS 88 publications with 312 meta-analyses of randomised controlled trials were included. Methodological quality was high to moderate in 23% and low to very low in 77% of the included publications. A high certainty of evidence was found for the beneficial effects of liquid meal replacement on reducing body weight (mean difference −2.37 kg, 95% confidence interval −3.30 to −1.44; n=9 randomised controlled trials included in the meta-analysis) and body mass index (−0.87, −1.32 to −0.43; n=8 randomised controlled trials), and of a low carbohydrate diet (<26% of total energy) on levels of haemoglobin A_{1c} (−0.47%, −0.60% to −0.34%; n=17 randomised controlled trials) and triglycerides (−0.30 mmol/L, −0.43 to −0.17; n=19 randomised controlled trials). A moderate certainty of evidence was found for the beneficial effects of liquid meal replacement, plant based, Mediterranean, high protein, low glycaemic index, and low carbohydrate diets (<26% total energy) on various cardiometabolic measures. The remaining results had low to very low certainty of evidence.

CONCLUSIONS The evidence indicated that diet has a multifaceted role in the management of type 2 diabetes. An energy restricted diet can reduce body weight and improve cardiometabolic health. Beyond energy restriction, dietary approaches such as plant based, Mediterranean, low carbohydrate (<26% total energy), or high protein diets, and a higher intake of omega 3 fatty acids can be beneficial for cardiometabolic health in individuals with type 2 diabetes.

SYSTEMATIC REVIEW REGISTRATION PROSPERO CRD42021252309.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type 2 diabetes is a major global health problem that can cause further health complications
⇒ Diet is essential in managing type 2 diabetes and preventing further diabetes related complications
⇒ To provide evidence based dietary recommendations for people with type 2 diabetes, the existing evidence needs to be systematically summarised and evaluated with established tools

WHAT THIS STUDY ADDS

⇒ This umbrella review of systematic reviews with meta-analyses of randomised controlled trials identified the dietary factors that can improve surrogate markers of disease and health in people with type 2 diabetes
⇒ Robust evidence indicated that in addition to energy restriction, dietary approaches, such as plant based, Mediterranean, low carbohydrate (<26% total energy), and high protein diets are beneficial for cardiometabolic health in individuals with type 2 diabetes

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This study identified the dietary recommendations that can be effective in improving surrogate markers of disease and health in people with type 2 diabetes
⇒ More randomised controlled trials with long term interventions, focusing exclusively on complications related to type 2 diabetes, are needed to provide robust evidence based recommendations for other dietary factors in the management of type 2 diabetes

Introduction

Type 2 diabetes is a major global health problem. In 2021, the International Diabetes Federation estimated that a total of 536.6 million individuals worldwide lived with diabetes, and this number is expected to increase.[1] Type 2 diabetes carries a huge financial burden on health systems and people with diabetes.[2 3] Type 2 diabetes is typically associated with obesity, abnormalities of lipid metabolism, and an increased risk of numerous complications and comorbidities.[4 5] These include cardiovascular and liver disease, kidney disease, diabetes related eye disease, and lower limb amputations.[6 7] Also, people with type 2 diabetes have about a 2.5 times higher risk of all cause mortality than people without diabetes.[8 9]

Lifestyle factors, such as diet, form the basis of the management of type 2 diabetes,[1 4 10] and over the past decades, the effects of different diets on managing type 2 diabetes have been studied. Meta-analyses of randomised controlled trials showed that Mediterranean,[11] vegetarian,[12] and ketogenic diets[13] lowered levels of haemoglobin A_{1c} (HbA_{1c}), whereas a higher intake of dietary fibre[14] and soy isoflavones,[15] and magnesium supplementation[16] improved concentrations of blood lipids. These findings suggest that changes in diet might be important for preventing further complications and progression of disease in individuals with type 2 diabetes. To provide evidence based dietary recommendations, however, the existing evidence needs to be systematically summarised and evaluated based on state-of-the-art approaches.

So far, several umbrella reviews have been conducted summarising the evidence on selected dietary factors and specific outcomes in diabetes.[17–20] None of the previous umbrella reviews, however, included meta-analyses with randomised controlled trials lasting at least 12 weeks,[17–20] not all focused exclusively on people with type 2 diabetes,[18] and not all assessed the certainty of evidence with the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) approach.[19] There is an urgent need to summarise all available evidence on this topic and, most importantly, to assess the certainty of evidence using the GRADE approach. Our aim in this umbrella review was to systematically summarise the most recent evidence on dietary interventions, including dietary patterns, food groups, and dietary supplements, on health outcomes in people with type 2 diabetes. The evidence was derived from systematic reviews with meta-analyses of randomised controlled trials that lasted at least 12 weeks. We also evaluated the certainty of evidence of these effects.

Methods

This umbrella review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[21] and the preferred reporting items for overviews of reviews (PRIOR statement) for healthcare interventions.[22]

Literature search

A systematic literature search was conducted in PubMed, Embase, Cochrane, and Epistemonikos, with predefined search terms, from inception to 24 April 2021, with an update on 23 May 2022. None of the studies included in the in 2021 screening were exclusively from Embase, and therefore this database was omitted from the update in 2022. No filters were applied during the literature search process. Online supplemental table S1 shows the detailed search strategies. We also reviewed studies received from PubMed Alert at weekly intervals up to 5 June 2022 and screened the reference lists of all included publications. The literature search originally identified meta-analyses of prospective cohort studies and randomised controlled trials, but for this study, we focused on meta-analyses of randomised controlled trials. The literature screening was conducted by two authors independently. Disagreements were resolved by consensus with a third author.

Eligibility criteria

The systematic reviews with (network) meta-analyses of randomised controlled trials included in our study met the following criteria: the effects of dietary factors (dietary patterns, food groups, and dietary supplements) were investigated; the intervention in randomised controlled trials lasted ≥12 weeks for any health outcome (eg, mortality, incidence of cardiovascular disease, body weight, levels of HbA_{1c}, and heath related quality of life); only individuals with type 2 diabetes were included; effect estimates were reported (eg, for continuous outcomes, mean difference or standardised mean difference with corresponding 95% confidence intervals, or standard error; or for dichotomous outcomes, risk ratio, including hazard ratio or odd ratio, with 95% confidence intervals).

We excluded studies that were not systematic (including narrative reviews), not meta-analyses, not based exclusively on populations with type 2 diabetes, and single study findings. We also excluded publications reporting on alternative dietary treatments or medical nutrition (eg, Chinese medicine, plant extracts, herbs, and Ramadan fasting), and meta-analyses of randomised controlled trials with exclusively active control groups (comparing two intervention arms with each other). We did not exclude studies based on the publication language.

If we identified more than one meta-analysis on the same effect, we chose one meta-analysis for each intervention to avoid inclusion of duplicate results. In this case, we included the meta-analysis with the largest number of randomised controlled trials and participants. If more than one meta-analysis had the same number of randomised controlled trials, we selected the meta-analysis with the largest number of participants. Because we only included meta-analyses that were based on a systematic literature search, we assumed that newer and larger meta-analyses included the same randomised controlled trials as older and smaller meta-analyses looking at the same research question. We always prioritised evidence from direct comparisons over network meta-analyses.

Data extraction

Data were extracted by one author and double checked by a second author. Discrepancies were discussed between the authors, involving a third author if necessary. Data extracted from each publication were name of the first author, publication year, intervention type, comparison, outcome, duration of

Table 1 | Summary of results with high to moderate certainty of evidence from umbrella review of systematic reviews with meta-analyses of randomised controlled trials on diet in the management of type 2 diabetes

Outcomes	Type of dietary intervention	Effect estimates (mean difference, risk ratio, or risk difference (95% CI))	Certainty of evidence*
Changes within the clinically meaningful range			
Body weight (kg)	► Liquid meal replacement	−2.37 (−3.30 to −1.44)	High ⊕⊕⊕⊕
	► 10% decrease in carbohydrate intake	−1.34 (−1.77 to −0.91)	Moderate ⊕⊕⊕◯
Body mass index	► Liquid meal replacement	−0.87 (−1.32 to −0.43)	High ⊕⊕⊕⊕
	► Plant based diet	−1.13 (−1.88 to −0.38)	Moderate ⊕⊕⊕◯
Waist circumference (cm)	► Liquid meal replacement	−2.24 (−3.71 to −0.76)	Moderate ⊕⊕⊕◯
	► Plant based diet	−2.41 (−3.50 to −1.32)	Moderate ⊕⊕⊕◯
Haemoglobin A_{1c} (%)	► Low carbohydrate diet (<26% total energy)	−0.47 (−0.60 to −0.34)	High ⊕⊕⊕⊕
Fasting blood glucose (mmol/L)	► Liquid meal replacement	−0.63 (−0.99 to −0.27)	Moderate ⊕⊕⊕◯
	► Ginger	−1.18 (−1.47 to −0.88)	Moderate ⊕⊕⊕◯
	► Psyllium	−1.78 (−2.33 to −1.23)	Moderate ⊕⊕⊕◯
Fasting insulin (μIU/mL)	► Liquid meal replacement	−1.97 (−3.88 to −0.07)	Moderate ⊕⊕⊕◯
HOMA-IR	► Cocoa	−0.82 (−1.38 to −0.25)	Moderate ⊕⊕⊕◯
	► Probiotics	−0.90 (−1.34 to −0.46)	Moderate ⊕⊕⊕◯
	► Anthocyanin	−1.08 (−1.86 to −0.30)	Moderate ⊕⊕⊕◯
Triglycerides (mmol/L)	► Low carbohydrate diet (<26% total energy)	−0.30 (−0.43 to −0.17)	High ⊕⊕⊕⊕
	► Mediterranean diet	−0.41 (−0.72 to −0.10)	Moderate ⊕⊕⊕◯
Total cholesterol (mmol/L)	► High protein diet (>25% total energy)	−0.21 (−0.31 to −0.11)	Moderate ⊕⊕⊕◯
	► Soy protein	−0.19 (−0.33 to −0.05)	Moderate ⊕⊕⊕◯
	► Psyllium	−0.24 (−0.31 to −0.16)	Moderate ⊕⊕⊕◯
Low density lipoprotein cholesterol (mmol/L)	► High protein diet (>25% total energy)	−0.10 (−0.18, -0.02)	Moderate ⊕⊕⊕◯
	► Low glycaemic index diet	−0.23 (−0.37 to −0.09)	Moderate ⊕⊕⊕◯
	► Soy protein	−0.18 (−0.31 to −0.05)	Moderate ⊕⊕⊕◯
High density lipoprotein cholesterol (mmol/L)	► Low carbohydrate diet (<26% total energy)	0.06 (0.01 to 0.10)	Moderate ⊕⊕⊕◯
Systolic blood pressure (mm Hg)	► Liquid meal replacement	−4.97 (−7.32 to −2.62)	Moderate ⊕⊕⊕◯
Diastolic blood pressure (mm Hg)	► Liquid meal replacement	−1.98 (−3.05 to −0.91)	Moderate ⊕⊕⊕◯
Reduced use of drug treatments	► Low carbohydrate diet (<26% total energy)	Risk ratio 0.24 (0.12 to 0.35)	Moderate ⊕⊕⊕◯
Changes not within the clinically meaningful range			
Body weight (kg)	► Mediterranean diet	−0.25 (−0.99 to 0.49)	Moderate ⊕⊕⊕◯
Body mass index	► Almonds	−0.36 (−0.53 to −0.20)	Moderate ⊕⊕⊕◯
Haemoglobin A_{1c} (%)	► 10% decrease in carbohydrate intake	−0.11 (−0.17 to −0.04)	High ⊕⊕⊕⊕
	► Non-nutritive sweeteners	0.02 (−0.13 to 0.17)	Moderate ⊕⊕⊕◯
Fasting blood glucose (mmol/L)	► Almonds	−0.03 (−0.17 to 0.12)	Moderate ⊕⊕⊕◯
QUICKI	► Vitamin D	0.02 (0.01 to 0.03)	Moderate ⊕⊕⊕◯
Triglycerides (mmol/L)	► 10% decrease in carbohydrate intake	−0.12 (−0.22 to −0.01)	High ⊕⊕⊕⊕
	► Moderate carbohydrate diet (<40% total energy)	−0.13 (−0.24 to −0.02)	Moderate ⊕⊕⊕◯
Low density lipoprotein cholesterol (mmol/L)	► Liquid meal replacement	0.02 (−0.10 to 0.14)	Moderate ⊕⊕⊕◯
	► 10% decrease in carbohydrate intake	−0.03 (−0.08 to 0.02)	Moderate ⊕⊕⊕◯
	► Low glycaemic index or glycaemic load diet	−0.26 (−0.43 to −0.09)	Moderate ⊕⊕⊕◯
Non-high density lipoprotein cholesterol (mmol/L)	► Liquid meal replacement	−0.02 (−0.11 to 0.07)	Moderate ⊕⊕⊕◯
High density lipoprotein cholesterol (mmol/L)	► All types of carbohydrate restriction	−0.04 (−0.08 to −0.00)	Moderate ⊕⊕⊕◯
	► Low glycaemic index or glycaemic load diet	−0.02 (−0.07 to 0.03)	Moderate ⊕⊕⊕◯
	► Low fat diet (<30% total energy)	0.01 (−0.03 to 0.05)	Moderate ⊕⊕⊕◯
Systolic blood pressure (mm Hg)	► All types of carbohydrate restriction	0.03 (−1.77 to 1.84)	Moderate ⊕⊕⊕◯
	► Ginger	−0.11 (−1.10 to 0.88)	Moderate ⊕⊕⊕◯
Diastolic blood pressure (mm Hg)	► Moderate carbohydrate diet (<40% total energy)	−0.21 (−1.21 to 0.79)	Moderate ⊕⊕⊕◯
Blood urea nitrogen (mg/dL)	► Probiotics	−1.22 (−1.94 to −0.51)	Moderate ⊕⊕⊕◯
C reactive protein (standardised mean difference)	► Resveratrol	−0.87 (−1.11 to −0.63)	Moderate ⊕⊕⊕◯
Major cardiovascular events	► Omega 3 fatty acids	Risk difference 0.94 (0.87 to 1.02)	High ⊕⊕⊕⊕

CI=confidence interval; HOMA-IR=homeostatic model assessment-insulin resistance; QUICKI=quantitative insulin sensitivity check index.
*Assessed with the GRADEpro tool.

the study, number and study design of randomised controlled trials, and number of participants in the intervention groups. Online supplemental table S2 lists the definitions and cut-off values for categorising dietary patterns in terms of the amount of energy derived from macronutrients. We also extracted summary effect estimates (mean difference, standardised mean difference, or risk ratio) with corresponding 95% confidence intervals, the statistical model used (fixed effect or random effects model), a measure of inconsistency between randomised controlled trials (I^2), publication bias, risk of bias, and certainty of evidence (if assessed according to the GRADE approach). Online supplemental table S2 has further details on data extraction.

Assessment of methodological quality and certainty of evidence

The methodological quality of each included publication was assessed with the validated A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 by two reviewers independently.[23] Online supplemental table S3 lists a detailed description of the tool, included domains, and grading system.

The certainty of evidence was evaluated with the GRADEpro tool.[24 25] GRADE rates the certainty of evidence as high, moderate, low, or very low. A high certainty of evidence means that it is very likely that the true effect lies on one side of a specified threshold or within a chosen range, a moderate certainty of evidence indicates moderate confidence that the true effect lies on one side of a specified threshold or within a chosen range and further studies might change the results, and low or very low certainty of evidence means that confidence in the meta-evidence available is limited.[26 27] Three reviewers, in pairs of two, independently rated the certainty of the evidence. Online supplemental table S4 lists a detailed description of the grading of the certainty of evidence.

Data analysis

For meta-analyses that used a random effects model and provided I^2 values and forest plots, we extracted the reported summary effect estimates with 95% confidence intervals. For meta-analyses that used a fixed effect model, or did not provide I^2 values or forest plots, we recalculated the mean difference, standardised mean difference, and summary risk ratio with corresponding 95% confidence intervals with the random effects model by DerSimonian and Laird.[28] Information on small study effects and publications bias was extracted from the included publications or, if not reported, was assessed by funnel plots and Egger's test (if ≥10 studies were included).[29 30] Online supplemental table S5 presents further details on the statistical methods. All analyses were conducted with Stata version 14.1.

Patient and public involvement

No patients or public were involved in setting the research question, the design of the study, the interpretation of the results, or the writing of the manuscript. The results of this study will be spread to the public via social media or press release.

Results

Literature search

Of 25 221 publications, 764 eligible articles were retrieved for screening of the full text of the article (online supplemental figure S1). Online supplemental table S6 lists the excluded studies and the reasons for exclusion. We identified 88 eligible publications of systematic reviews with meta-analyses of randomised controlled trials for inclusion in our umbrella review.

Description of published meta-analyses

Online supplemental table S7 presents the characteristics and results of all of the included systematic reviews with meta-analyses of randomised controlled trials. Eighty eight publications, with 310 meta-analyses of randomised controlled trials, investigated the effectiveness of dietary patterns (liquid meal replacement, energy, carbohydrate, and fat restriction, low glycaemic index and glycaemic load, high protein, Mediterranean, plant based, vegetarian, and ketogenic diets, and intermittent fasting), foods (mixed nuts, tree nuts, walnuts, almonds, blueberries and cranberries, olive oil, cocoa products, cinnamon, curcumin, ginger, soy and soy isoflavones, and non-nutritive sweeteners), nutrients (monounsaturated fatty acids, omega 3 fatty acids, α-lipolenic acid, L-carnitine, and salt), micronutrients (magnesium, chromium, and zinc), vitamins (niacin, and vitamins E, C, and D), phytochemicals (anthocyanins, flavonoids, polyphenols, and resveratrol), fibre (psyllium, soluble fibre, and guar gum), and probiotics (online supplemental table S7).

Outcomes included anthropometric, glycaemic, and lipid markers, blood pressure, kidney, liver, and inflammation parameters, as well as quality of life, reduced use of drug treatments, constipation, and major cardiovascular events. The number of participants in meta-analyses of randomised controlled trials ranged from 44 to 28 199, and intervention time from 12 weeks to 96 months. In total, 293 of the included meta-analyses were pairwise meta-analyses and 17 were network meta-analyses,[12 31] and 15% of the meta-analyses included ≥10 randomised controlled trials. Publication bias was detected for 2.2% of the results of meta-analyses of randomised controlled trials, but 59.4% of meta-analyses included ≤5 studies (online supplemental table S7).

Methodological quality was rated as high for 18% (n=16), moderate for 5% (n=4), low for 22% (n=19), and critically low for the remaining 55% (n=49) of publications (online supplemental table S8). The

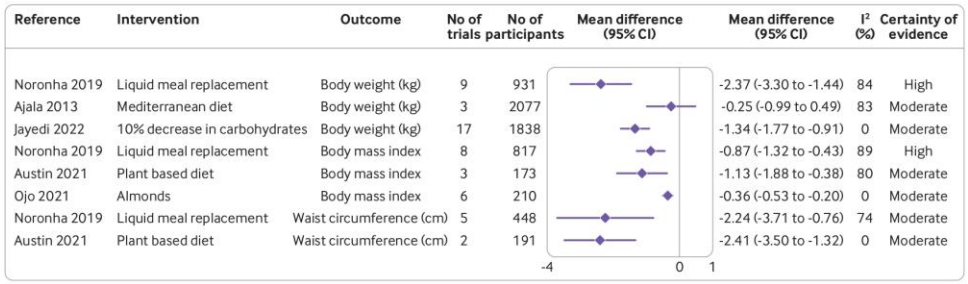

Figure 1 | Effect of different dietary factors on anthropometric measures (body weight, body mass index, and waist circumference) in people with type 2 diabetes.[32–36] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval

most common reasons for downgrading the methodological quality were missing study protocol, inappropriate methods for the search strategy (literature search only by one investigator, search strategy not shown, or included reports restricted to the English language), and lack of evaluation or discussion, or both, of the effect of risk of bias on the results.

Evidence for the effect of diet on managing type 2 diabetes: meta-analyses of randomised controlled trials

The certainty of evidence was rated as high for seven (2%), moderate for 40 (13%), low for 120 (39%), and very low for 143 (46%) outcomes (online supplemental tables S9–S32). Table 1 summarises the results of the meta-analyses with high to moderate certainty of evidence and with clinically meaningful changes. Figures 1–6 show the summary effect estimates of the included meta-analyses of randomised controlled trials with high and moderate certainty of evidence. Online supplemental figures S2–S10 show the results of meta-analyses of randomised controlled trials with low and very low certainty of evidence.

Anthropometric measures

The certainty of evidence was high for the efficacy of liquid meal replacement on clinically relevant reductions in body weight and body mass index (figure 1). Liquid meal replacement reduced body weight by 2.37 kg (95% confidence interval −3.30 to −1.44; I^2=84%; n=9 randomised controlled trials) and body mass index by 0.87 (−1.32 to −0.43; I^2=89%; n=8 randomised controlled trials) compared with a control diet.[32] Plant based diets also effectively reduced body mass index by 1.13 (−1.88 to −0.38; I^2=80%; n=3 randomised controlled trials) with moderate certainty of evidence.[33]

Moderate certainty of evidence was found for a reduction in waist circumference after liquid meal replacement (−2.24 cm, 95% confidence interval −3.71 to −0.76; I^2=74%; n=5 randomised controlled trials) and plant based diets (−2.41 cm, −3.50 to −1.32; I^2=0%; n=2 randomised controlled trials).[32 33] Improvement in anthropometric measures was also seen for a decrease in carbohydrate intake of 10%,[34] adherence to a Mediterranean diet,[35] and increased intake of almonds,[36] but effect estimates were small and not clinically relevant (figure 1). The certainty

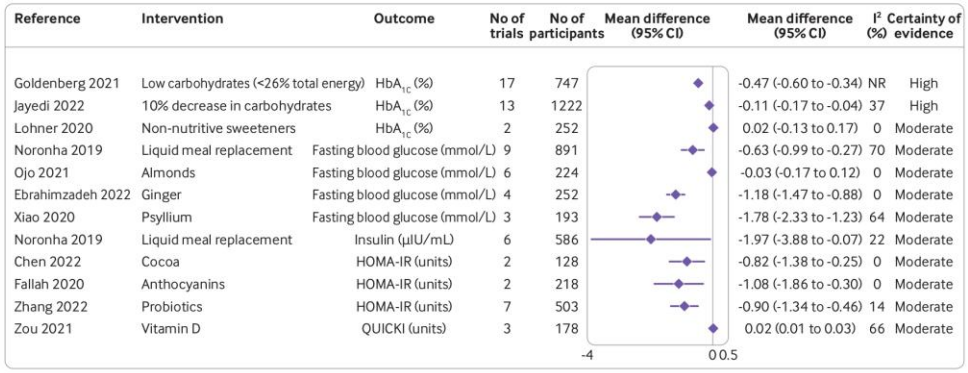

Figure 2 | Effect of different dietary factors on glycaemic measures in people with type 2 diabetes.[14 32 34 36–41 61 62] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval; HbA_{1c}=haemoglobin A_{1c}; HOMA-IR=homeostatic model assessment-insulin resistance; NR=not reported; QUICKI=quantitative insulin sensitivity check index

Reference	Intervention	Outcome	No of trials	No of participants	Mean difference (95% CI)	I² (%)	Certainty of evidence
Goldenberg 2021	Low carbohydrates (<26% total energy)	Triglycerides (mmol/L)	19	860	-0.30 (-0.43 to -0.17)	NR	High
Jayedi 2022	10% decrease in carbohydrates	Triglycerides (mmol/L)	13	1423	-0.12 (-0.22 to -0.01)	69	High
Neuenschwander 2019	Mediterranean diet	Triglycerides (mmol/L)	NMA	271	-0.41 (-0.72 to -0.10)	NA	Moderate
Korsmo-Haugen 2019	Moderate carbohydrates (<40% total energy)	Triglycerides (mmol/L)	16	1391	-0.13 (-0.24 to -0.02)	57	Moderate
Yu 2020	High protein	Total cholesterol (mmol/L)	10	968	-0.21 (-0.31 to -0.11)	73	Moderate
Baranska 2021	Soy protein or isoflavone	Total cholesterol (mmol/L)	4	597	-0.19 (-0.33 to -0.05)	0	Moderate
Xiao 2020	Psyllium	Total cholesterol (mmol/L)	2	174	-0.24 (-0.31 to -0.16)	0	Moderate
Noronha 2019	Liquid meal replacement	Low density lipoprotein cholesterol (mmol/L)	9	891	0.02 (-0.10 to 0.14)	68	Moderate
Jayedi 2022	10% decrease in carbohydrates	Low density lipoprotein cholesterol (mmol/L)	13	1901	-0.03 (-0.08 to 0.02)	9	Moderate
Ojo 2019	Low glycaemic index	Low density lipoprotein cholesterol (mmol/L)	5	422	-0.23 (-0.37 to -0.09)	8	Moderate
Neuenschwander 2019	Low glycaemic index or glycaemic load	Low density lipoprotein cholesterol (mmol/L)	NMA	446	-0.26 (-0.43 to -0.09)	NA	Moderate
Yu 2020	High protein	Low density lipoprotein cholesterol (mmol/L)	12	1036	-0.10 (-0.18 to -0.02)	78	Moderate
Baranska 2021	Soy protein or isoflavone	Low density lipoprotein cholesterol (mmol/L)	4	556	-0.18 (-0.31 to -0.05)	0	Moderate
Noronha 2019	Liquid meal replacement	Non-high density lipoprotein cholesterol (mmol/L)	9	891	-0.02 (-0.11 to 0.07)	29	Moderate
Silverii 2020	All types of carbohydrate restriction	High density lipoprotein cholesterol (mmol/L)	17	913	-0.04 (-0.08 to -0.00)	24	Moderate
Goldenberg 2021	Low carbohydrates (<26% total energy)	High density lipoprotein cholesterol (mmol/L)	16	647	0.06 (0.01 to 0.10)	NR	Moderate
Neuenschwander 2019	Low glycaemic index or glycaemic load	High density lipoprotein cholesterol (mmol/L)	NMA	430	-0.02 (-0.07 to 0.03)	NA	Moderate
Neuenschwander 2019	Low fat (<30% total energy)	High density lipoprotein cholesterol (mmol/L)	NMA	2264	0.01 (-0.03 to 0.05)	NA	Moderate

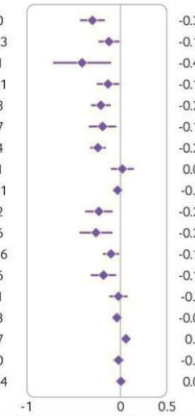

Figure 3 | Effect of different dietary factors on blood lipid measures in people with type 2 diabetes.[14 15 31 32 34 37 42–44 63] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval; NA=not available; NR=not reported; NMA=network meta-analysis

of evidence for the effect of other dietary factors was low to very low (online supplemental figure S2).

Glycaemic markers

A low carbohydrate diet (<26% total energy) produced a clinically relevant reduction in levels of HbA_{1c} of 0.47% (95% confidence interval −0.60% to −0.34%; I^2 not reported; n=17 randomised controlled trials) with a high certainty of evidence (figure 2).[37] HbA_{1c} levels were also reduced after a decrease in carbohydrate intake of 10%,[34] but the effect estimate was small and not clinically relevant.

A moderate certainty of evidence was found for reduced concentrations of fasting blood glucose after liquid meal replacement (−0.63 mmol/L, 95% confidence interval −0.99 to −0.27; I^2=70%; n=9 randomised controlled trials), and supplementation with ginger (−1.18 mmol/L, −1.47 to −0.88; I^2=0%; n=4 randomised controlled trials) and psyllium (−1.78 mmol/L, −2.33 to −1.23; I^2=64%; n=3 randomised controlled trials).[14 32 38] Liquid meal replacement reduced insulin concentrations by 1.97 µIU/mL (−3.88 to −0.07; I^2=22%; n=6 randomised controlled trials), with moderate certainty of evidence.[32] Supplementation with cocoa, probiotics, and anthocyanins decreased the homeostatic model assesment-insulin resistance (HOMA-IR) index with moderate certainty of evidence by −0.82 units (−1.38 to −0.25; I^2=0%; n=2 randomised controlled trials), −0.90 units (−1.34 to −0.46; I^2=14%; n=7 randomised controlled trials), and −1.08 units (−1.86 to −0.30; I^2=0%; n=2 randomised controlled trials), respectively.[39–41] The certainty of evidence for the effect of other dietary factors was low to very low (online supplemental figure S3).

Blood lipids

The certainty of evidence was high for a decrease in carbohydrate intake of 10% and low carbohydrate diet (<26% total energy) to lower concentrations of triglycerides by 0.12 mmol/L (95% confidence interval −0.22 to −0.01; I^2=69%; n=13 randomised controlled trials) and 0.30 mmol/L (−0.43 to −0.17; I^2 not reported; n=19 randomised controlled trials), respectively (figure 3).[34 37] Moderate carbohydrate restriction (<45% total energy) and a Mediterranean diet reduced concentrations of triglycerides by −0.13 mmol/L (−0.24 to −0.02; I^2=57%; n=16 randomised controlled trials) and −0.41 mmol/L (−0.72 to −0.10; I^2 not available;

Reference	Intervention	Outcome	No of trials	No of participants	Mean difference (95% CI)	I² (%)	Certainty of evidence
Noronha 2019	Liquid meal replacement	Systolic blood pressure (mm Hg)	7	754	-4.97 (-7.32 to -2.62)	53	Moderate
Silverii 2020	All types of carbohydrate restriction	Systolic blood pressure (mm Hg)	14	905	0.03 (-1.77 to 1.84)	8	Moderate
Ebrahimzadeh 2022	Ginger	Systolic blood pressure (mm Hg)	2	166	-0.11 (-1.10 to 0.88)	0	Moderate
Noronha 2019	Liquid meal replacement	Diastolic blood pressure (mm Hg)	7	754	-1.98 (-3.05 to -0.91)	15	Moderate
Korsmo-Haugen 2019	Moderate carbohydrates (<40% total energy)	Diastolic blood pressure (mm Hg)	12	944	-0.21 (-1.21 to 0.79)	0	Moderate

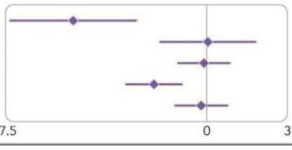

Figure 4 | Effect of different dietary factors on blood pressure in people with type 2 diabetes.[32 38 42 63] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval

Figure 5 | Effect of different dietary factors on risk reduction in people with type 2 diabetes.[37 45] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval; NR=not reported

network meta-analysis), respectively, with moderate certainty of evidence.[31 42] A moderate certainty of evidence was found for reduction in total cholesterol concentrations after a high protein diet (mean difference −0.21 mmol/L, −0.31 to −0.11; I^2=73%; n=10 randomised controlled trials), supplementation with psyllium (mean difference −0.24 mmol/L, −0.31 to −0.16; I^2=0%; n=2 randomised controlled trials), and soy protein (mean difference −0.19 mmol/L, −0.33 to −0.05; I^2=0%; n=4 randomised controlled trials).[14 15 43]

The certainty of evidence was moderate for the low density lipoprotein cholesterol lowering effect of a low glycaemic index diet (mean difference −0.23 mmol/L, 95% confidence interval −0.37 to −0.09; I^2=8%; n=5 randomised controlled trials), a high protein diet (mean difference −0.10 mmol/L, −0.18 to −0.02; I^2=78%; n=12 randomised controlled trials), and a higher intake of soy protein (mean difference −0.18 mmol/L, −0.31 to −0.05; I^2=0%; n=4 randomised controlled trials).[15 43 44] A low carbohydrate diet (<26% total energy) might increase concentrations of high density lipoprotein cholesterol with moderate certainty of evidence (mean difference 0.06 mmol/L, 0.01 to 0.10; I^2 not reported; n=16 randomised controlled trials).[37] Evidence for the effect of other dietary factors was low to very low (online supplemental figure S4).

Blood pressure

Liquid meal replacement diets reduced both systolic and diastolic blood pressure by 4.97 mm Hg (95% confidence interval −7.32 to −2.62; I^2=53%; n=7 randomised controlled trials) and 1.98 mm Hg (−3.05 to −0.91; I^2=15%; n=7 randomised controlled trials), respectively, with moderate certainty of evidence (figure 4).[32] Evidence for the effect of other dietary factors was low to very low (online supplemental figure S5).

Other outcomes

A high certainty of evidence was found for supplementation with omega 3 fatty acids and risk of major cardiovascular events, but the 95% confidence interval was imprecisely estimated and the risk reduction was marginal (figure 5; summary risk ratio 0.94, 0.87 to 1.02; I^2=20%; n=3 randomised controlled trials).[45] A low carbohydrate diet (<26% total energy) reduced the use of drug treatments by an additional 24 per 100 individuals (risk difference 0.24, 0.12 to 0.35; I^2 not reported; n=7 randomised controlled trials, moderate certainty of evidence).[37] Probiotic supplements reduced concentrations of blood urea nitrogen, a marker of kidney function (mean difference −1.22 mg/dL, −1.94 to −0.51; I^2=0%; n=4 randomised controlled trials). Supplementation with resveratrol reduced concentrations of C reactive protein (standardised mean difference −0.87, −1.11 to −0.63; I^2=0%; n=3 randomised controlled trials), with moderate certainty of evidence (figure 6).[46 47] Evidence for the effect of other dietary factors was low to very low (online supplemental figures S2–S10).

Discussion

Main findings

In this umbrella review, we included 88 publications, with 310 meta-analyses of randomised controlled trials for different dietary factors and health outcomes, mainly surrogate markers of disease and health, in populations with type 2 diabetes. We found a high certainty of evidence and clinically important changes for liquid meal replacement diets in reducing body weight and body mass index, as well as for a low carbohydrate diet (<26% total energy) in lowering levels of HbA_{1c} and triglycerides. A moderate certainty of evidence with clinically important changes was found for plant based diets and reduced anthropometric measures; liquid meal replacement diets, and supplementation with

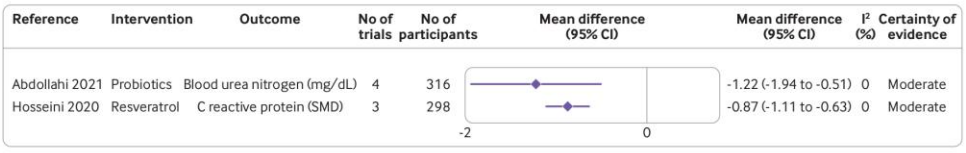

Figure 6 | Effect of different dietary factors on other outcomes in people with type 2 diabetes.[46 47] Results from meta-analyses of randomised controlled trials with high to moderate certainty of evidence. CI=confidence interval; SMD=standardised mean difference

fibre, ginger, anthocyanins, or probiotics improved glycaemic measures; and a high protein diet, soya, or fibre improved blood lipids. For other results, no clinically relevant differences were found or the certainty of evidence was low or very low.

Comparison with existing dietary guidelines

Dietary interventions based on energy restriction for weight loss are the focus of current guidelines for the management of type 2 diabetes.[48–53] Clinically important weight loss of 5-10% can improve insulin sensitivity, glycaemic control, blood pressure, and dyslipidaemia.[48 49 53] Also, the guidelines suggest that low calorie meal replacement plans are relatively easy to adhere to and allow for clinically significant weight loss in people with type 2 diabetes.[48 50 53] We found a reduction in body weight of 2.4 kg after at least 12 weeks of liquid meal replacement diet.

Current guidelines for type 2 diabetes recommend vegetarian or plant based diets and Mediterranean diets for reducing body weight.[48 49 52] Our umbrella review confirmed the beneficial effect of plant based diets on reducing body mass index and waist circumference. Also, some of the current guidelines conclude that short term low carbohydrate interventions have a beneficial effect on anthropometric measures, but no clear recommendations exist for the amount of carbohydrates that should be restricted.[48 49] Our study showed that a decrease in body weight was greater in interventions with low (<26% total energy) or very low (<15% total energy) carbohydrate intake than in interventions with moderate (<45% total energy) carbohydrate intake for at least 12 weeks.

We found a low certainty of evidence for the effects of a Mediterranean or plant based diet on glycaemic measures. Our findings of the beneficial effect of low carbohydrate diets on levels of HbA_{1c}, however, are in line with current guidelines.[49 50] Increased intake of dietary fibre is emphasised in all guidelines, and our results are consistent with the positive effect of fibre rich foods, especially psyllium supplements, on fasting blood glucose levels.[49 53] Adding to the current guidelines, we identified a moderate certainty of evidence for the beneficial effects of ginger supplements, as a plant, capsule, or powder, on fasting blood glucose levels, and the potential importance of polyphenols or polyphenol rich products (eg, cocoa) on HOMA-IR.

Our umbrella review supports evidence of the beneficial effects of a Mediterranean diet on triglyceride levels, but we found only a low certainty of evidence for its effect in reducing levels of high and low density lipoprotein cholesterol. In agreement with current guidelines, we also found beneficial effects of low carbohydrate and low glycaemic index diets on levels of triglycerides and low and high density lipoprotein cholesterol, and of higher fibre intake on levels of total cholesterol.[48–50 53] Current Canadian, German, and European guidelines recommend no change in protein intake, which for most people with normal kidney function is 15-20% and 10-25% of total energy.[48 50 53] Thus our findings of a beneficial effect of a high protein diet (>25% total energy) on levels of total cholesterol and low density lipoprotein cholesterol provide novel evidence in this context. A previous meta-analysis, however, showed that the health benefits are from an increased intake of plant based rather than animal based protein sources.[54] Furthermore, our study provides evidence of the beneficial effects of soy proteins on levels of total cholesterol and low density lipoprotein cholesterol. Pulses are considered a good alternative to meat and a good source of fibre and are therefore recommended for controlling levels of blood lipids.[48 50]

In common with current guidelines, we found insufficient evidence to recommend reducing total fat intake to improve cardiometabolic measures in people with type 2 diabetes.[48 50] American and European guidelines recommend a higher intake of monounsaturated and polyunsaturated fatty acids to improve glucose metabolism, but the evidence supporting this recommendation, according to our results, is weak.[49 53] We found that studies of supplementation with monounsaturated or polyunsaturated fatty acids showed improvements in levels of HbA_{1c} and insulin, and in HOMA-IR, but the estimates were imprecisely estimated and the number of participants included was small (≤800). Also, a subgroup analysis comparing different doses of omega 3 fatty acid supplements was performed in one meta-analysis,[45] and a stronger risk reduction of major cardiovascular events was seen in the group receiving >3 g/day of omega 3 fatty acids, whereas no precisely estimated effect was found in the group receiving lower doses. This finding might explain the observed effect of omega 3 fatty acids on the incidence of major cardiovascular events in people with type 2 diabetes in our umbrella review. Moreover, a recent systematic review and meta-analysis of randomised controlled trials with an intervention duration of at least 3.9 years showed that supplementation with omega 3 fatty acids reduced cardiovascular events in people with type 1 and type 2 diabetes (risk ratio 0.93, 95% confidence interval 0.90 to 0.97; n=8 randomised controlled trials). The effect was marginal but precisely estimated.[55]

Strengths and limitations

Our study has several strengths. Our umbrella review included meta-analyses of all possible dietary interventions and their effect on many health outcomes in populations with type 2 diabetes. We summarised the evidence from randomised controlled trials that lasted at least 12 weeks, giving a more reliable assessment of the effectiveness of the interventions. We recalculated the results of meta-analyses that used a fixed effect model, or did not provide I^2 values or forest plots, to ensure valid meta-estimates with 95% confidence intervals to provide an evaluation of the certainty of evidence based on the GRADEpro

approach. Finally, we detected gaps in the evidence that indicate the need for future research.

The main limitation of our umbrella review was that recently published randomised controlled trials not yet included in systematic reviews and meta-analyses were not considered in our report.[56–58] Also, we did not explore subgroup analyses (eg, by sex, race, or duration of diabetes) or sensitivity analyses (eg, excluding studies with a high risk of bias). We used the DerSimonian and Laird approach[28] for recalculation of extracted estimates with the random effects meta-analyses, but the Hartung and Knapp method might perform better in terms of more adequate error rates, especially when the number of studies was small.[59]

In terms of the limitations of the publications included in our umbrella review, studies of interventions lasting at least 12 weeks provide more reliable estimates than shorter trials, but these studies do not represent long term interventions. Also, the number of randomised controlled trials in most meta-analyses was small (13 meta-analyses with ≥10 randomised controlled trials). Consequently, the number of participants was also low (n<800 for 83% of meta-analyses of randomised controlled trials). This limitation was one of the main reasons for downgrading the certainty of evidence because of imprecision. Other reasons for downgrading the certainty of evidence were the high risk of bias in the randomised controlled trials and inconsistency of the results. Furthermore, the methodological quality of most included publications was low to very low.

In meta-analyses of randomised controlled trials, a high risk of bias caused by lack of blinding of participants to the dietary intervention is a concern. For dietary interventions based on health promoting changes in diet (eg, advice on a Mediterranean diet, where participants are actively instructed and encouraged to change their diet), however, blinding to the intervention might not be feasible. Furthermore, low compliance with the assigned dietary regimens and high dropout rates were commonly seen in randomised controlled trials, especially for low carbohydrate and ketogenic diets,[60] potentially resulting in underestimation of their actual effect. For example, one meta-analysis found greater clinically significant weight loss in those with greater adherence than in those with lower adherence to a very low carbohydrate diet,[37] and another meta-analysis reported inadequate compliance with the ketogenic diet, as assessed by urinary measurements of ketones.[13] Systematic reviews of other dietary interventions lacked a description of compliance with the intervention. Also, study arms did not always receive isocaloric diets, making it difficult to differentiate between the effects of change in dietary patterns, foods, or nutrients on the reduction in energy intake. Some of the meta-analyses conducted subgroup analyses, however, and did not find differences when calories were restricted or matched with controls in the trials.[33 34 37]

Study implications

Robust evidence exists that in people with type 2 diabetes, liquid meal replacements decrease energy intake and thus body weight. For people who prefer a dietary approach, plant based or carbohydrate restricted diets are also effective in reducing anthropometric measure. Other dietary regimens, such as a ketogenic diet or intermittent fasting, reduced body weight, but the certainty of evidence was low or very low.

Many dietary interventions effectively improved glycaemic measures, but the certainty of the evidence was robust only for liquid meal replacement diets and restricting carbohydrates. Intake of fibre rich foods, polyphenols, probiotics, and ginger was also beneficial for glycaemic control. For control of blood lipids, a low carbohydrate (<26% total energy), Mediterranean, or high protein diet is recommended for people with type 2 diabetes, with the advice to change the protein source to plant based alternatives. Energy restriction was the only effective approach in reducing blood pressure with robust evidence. Restriction of salt intake also showed beneficial effects, but the certainty of evidence was very low and thus recommendations cannot be made from the current body of evidence.

For clinical outcomes, robust evidence exists only for a low carbohydrate diet and reduction in the use of drug treatments. For other outcomes, including kidney function parameters, inflammatory markers, liver enzymes, and patient relevant outcomes (eg, remission of diabetes, health related quality of life, and incidence of cardiovascular disease), meta-analyses are already available, but the certainty of evidence was rated as low or very low, and definitive conclusions on these findings cannot be drawn. In summary, people with type 2 diabetes can be advised to reduce their energy intake if they have obesity or overweight, decrease their carbohydrate intake, or increase their consumption of foods from plant sources (especially plant based proteins) or from Mediterranean-style diets (foods high in polyunsaturated fatty acids, such as fish and nuts, or foods high in polyphenols, such as fruit, vegetables, and legumes).

To strengthen the certainty of evidence for many of the findings on diet and the management of type 2 diabetes and its complications, future studies with a low risk of bias are needed. More randomised controlled trials should investigate the effects of long term (at least six months) dietary interventions, as well as considering isocaloric comparisons between intervention and control arms. Also, more research on dietary patterns (eg, DASH (dietary approaches to stop hypertension), Nordic, and portfolio diets), fasting approaches, single foods (eg, dairy products, fish, or meat), and single nutrients (eg, specific fatty acids) is needed. Finally, future systematic reviews and meta-analyses should follow current guidelines for conducting and reporting on included studies

(eg, reports should be transparent about the methods used and critically examine the effect of risk of bias on meta-findings).

Conclusions

In this umbrella review, we identified the dietary factors with robust evidence of health benefits, expressed as surrogate disease and health markers in people with type 2 diabetes. An energy restricted diet can reduce body weight and improve cardiometabolic health. In addition to energy restriction, dietary approaches, such as a plant based, Mediterranean, low carbohydrate (<26% total energy), or high protein diet, are beneficial for cardiometabolic health in individuals with type 2 diabetes. For evidence based recommendations of the effectiveness of other dietary factors in the management of type 2 diabetes, more randomised controlled trials and systematic reviews with meta-analyses focusing on long term interventions are needed.

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Acknowledgements We thank Andrew Reynolds, Department of Medicine, University of Otago, Dunedin, New Zealand; Grace Austin, Hunter Medical Research Institute, University of Newcastle, New Lambton, Australia; Likun Ma, Department of Cardiology, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; Eunyoung Kim, Evidence-Based and Clinical Research Laboratory, Department of Health, Social, and Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul, Republic of Korea; Kaijian Hou, Endocrine Department, Longhu Hospital, First Affiliated Hospital of Shantou University Shantou City, China; Shaun Mason, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Victoria, Australia; Jean-Philippe Drouin-Chartier, Department of Nutrition, Harvard T H Chan School of Public Health, Boston, MA, USA; and Sakineh Shab-Bidar, Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, for sending additional data needed for the meta-analysis.

Contributors SS designed the research. ES and TS conducted the literature search and literature screening. ES and TS extracted the data. ES, AS-P, and TS assessed the methodological quality of the included publications. ES, SS, and LS evaluated the certainty of evidence. ES, JB, and SS analysed the data and wrote the first draft of the paper. All authors interpreted the data, read the manuscript, and approved the final version. ES and SS are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria were omitted. Transparency: The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Funding The German Diabetes Centre is funded by the German Federal Ministry of Health and the Ministry of Innovation, Science, Research, and Technology of the State North Rhine Westphalia. This study was also supported in part by a grant from the German Federal Ministry of Education and Research to the German Centre for Diabetes Research. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the German Federal Ministry of Health and the Ministry of Innovation, Science, Research, and Technology of the State North Rhine Westphalia, and the German Federal Ministry of Education and Research for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Not required because only (secondary) data from published studies were used.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data are available upon reasonable request. All data for this study were extracted from published meta-analyses, all of which are available and accessible.

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2023-000664).

Online supplementary information can be accessed at the following link:
https://bmjmedicine.bmj.com/content/2/1/e000664#supplementary-materials

Chapter 4

Dietary Factors and All-Cause Mortality in Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Prospective Observational Studies

Janett Barbaresko, Alexander Lang, Edyta Szczerba, Christina Baechle, Julia Beckhaus, Lukas Schwingshackl, Manuela Neuenschwander, Sabrina Schlesinger

Diabetes Care, 2023, 46(2): 469-477, doi: 10.2337/dc22-1018

Summary

People with T2D are at increased risk of premature mortality. Current dietary recommendations are largely based on studies not exclusively conducted in T2D population and often rely on surrogate markers, as long-term evidence from observational studies on diet-health associations is limited. Single prospective cohort studies have shown that adherence to dietary patterns such as the Mediterranean or DASH diet, as well as higher consumption of vegetables, fruit, and protein, has been associated with a reduced risk of mortality in this population. However, the impact of specific dietary factors on mortality in T2D has not yet been comprehensively summarized. Therefore, in this study we aimed to conduct a systematic review with meta-analysis on associations between various dietary factors, incuding dietary patterns, food groups, foods, macro- and micronutrients, and secondary plant compounds, and the risk of all-cause mortality in individuals with T2D derived from prospective observational studies and evaluate the CoE of these associations.

From 28,251 identified articles, 1,028 full-texts were assessed, and 107 studies were eligible for inclusion. The vast majority of studies (n=87) were judged to have a serious risk of bias, primarly due to the confounding domain. We found moderate CoE for inverse associations between higher fish and whole grain intake and all-cause mortality risk (per 1 serving fish /week: 0.95 (0.92; 0.99), per 20g whole grain/d: 0.84 (0.71; 0.99)). Higher intakes of fiber (per 5 g/d: 0.86 (0.81; 0.91)), MUFA (per 10 g/d: 0.91 (0.80; 1.03)) and n-3 PUFA (per 0.1 g/d: 0.87 (0.82; 0.92)) were also inversely associated with all-cause mortality, whereas higher animal protein intake was linked to an increased risk (per 40 g/d: 1.05 (0.99; 1.13)). Additionally, higher intakes of vegetables, plant-based protein, or coffee were inversely associated, and higher egg and cholesterol intake were positively associated with all-cause mortality risk; however, the CoE for these associations was low to very low.

In order to improve long-term health outcomes in this population, dietary strategies should emphasize higher intakes of fish, whole grains, fiber, and n-3 PUFAs while limiting animal protein. Further studies are needed to strengthen these associations and to provide evidence on additional dietary factors and mortality risk in people with T2D.

Diabetes Care
American Diabetes Association

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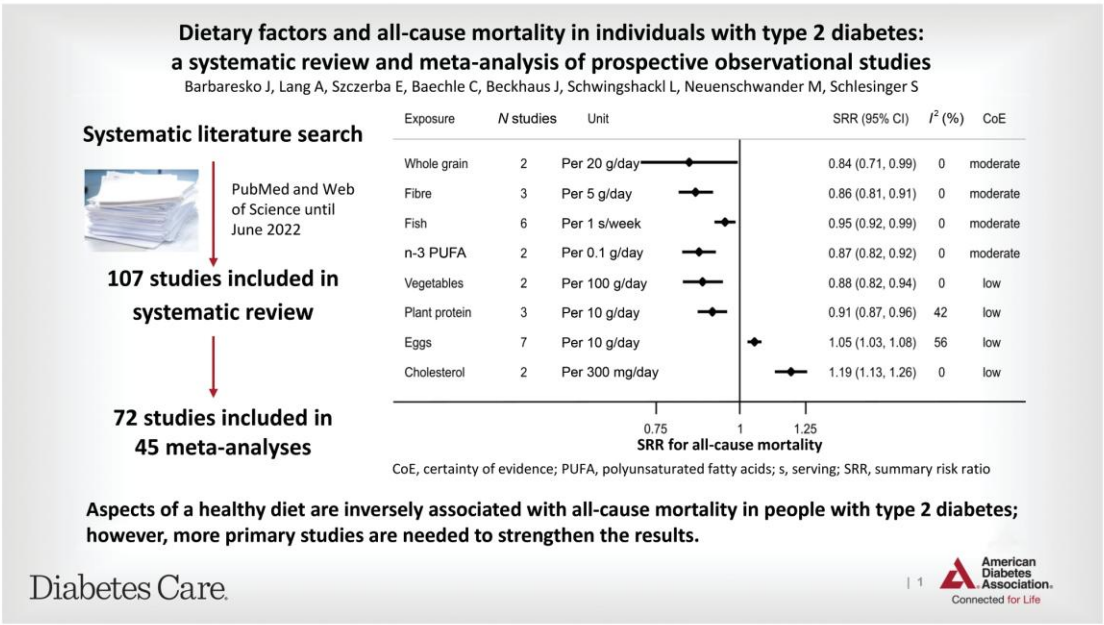
Diabetes Care 2023;46(2):469–477 | https://doi.org/10.2337/dc22-1018



ARTICLE HIGHLIGHTS

- For people with type 2 diabetes, evidence-based guidelines are needed on diet related to clinically relevant outcomes such as mortality, and, thus, systematic reviews and meta-analyses on this topic are needed.
- Are dietary factors related to all-cause mortality among individuals with type 2 diabetes?
- Higher intake of whole grain, fiber, fish, and n-3 polyunsaturated fatty acids were inversely associated with mortality in individuals with type 2 diabetes (moderate certainty of evidence by Grades of Recommendation, Assessment, Development, and Evaluation [GRADE] approach).
- Aspects of a healthy diet are inversely associated with all-cause mortality in individuals with type 2 diabetes; however, more primary studies are needed to strengthen the results.

Diabetes Care Volume 46, February 2023

Dietary Factors and All-Cause Mortality in Individuals With Type 2 Diabetes: A Systematic Review and Meta-analysis of Prospective Observational Studies

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Diabetes Care 2023;46:469–477 | https://doi.org/10.2337/dc22-1018

BACKGROUND

Type 2 diabetes is a major health concern associated with mortality. Diet may influence the progression of diabetes; however, systematic reviews are lacking.

PURPOSE

This study systematically summarized the evidence on diet and all-cause mortality in individuals with type 2 diabetes.

DATA SOURCES

PubMed and Web of Science were searched until June 2022.

STUDY SELECTION

Prospective observational studies investigating dietary factors in association with all-cause mortality in individuals with type 2 diabetes were selected.

DATA SYNTHESIS

We identified 107 studies. Moderate certainty of evidence was found for inverse associations of higher intakes of fish (summary risk ratios per serving/week: 0.95; 95% CI 0.92, 0.99; *n* = 6 studies), whole grain (per 20 g/day: 0.84; 95% CI 0.71, 0.99; *n* = 2), fiber (per 5 g/day: 0.86; 95% CI 0.81, 0.91; *n* = 3), and n-3 polyunsaturated fatty acids (per 0.1 g/day: 0.87; 95% CI 0.82, 0.92; *n* = 2) and mortality. There was low certainty of evidence for inverse associations of vegetable consumption (per 100 g/day: 0.88; 95% CI 0.82, 0.94; *n* = 2), plant protein (per 10 g/day: 0.91; 95% CI 0.87, 0.96; *n* = 3), and for positive associations of egg consumption (per 10 g/day: 1.05; 95% CI 1.03, 1.08; *n* = 7) and cholesterol intake (per 300 mg/day: 1.19; 95% CI 1.13, 1.26; *n* = 2). For other dietary factors, evidence was uncertain or no association was observed.

CONCLUSIONS

Higher intake of fish, whole grain, fiber, and n-3 polyunsaturated fatty acids were inversely associated with all-cause mortality in individuals with type 2 diabetes. There is limited evidence for other dietary factors, and, thus, more research is needed.

Diabetes is a major public health concern worldwide and is associated with several comorbidities and mortality. In 2021, it was estimated that ∼537 million people aged between 20 and 79 years lived with diabetes globally (1). The estimated number of deaths due to diabetes or its complications was 6.7 million people in 2021 (1). As hyperglycemia is associated with several comorbidities and subsequently

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Received 24 May 2022 and accepted 12 November 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21561987.

This article is featured in a podcast available at diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

META-ANALYSIS

with premature mortality, the glycemic management and secondary prevention of these comorbidities is of high public health interest.

For the primary prevention of type 2 diabetes, many modifiable risk factors, such as an unfavorable diet, are well known (2). Regarding diet, there are dietary recommendations available for individuals with type 2 diabetes, for example, from the International Diabetes Federation (IDF) or from the American Diabetes Association (ADA). The IDF clinical practice recommendations for the management of type 2 diabetes include a reduced daily caloric intake for overweight and obese individuals, the preference of high-fiber and low-glycemic–index foods, and the avoidance of sugar, sweets, and sweetened beverages (3). In contrast, the ADA *Standards of Medical Care in Diabetes* is more comprehensive and includes, for example, a Mediterranean diet, higher intakes of nonstarchy vegetables, fruits, and whole grains, as well as dairy products, polyunsaturated fatty acids (PUFA), and a limited intake of saturated and *trans*-fatty acids (4). However, these dietary guidelines are mostly not evidence-based, refer to surrogate markers, such as glycemic control or lipids, or are based on findings from the general population. Thus, specific recommendations for individuals with type 2 diabetes are scarce. So far, individual studies have investigated dietary factors, such as the Mediterranean diet (5), intake of fruit (6), vegetables (7), or protein (8), in association to all-cause mortality in individuals with type 2 diabetes. Recently, a few meta-analyses investigating a single dietary exposure in association to all-cause mortality among individuals with type 2 diabetes have been published (9,10). However, the impact of different dietary factors on mortality in type 2 diabetes has not been comprehensively summarized, and the risk of bias in primary studies and certainty of evidence needs to be assessed by using validated tools.

Therefore, the aim of the present systematic review and meta-analysis was to summarize the currently available evidence on dietary factors, including dietary patterns, food groups, foods, macro- and micronutrients, and secondary plant compounds, and the risk of all-cause mortality in individuals with type 2 diabetes derived from prospective observational studies and evaluate the certainty of evidence of these associations.

RESEARCH DESIGN AND METHODS

This report was planned, conducted, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (11) and registered in PROSPERO (registration number: CRD42018110669). A detailed protocol of the project has been published previously (12), and in this first report, we focus on all-cause mortality. There were no deviations from the protocol.

Eligibility Criteria

A detailed description of the inclusion and exclusion criteria is shown in the Supplemental Material. Briefly, we included studies if the following criteria were met: *1*) participants with type 2 diabetes aged ≥18 years; *2*) any dietary factors, including dietary patterns, food groups, foods, macro- and micronutrients, and secondary plant compounds, supplements, and biomarkers of dietary intake; *3*) all-cause mortality; and *4*) prospective observational studies published in a peer-reviewed journal.

Search Strategy and Study Selection Process

The systematic literature search was performed in PubMed and Web of Science using predetermined search terms. No filters (e.g., publication language) were applied. In this context, we did not identify any relevant articles that were not in English. The full search strategy is presented in Supplementary Table 1. The systematic literature search was lastly updated on 7 June 2022.

The whole study selection process was conducted by two researchers independently. Any disagreements between the two researchers were resolved by consensus or by consultation of a third researcher. Reference lists of eligible studies and relevant reviews were screened to identify additional relevant studies.

If there were multiple publications of the same study population, we included the most recent and comprehensive report including the largest sample size and/or cases and longest duration of follow-up.

Data Extraction

One reviewer extracted the data from all identified studies using a predefined data extraction form, and a second reviewer checked the data for accuracy. The data extracted can be found in the Supplementary Material. We successfully contacted authors for relevant missing data (13–16). We excluded studies from the meta-analyses if we were unable to obtain relevant data.

Risk of Bias and Certainty of Evidence

We evaluated the potential risk of bias using the Risk Of Bias In Non-randomised Studies–of Interventions (ROBINS-I) tool (17). In brief, the tool is divided into seven domains: *1*) bias due to confounding, *2*) bias in selection of participants into the study, *3*) bias in measurement of the exposure, *4*) bias due to misclassification of exposure during follow-up, *5*) bias due to missing data, *6*) bias in measurement of outcomes, and *7*) bias in selection of reported results. A detailed description of the instrument and justification of the rating is presented in Supplementary Table 2. Two reviewers independently assessed the risk of bias, and any discrepancies were discussed to reach a consensus.

The certainty of evidence for each dietary exposure in association to all-cause mortality was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (18). The GRADE approach takes into account the within-study risk of bias, inconsistency, indirectness and imprecision between the studies, publication bias, magnitude of the effect, and dose-response relationship. The GRADE approach classifies the certainty of evidence in one of four levels: high, moderate, low, and very low. High certainty of evidence indicates that there is a high confidence in the effect estimate and that further research probably will not change the effect estimate, whereas a moderate certainty of evidence indicates a moderate confidence in the effect estimate and that further studies may change the effect estimate. Furthermore, a low certainty of evidence indicates low confidence in the effect estimate and that further studies will likely change the effect estimate, and very low certainty of evidence indicates that there is very limited and uncertain meta-evidence available. Two reviewers independently rated the certainty of evidence. Any disagreements between the two investigators were resolved by consensus.

Statistical Analysis

To calculate summary risk ratios (SRRs) and corresponding 95% CIs, we conducted

meta-analyses using a random-effects model when two or more studies on the same exposure and all-cause mortality were available (19). We summarized studies on dietary intake and studies on biomarkers of dietary intake separately. A detailed description of the statistical analysis is provided in the Supplemental Material. Briefly, we conducted dose-response meta-analyses whenever possible; otherwise, high versus low meta-analyses were conducted if data for dose-response meta-analyses were missing and no additional data could be obtained. We conducted subgroup analyses and meta-regression to investigate possible sources of heterogeneity across studies, such as sex, age, study length, and duration of diabetes, if at least 10 studies were available. Moreover, potential publication bias was investigated visually using funnel plots and the Egger test if at least 10 studies were available. A P value <0.1 indicated potential publication bias. All data analyses were performed using Stata 14.2 (StataCorp, College Station, TX) statistical software.

RESULTS

We identified 28,251 articles after removing duplicates (Fig. 1). After title and abstract screening, 1,028 articles were read in full text. Of these, 90 studies were eligible for inclusion. The list of included and excluded articles with reasons are provided in Supplementary Table 3. In addition, we identified 17 articles through reference screening. In total, 107 articles were included in the present systematic review, of which 76 studies investigated dietary intake, and 31 studies investigated biomarkers of dietary intake. One study on dietary vitamin B_{12} supplements was found.

The characteristics and the respective references of all included studies are presented in Supplementary Table 4. There were 42 studies conducted in the U.S., 37 studies in Europe, 24 studies in Asia, 1 study in Australia, and 3 studies were conducted internationally. The mean follow-up duration was 9.9 (minimum 1–maximum 34) years. The mean sample size was 5,879 (minimum 131–maximum 47,422). Of the 76 studies investigating dietary intake, 53 used a food frequency questionnaire or dietary history questionnaire, 12 studies used 24-h dietary recalls, 1 study used a 3-day dietary record, and 10 studies used questionnaires/instruments that were not specified.

There were 21 studies judged as being at moderate risk of bias, and 87 studies were judged as being at serious risk of bias (Supplementary Fig. 1). Overall, ~80% of the studies were rated as being at serious risk of bias in the confounding domain (Supplementary Fig. 2), indicating that most of the studies did not adjust for the most relevant confounders: Age was considered in 98% of the studies, sex in 94%, education in 65%, smoking in 84%, physical activity in 69%, and diabetes duration/severity in 45% only. Of the studies investigating dietary intake, 59% considered total energy intake in the analysis. More than 50% of the studies were rated as being at serious risk of bias due to the selection of the participants.

Of the 107 articles, 72 studies were included in the meta-analyses, and 35 articles could not be included in a meta-analysis because there were <2 studies available for the same exposure or due to missing data for a dose-response meta-analysis.

Dietary Patterns and All-Cause Mortality in Individuals With Type 2 Diabetes

The results of the meta-analyses of dietary patterns and all-cause mortality are presented in Fig. 2 and Supplementary Fig. 3. We identified 20 studies investigating a dietary pattern, including the Mediterranean diet (5,20–22), Alternate Healthy Eating Index (23,24), Dietary Approaches to Stop Hypertension (DASH) diet (14,22), Dietary Inflammatory Index (25–27), low-carbohydrate high-protein diet (28,29), low-carbohydrate score (16,30), or other dietary indices and behaviors (31–36). The certainty of evidence was rated as

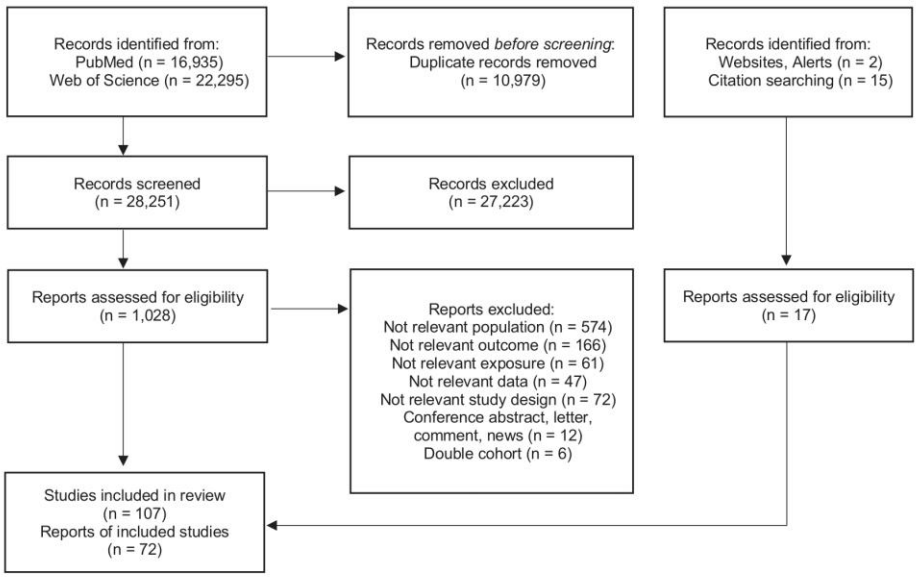

Figure 1—Flowchart illustrating the literature search process.

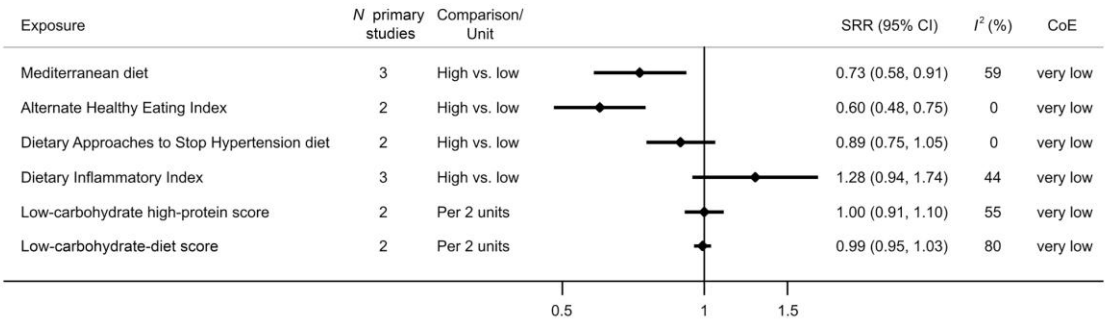

Figure 2—Associations between dietary patterns and all-cause mortality in individuals with type 2 diabetes. SRRs with 95% CIs were estimated using random-effects models. CoE, certainty of evidence.

very low for all findings (Supplementary Table 5).

Foods and Food Groups and All-Cause Mortality in Individuals With Type 2 Diabetes

The results of the meta-analyses on foods or food groups and all-cause mortality are presented in Fig. 3 and Supplementary Fig. 4. We found an inverse association between fish consumption and all-cause mortality (SRR for an increase of one serving/week: 0.95; 95% CI 0.92, 0.99; $\tau^2 < 0.001$; prediction interval [PI] 0.90, 1.01; $I^2 = 0\%$; $n = 6$ studies, moderate certainty of evidence) (24,37–41). There was no indication for nonlinearity (Supplementary Fig. 5). Moreover, moderate certainty of evidence was found for the association of whole-grain intake and all-cause mortality (SRR for an increment of 20 g/day: 0.84; 95% CI 0.71, 0.99; $\tau^2 < 0.001$; $I^2 = 0\%$; $n = 2$ studies) (24,42). Intake of vegetables was inversely associated (SRR per 100 g/day: 0.88; 95% CI 0.82, 0.94; $\tau^2 < 0.001$; $I^2 = 0\%$; $n = 2$ studies, low certainty of evidence) (7,24), and egg consumption was positively associated with all-cause mortality (SRR per 10 g/day: 1.05; 95% CI 1.02, 1.07; $\tau^2 < 0.001$; PI 0.98, 1.12; $I^2 = 56\%$; $n = 7$ studies, low certainty of evidence) (24,38,39,43–46).

We further conducted meta-analyses on intake of nuts, dairy, meat, sugar and sweets, tea, soft drinks and juices, showing no associations and rated with low certainty of evidence (Fig. 3). The certainty of evidence of the associations between intake of fruit, cereal, and coffee and all-cause mortality was very low.

Eleven studies (21,47–56) were available for coffee consumption (high vs. low meta-analysis); thus, we performed subgroup analyses and meta-regression (Supplementary Table 6). No differences were found with respect to sex, geographic location, duration of follow-up, number of cases, dietary assessment method, risk of bias, and adjustment for education, total energy intake, smoking, physical activity, or diabetes duration. There was an indication for publication bias according to the funnel plot (Supplementary Fig. 6) and the Egger test ($P = 0.067$), indicating that there might be a lack of studies with a null effect or positive association.

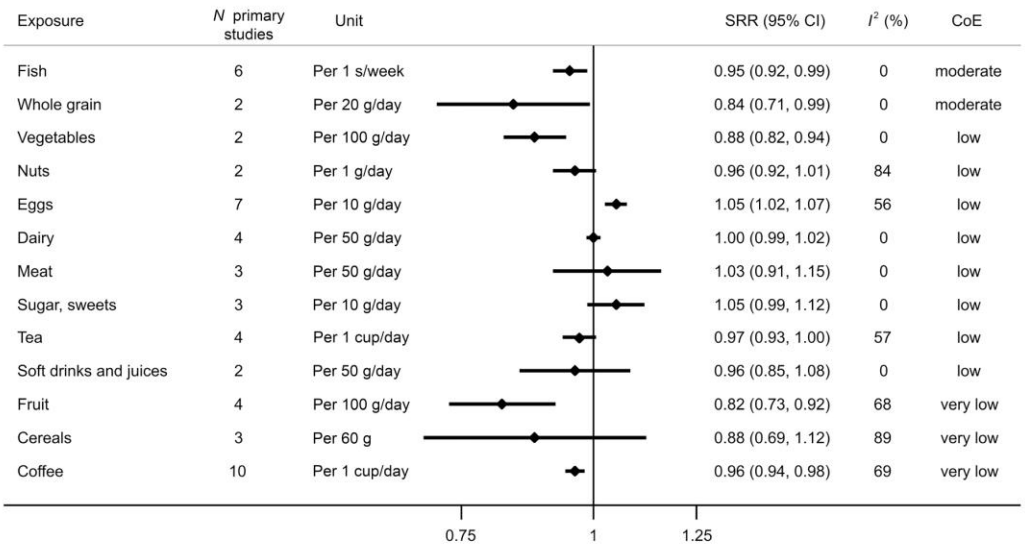

Figure 3—Associations between foods and food groups and all-cause mortality in individuals with type 2 diabetes. SRRs with 95% CIs were estimated using random-effects models. CoE, certainty of evidence; S, serving.

Energy and Macronutrients and All-Cause Mortality in Individuals With Type 2 Diabetes

The results of the meta-analyses on energy and macronutrient intake and all-cause mortality are presented in Fig. 4 and Supplementary Fig. 7. Intake of fiber (SRR per 5 g/day: 0.86; 95% CI 0.81, 0.91; $\tau^2 < 0.001$; PI 0.88, 1.06; $I^2 = 0\%$; $n = 3$ studies) (42,57,58) and n-3 PUFA intake were inversely associated with all-cause mortality (SRR per 0.1 g/day: 0.87; 95% CI 0.82, 0.92; $\tau^2 < 0.001$; $I^2 = 0\%$; $n = 2$ studies) (37,59), rated with moderate certainty of evidence. Intake of monounsaturated fatty acids (38,59) tended to be inversely and animal protein (24,60) tended to be positively associated with all-cause mortality, but the estimates were imprecisely estimated (moderate certainty of evidence).

Furthermore, dietary cholesterol was positively (SRR per 300 mg/day: 1.19; 95% CI 1.12, 1.25; $\tau^2 < 0.001$; $I^2 = 0\%$; $n = 2$ studies) (45,46) and intake of plant protein was inversely associated with all-cause mortality (SRR per 10 g/day: 0.91; 95% CI 0.86, 0.95; $\tau^2 < 0.001$; $I^2 = 42\%$, $n = 3$) (13,24,60), both rated as low certainty of evidence. Higher intake of saturated fatty acids pointed to an increased relative risk, but the estimate was imprecisely estimated, and the certainty of evidence was low. No association was found for carbohydrate intake.

Very low certainty of evidence was found for the intake of total energy, total PUFA, and protein.

The results of the substitution analyses are shown in Supplementary Fig. 8. Moderate certainty of evidence was observed for the replacement of 2% energy from carbohydrates by plant protein inversely associated with all-cause mortality (SRR 0.76; 95% CI 0.66, 0.87; $I^2 = 0\%$; $n = 2$ studies) (30,61), and for the substitution of 2% energy from carbohydrates with saturated fatty acids positively associated with all-cause mortality (SRR 1.10; 95% CI 1.04, 1.16; $I^2 = 0\%$; $n = 2$ studies) (30,62). No association was found for the substitution of carbohydrates with PUFA, monounsaturated fatty acids, and animal protein, graded with low to moderate certainty of evidence (Supplementary Table 5).

Micronutrients and Secondary Plant Compounds and All-Cause Mortality in Individuals With Type 2 Diabetes

The results of the meta-analyses on the intake of micronutrients and secondary plant compounds and relative risk of all-cause mortality are presented in Fig. 5 and Supplementary Fig. 9. We found no association for caffeine consumption (53,63) and serum folate (64–66) (moderate and low certainty of evidence, respectively).

Very low certainty of evidence was found for all other associations: sodium intake, urinary sodium, serum 25(OH) vitamin D, serum calcium, serum phosphorus, plasma/serum phylloquinone, and serum vitamin B_{12}.

Alcohol Consumption and All-Cause Mortality in Individuals With Type 2 Diabetes

Alcohol intake was investigated in 13 studies (21,23,24,31,32,38,67–73). Seven studies could be used for high consumption versus no consumption (Supplementary Fig. 10*A*) and three studies for nonlinear dose-response meta-analysis (Supplementary Fig. 10*B*). The certainty of evidence was very low for alcohol intake and all-cause mortality.

Single-Study Findings

Several dietary factors have been investigated only in one study, and, thus, a meta-analysis was not possible. Lower retinol levels were associated with higher relative risk of all-cause mortality (74). In agreement with dietary intake data, plasma docosahexaenoic acid and plasma n-3 PUFA were inversely associated with all-cause mortality, whereas no association was found for plasma monounsaturated fatty acids, saturated fatty acids, n-6 fatty acids, and linoleic acid (75). Moreover, inverse associations were found for selenium intake, green tea consumption (49), and intake of legumes (7) and all-cause mortality. Red blood cell folate (76) and choline intake from phosphatidylcholine (77) were positively associated with all-cause mortality.

No association was found for glycemic index, glycemic load, sugar or starch (57), and for a dietary pattern based on high intakes of "olive oil and vegetables," "eggs and sweets," and "pasta and meat" regarding all-cause mortality (5). Moreover, there was no association between α-tocopherol levels (78), serum ferritin (79), serum vitamin E (80), and all-cause mortality in individuals with type 2 diabetes.

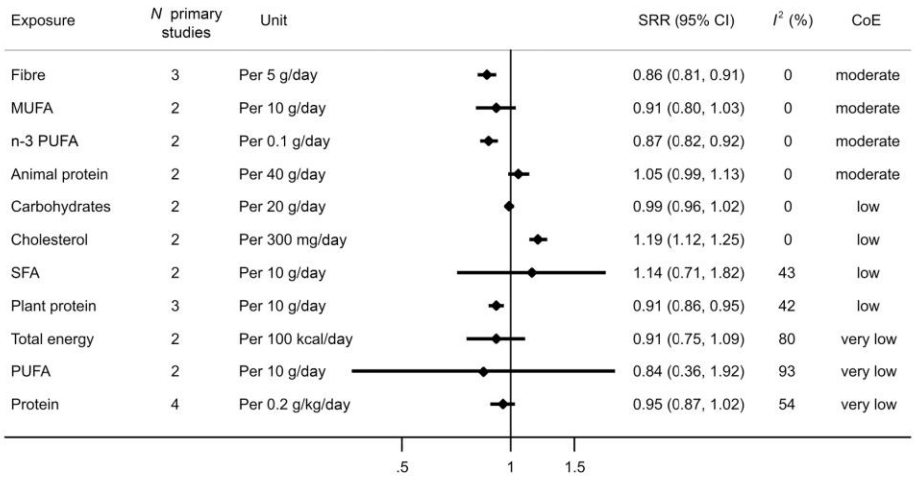

Figure 4—Associations between total energy intake and macronutrients and all-cause mortality in individuals with type 2 diabetes. SRRs with 95% CIs were estimated using random-effects models. CoE, certainty of evidence; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

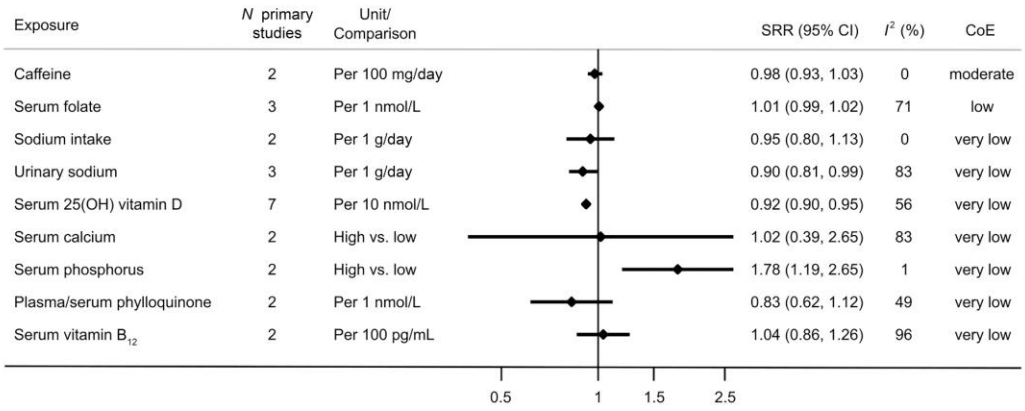

Figure 5—Associations between micronutrients and secondary plant compounds and all-cause mortality in individuals with type 2 diabetes. SRRs with 95% CIs were estimated using random-effects models. CoE, certainty of evidence.

CONCLUSIONS

In the present systematic review and meta-analysis, we provided a comprehensive overview of 107 studies investigating dietary factors and all-cause mortality in individuals with type 2 diabetes. We were able to conduct 45 meta-analyses. Higher intakes of fish, whole grain, fiber, and n-3 PUFA were inversely associated with the relative risk of all-cause mortality, rated as moderate certainty of evidence. Moreover, higher intakes of vegetable and plant protein may be inversely associated with all-cause mortality in individuals with type 2 diabetes, rated as low certainty of evidence. In contrast, higher intakes of eggs and cholesterol may be positively associated with all-cause mortality (low certainty of evidence). For other dietary factors, no association was found and/or the evidence was very uncertain.

Comparison With Other Studies and the General Population

A large body of evidence exists with regard to the prevention of type 2 diabetes (2). In addition, many meta-analyses on dietary factors and risk of all-cause mortality in the general population have been published. However, little is known on the secondary prevention of comorbidities and mortality in individuals with type 2 diabetes.

Our meta-analysis showed that higher intake of fish was associated with reduced relative risk of all-cause mortality in individuals with type 2 diabetes, which is comparable to findings of the general population (81). In addition, Jayedi et al. (10) also conducted a meta-analysis on fish consumption and mortality in individuals with type 2 diabetes and also found an inverse association as in the present meta-analysis. However, the authors included only three studies in the linear dose-response meta-analysis, and the SRR was somewhat lower (SRR 0.91 vs. 0.95).

Furthermore, we found that whole-grain and fiber intake were associated with reduced relative risk of all-cause mortality in individuals with type 2 diabetes, which is also comparable to meta-findings in the general population (82,83). Interestingly, the associations seem to be a stronger among individuals with type 2 diabetes compared with the general healthy population. Whole-grain products are rich in fiber, which has been shown to improve glycemic control, body weight control, and blood lipids in individuals with diabetes (84). Thus, fiber is an important dietary compound for diabetes management to prevent cardiovascular complications and mortality.

A meta-analysis of four prospective studies showed that an increment of 0.2 g of n-3 PUFA per day decreased the relative risk of all-cause mortality by 7% (81). With regard to our meta-analysis, the associations seem to be stronger in individuals with type 2 diabetes. As fish is an important source of n-3 PUFA, this result is in agreement with the meta-findings on fish consumption and mortality. Long-chain n-3 PUFAs have been hypothesized to have several beneficial effects on the vascular system, foremost antihypertensive, anti-inflammatory effects, and improved lipid profile (85), and, thus, it is possible that individuals with diabetes can especially benefit from n-3 PUFA intake.

In a meta-analysis based on 22 cohort studies, a dietary increment of 200 g of vegetables per day was associated with a 13% decreased risk of all-cause mortality in the general population (86). Compared with our meta-analysis, the risk estimate is quite similar, although we used a dose of 100 g/day. Moreover, in agreement with our findings, higher intake of plant protein has been shown to be inversely associated with all-cause mortality in the general population (87).

A meta-analysis of prospective cohort studies found a positive association of higher intake of eggs and cholesterol with all-cause mortality in the general population (88). One egg per day was associated with a relative risk of 1.07, indicating that there might be a weaker association in the general population compared with individuals with type 2 diabetes.

The Mediterranean diet is rich in many dietary factors mentioned above, and an inverse association was observed in the present meta-analysis. However, the certainty of evidence was very low, mainly due to serious risk of bias in the primary studies. For many other dietary factors, no association was found (e.g., meat, sugar and sweets, animal protein), or the association was graded with very low certainty of evidence (e.g., fruit and coffee consumption). Explanations for these findings could be the small number of studies for these meta-analyses, the high heterogeneity between studies, and the risk of bias of the studies.

Strengths and Limitations

The major strength of the present systematic review and meta-analysis is the comprehensive overview of the currently available evidence of dietary factors and all-cause mortality among individuals with type 2 diabetes. We assessed the risk of bias in all included studies and evaluated the certainty of evidence for all associations by applying validated tools. Moreover, we included only prospective observational studies, which reduces sources of bias, such as recall bias, and conducted linear and nonlinear dose-response analyses whenever possible.

Limitations of the present work include the serious risk of bias evaluated for most studies included in the meta-analyses. The main body of evidence in the current study came from studies at serious risk of bias, mainly due to uncontrolled confounding and selection of the participants into the study. More than half of the studies did not adjust for diabetes duration, and 41% of the studies investigating dietary factors did not consider total energy intake in the analysis. Moreover, as we included observational studies, residual confounding cannot be ruled out.

Dietary intake was assessed by self-reports in most studies. Thus, potential misclassification of the exposure cannot be ruled out. Biomarkers of dietary intake were used in 31 studies (29%), which may be a more objective measurement of dietary exposure. However, biomarkers are not available for all dietary factors. Moreover, since the exposure was measured only at baseline in most studies, changes in dietary behavior during follow-up could not be taken into account. However, large studies, such as the Nurses' Health Study and Health Professional Follow-up Study, took dietary changes into account, and the risk estimates were similar to the overall findings of the meta-analyses.

Furthermore, in several studies, it was not clear whether only participants with type 2 diabetes were included or whether also participants with type 1 diabetes were included. However, as the proportion of type 1 diabetes is small compared with type 2 diabetes, we expect that the number of participants with type 1 diabetes is very low in the included studies.

Owing to the small number of studies in many meta-analyses, the effect estimates were mostly imprecisely estimated (wide 95% CIs), and, thus, drawing conclusions may be limited. Furthermore, we were not able to conduct subgroup analyses and investigate publication bias except for the association between coffee consumption and all-cause mortality. Moreover, we were not able to conduct stratified analyses for subgroups of individuals with diabetes, such as those with a different disease status, taking different treatments, or with comorbidities. Some individuals may respond differentially to dietary intake, and thus, associations might differ between subgroups of individuals with diabetes.

Future Research Implications

The main reason for downgrading of the certainty of evidence was the serious risk of bias evaluated for the main part of the studies, resulting in many associations with low or very low certainty of evidence. Thus, future studies should take into account important confounders, such as diabetes duration, diabetes treatment, socioeconomic status, and total energy intake, to strengthen the evidence. Furthermore, some studies were not primarily designed for our research question, and in most studies, prevalent cases of diabetes were included. So, future studies should be designed to include individuals with newly diagnosed type 2 diabetes to minimize selection bias. Moreover, future studies should use validated dietary assessment methods and consider changes of dietary behaviors during follow-up to increase the reliability of the exposure assessment and thus, increase the certainty of evidence.

Conclusion

This is the first systematic review and meta-analysis that comprehensively summarizes the currently available evidence on dietary factors and all-cause mortality in individuals with type 2 diabetes. We could show that higher intakes of fish, whole grain, fiber, and n-3 PUFA were inversely associated with all-cause mortality. Moreover, evidence suggests that higher intakes of vegetable and plant protein may be associated with all-cause mortality, whereas higher intakes of eggs and cholesterol may be positively associated with all-cause mortality in individuals with type 2 diabetes. More primary studies are needed to provide robust and comprehensive evidence on dietary factors and the progression of diabetes.

Funding. The German Diabetes Center (DDZ) is funded by the German Federal Ministry of Health and the Ministry of Science and Culture of the State North Rhine-Westphalia. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD).

The funders had no role in study design or data collection, analysis, and interpretation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.Ba. conducted the statistical analyses. J.Ba., A.L., E.S., C.B., J.Be., L.S., M.N., and S.S. critically reviewed and approved submission of the final manuscript. J.Ba., A.L., E.S., J.Be., M.N., and S.S. conducted the systematic literature search. J.Ba., A.L., J.Be., M.N., and S.S. were involved in data acquisition. J.Ba., E.S., C.B., L.S., and S.S. conducted the assessment of risk of bias. J.Ba. and L.S. rated the certainty of evidence. J.Ba. and S.S. designed the study question and developed the search term of the systematic review and meta-analysis. J.Ba., and S.S. interpreted the results. J.Ba. and S.S. drafted the first version of the manuscript. S.S. assisted with the statistical analysis. J.Ba. and S.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented as an abstract at the 58th Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, 19–23 September 2022. The abstract was published in Diabetologia 2022;65(Suppl. 1):1–469.

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Online supplementary information can be accessed at the following link: https://diabetesjournals.org/care/article/46/2/469/148339/Dietary-Factors-and-All-Cause-Mortality-in

Chapter 5

Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet is associated with lower visceral and hepatic lipid content in recent-onset type 1 diabetes and type 2 diabetes

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Diabetes Obes Metab, 2024, 26(10): 4281-4292, doi: 10.1111/dom.15772

Summary

Overweight and obesity are common among individuals with T2D and are becoming increasingly prevalent in those with T1D. Presence of adipose tissue accumulation, especially around visceral cavity in form of VAT and around organs, like HLC, are associated with diabetes progression and increased risk of complications. Lifestyle interventions, including dietary changes, have been shown to be effective in reducing body weight, VAT, and HLC. Therefore, in this study we aimed to (i) investigate the association between the DASH score with SAT, VAT volumes and HLC in people with recent onset T1D and T2D, (ii) to examine whether changes in the DASH diet were associated with changes in these outcomes, and (iii) to quantify the extent to which BMI, waist circumference, whole body insulin sensitivity (M-value), Adipo-IR and non-esterified fatty acids explained observed associations.

Our study included 335 participants with recent-onset T1D and T2D from the GDS, with a mean DASH score of 24 in both groups. We found an inverse association between higher baseline DASH sore and HLC in people with T2D (per 5 points: ß-regression coefficient -1.5% (95% CI -2.7; -0.3)). Over 5 years, a 5-point increase in the DASH score was associated with decreased VAT in people with T2D (-514 cm^3 (-800; -228)). Similar, but imprecise, associations were observed for VAT changes in people with T1D (-403 cm^3 (-861; 55)) and for HLC in people with T2D (-1.3% (-2.8; 0.3)). BMI and waist circumference changes explained 16% and 8% of the associations between DASH and VAT changes in T1D and 48% and 32% in T2D, respectively. Additionally, in people with T2D, Adipo-IR changes explained 47% of the association between DASH and HLC changes.

In conclusion, the cross-sectional analysis suggests a beneficial association between the DASH diet and HLC in newly diagnosed T1D and T2D. Over time, decreased adherence to a DASH-style can increase VAT and HLC in both T1D and T2D. These associations are partly mediated by changes in BMI and waist circumference, while improved Adipo-IR in T2D plays and important role in the association between changes in the DASH diet and HLC.

Received: 27 April 2024 | Revised: 21 June 2024 | Accepted: 23 June 2024

DOI: 10.1111/dom.15772

ORIGINAL ARTICLE

WILEY

Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet is associated with lower visceral and hepatic lipid content in recent-onset type 1 diabetes and type 2 diabetes

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Abstract

Aim: To investigate the associations of the Dietary Approaches to Stop Hypertension (DASH) score with subcutaneous (SAT) and visceral (VAT) adipose tissue volume and hepatic lipid content (HLC) in people with diabetes and to examine whether changes in the DASH diet were associated with changes in these outcomes.

Methods: In total, 335 participants with recent-onset type 1 diabetes (T1D) and type 2 diabetes (T2D) from the German Diabetes Study were included in the cross-sectional analysis, and 111 participants in the analysis of changes during the 5-year follow-up. Associations between the DASH score and VAT, SAT and HLC and their changes were investigated using multivariable linear regression models by diabetes type. The proportion mediated by changes in potential mediators was determined using mediation analysis.

Prior presentation: A poster presentation with preliminary results of this study was held at the 18th Annual Conference of the German Society for Epidemiology (DGEpi) on 26-28 September 2023 in Würzburg, Germany.

Michael Roden and Sabrina Schlesinger shared last co-authorship.

Results: A higher baseline DASH score was associated with lower HLC, especially in people with T2D (per 5 points: −1.5% [−2.7%; −0.3%]). Over 5 years, a 5-point increase in the DASH score was associated with decreased VAT in people with T2D (−514 [−800; −228] cm^3). Similar, but imprecise, associations were observed for VAT changes in people with T1D (−403 [−861; 55] cm^3) and for HLC in people with T2D (−1.3% [−2.8%; 0.3%]). Body mass index and waist circumference changes explained 8%-48% of the associations between DASH and VAT changes in both groups. In people with T2D, adipose tissue insulin resistance index (Adipo-IR) changes explained 47% of the association between DASH and HLC changes.

Conclusions: A shift to a DASH-like diet was associated with favourable VAT and HLC changes, which were partly explained by changes in anthropometric measures and Adipo-IR.

KEYWORDS
body composition, cohort study, observational study, type 1 diabetes, type 2 diabetes, weight control

1 | INTRODUCTION

The majority of individuals diagnosed with type 2 diabetes (T2D) are overweight or obese[1] and approximately 60% have metabolic dysfunction-associated steatotic liver disease (MASLD).[2] Evidence has revealed an emerging trend of overweight individuals with type 1 diabetes (T1D) experiencing insulin resistance caused by sedentary lifestyles, excessive calorie intake and intensive insulin therapy.[3] Thus, accumulation of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and liver lipids is often observed in people with T1D and T2D,[3,4] and constitutes additional risk factors for cardiovascular, kidney and liver diseases.[5,6] Therefore, lifestyle changes, including dietary changes, are crucial for diabetes management, primarily because of weight loss and the reduction of VAT and SAT accumulation.[7]

Initially developed for people with hypertension, the Dietary Approaches to Stop Hypertension (DASH) diet is a simple dietary index that is easy to understand and implement; it emphasizes a high intake of fruit and vegetables, nuts, legumes and low-fat dairy products, combined with a low intake of sodium, sugar-sweetened beverages (SSBs) and red and processed meat.[8] Intake of vegetables, nuts, meat and SSB is associated with the onset of diabetes,[9] while higher intake of vegetables, nuts, legumes and lower intake of meat, sodium and SSB with improvements in insulin sensitivity, glycaemic control, blood pressure and blood lipids in people with T2D.[10–13] Because of its balanced nutritional composition, the DASH diet represents a potentially valuable dietary strategy for managing diabetes. A few studies have indicated an inverse association between DASH score and VAT and hepatic lipid content (HLC) in people with MASLD or metabolic dysfunction.[14,15] In individuals with T2D, a small intervention study showed that the DASH diet improved liver enzymes,[16] while another cross-sectional study identified a beneficial association between DASH diet adherence and enhanced insulin sensitivity.[17] However, it is possible that the observed benefits of the DASH diet on HLC and VAT are mainly driven by weight loss.

The existing evidence on the health impact of the DASH diet in people with diabetes is limited. No study has focused on SAT, VAT and HLC in this group or considered possible changes in DASH diet adherence over time. Baseline data may not accurately represent an individual's long-term dietary habits, and assessing dietary changes over time enables more reliable measures of cumulative exposure, accounting for shifts in habits over time. Furthermore, the question remains whether changes in anthropometric measures can fully explain changes observed between the DASH diet and adipose tissue distribution, or whether other direct effects exist.

We aimed to investigate the association between adherence to the DASH diet and SAT, VAT and HLC in people with newly diagnosed T1D or T2D, and to examine whether changes in DASH diet adherence were associated with changes in these outcomes over time. In addition, we investigated the mediation effects of changes in body mass index (BMI), waist circumference (WC), whole-body insulin sensitivity (M-value), adipose tissue insulin resistance index (Adipo-IR) and non-esterified fatty acids (NEFA) on the association between changes in the DASH score on changes in SAT, VAT and HLC.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

The German Diabetes Study (GDS) is an ongoing prospective cohort study investigating the factors and mechanisms behind diabetes-related co-morbidities and complications. The study complies with the Declaration of Helsinki, was approved by the ethics committee of the University of Düsseldorf (ref. 4508) and was registered at

Clinicaltrials.gov (NCT01055093). All participants provided their written informed consent.[18]

Participants aged 18-69 years and diagnosed with T1D or T2D within the last 12 months according to the American Diabetes Association criteria were eligible. Detailed inclusion and exclusion criteria are provided elsewhere.[18] All participants underwent a comprehensive examination at both baseline and after a 5-year follow-up comprising clinical examinations, laboratory measurements and standardized questionnaires. No dietary recommendations were given to the participants as part of the study, but it is possible that participants implemented dietary modifications, because they received guideline-based dietary recommendations from their physicians.

Those participants enrolled in the study centre in Düsseldorf (German Diabetes Centre) from August 2012 to December 2022, with available baseline information on dietary intake and whole-body magnetic resonance imaging (MRI) and liver proton magnetic resonance spectroscopy (^{1}H-MRS) measurements, were included in a cross-sectional analysis. Participants with available dietary information and SAT, VAT and HLC quantification, both at baseline and after the 5-year follow-up, were included in the analyses of changes (Figure S1). We excluded observations with implausible energy intake (men: <800 kcal/>4000 kcal, women: <500/>3500 kcal) ($n = 12$).[19] In total, 335 individuals (T1D, $n = 151$; T2D, $n = 184$) had available baseline dietary information and SAT, VAT and HLC measurements and represented the final study population. Dietary information and SAT, VAT and HLC quantification after the 5-year follow-up were available in 111 participants (T1D, $n = 49$; T2D, $n = 62$).

2.2 | Data collection

2.2.1 | DASH score

Dietary information was obtained from a validated semi-quantitative food frequency questionnaire (FFQ)[20] assessing habitual food consumption frequencies of 148 food items in the last 12 months, considering average portion size. The DASH score is based on foods and nutrients, focusing on eight components: a high intake of fruit, vegetables, nuts and legumes, low-fat dairy products and whole grains, as well as a low intake of sodium, SSBs, red and processed meat.[8,21] The FFQ did not collect information on whole-grain pasta, rice or flour, but distinguished between refined and whole-grain bread. Therefore, we included whole-grain bread in the DASH score, given its significance as a major source of whole grains in Germany.[22] Furthermore, the FFQ does not differentiate between SSBs and non-SSBs; however, in addition to the main FFQ, participants completed an extended validated questionnaire, which asked separately about the consumption of 'sugar-free' soft drinks. This allowed for differentiation between the mean intake of SSBs and non-SSBs, and inclusion of SSBs only in the DASH score.[23] Each component's daily intake was calculated and sex-specific quintiles were generated based on intake ranking. Regarding the intake of fruit, vegetables, nuts and legumes, low-fat dairy products and whole-grain bread, the first quintile (low intake) scored 1 point, while the fifth quintile (high intake) earned 5 points. For the intake of sodium, SSBs, as well as red and processed meat, the scoring was reversed. The sum of the points constitute the overall DASH score, ranging from 8 (lowest adherence) to 40 points (highest adherence).

2.2.2 | MRI-determined SAT and VAT volumes and ^{1}H-MRS–determined HLC

All magnetic resonance (MR) measurements were performed after overnight fasting on a 3-T MR scanner (Achieva dStream, X-series; Philips Healthcare, Best, the Netherlands). SAT and VAT volumes (cm^3) were quantified by whole-body MRI by employing T1-weighted fast spin-echo and postprocessing by a trained operator using SliceOmatic v. 5.0 software (Tomovision, Montreal, Canada).[24] HLC was quantified using ^{1}H-MRS in single-voxel stimulated echo acquisition mode.[24,25] Values of HLC are based on the determination of CH_2/($CH_2 + H_2O$) and given as percentages.

2.2.3 | Covariable assessment

Information on age, sex, smoking status, diabetes treatment, use of antihypertensive and lipid-lowering medication, socioeconomic status (SES), alcohol and energy intake, physical activity, anthropometric measures, M-value, Adipo-IR and NEFA was collected. Detailed information on the assessment of covariates has been provided elsewhere.[18,20,26–29]

2.3 | Statistical analysis

Categorical variables are described as numbers and percentages, continuous normally distributed variables as mean values and standard deviations or medians, and 25th and 75th percentiles in cases of skewed data. Because outcome data were not available for the whole GDS cohort, we compared characteristics between participants with and without available MRI/MRS measurements to investigate any systematic differences.

Multivariable linear regression models were used to investigate the associations between DASH score and SAT, VAT and HLC, obtaining β-coefficients with 95% confidence intervals (CIs). The DASH score was used as a continuous measure (per 5 points) and as tertiles of adherence. Second, by subtracting the baseline values from the follow-up values, we investigated whether changes in the DASH score over the 5-year follow-up period were associated with 5-year SAT, VAT and HLC changes. Negative values indicated a decrease in the DASH score or SAT, VAT and HLC during the 5 years, while positive values represented an increase. To examine the shape of the associations, natural cubic splines with three knots were modelled.[30] Confounders were selected a priori based on the literature. There were 58 observations with missing values in the confounders, which were

imputed using multiple imputation.[31] The following confounders were chosen: model I, age (years) and sex (men/women); model II, model I + smoking status (non-smokers/current smokers/former smokers), physical activity (continuous), SES (continuous), energy intake (continuous, kcal/day), alcohol (continuous, g/day), indicated changes in diet during the last 12 months (partial or yes/no) and treatment of diabetes (dietary advice/pharmacological treatment/no; only in the T2D group because 94% of the T1D group was on pharmacological treatment). In the cross-sectional analyses, we additionally adjusted for BMI (kg/m^2) in model III to assess the influence of overall adiposity. In the analyses of changes, the baseline DASH score and SAT, VAT and HLC levels were considered as further relevant confounders. We also adjusted for antihypertensive, lipid-lowering medication use and new diabetes medication reported after the 5-year follow-up; however, the results did not change and we left these covariates out of the final model.

In the analyses of changes, we conducted a mediation analysis to investigate the extent to which the associations between the DASH score changes and changes in VAT, SAT and HLC were mediated by changes in overall adiposity (defined by BMI), abdominal adiposity (defined by WC), M-value, Adipo-IR (only in participants with T2D not using insulin [$n = 50$]) and NEFA concentration.[32] Detailed descriptions are provided in Tables S1 and S2.

Furthermore, we conducted a subgroup analysis by sex to identify differences between men and women and added an interaction term in the fully adjusted model. We also investigated changes in the intake of each specific food component included in the DASH score separately to identify the food groups that contributed most to the observed associations.

All analyses were performed separately for people with T1D and those with T2D.

For all statistical analyses, SAS version 9.4 (SAS Institute, Cary, NC) was used.

3 | RESULTS

3.1 | Characteristics

Table 1 presents characteristics of the study population, stratified by diabetes type and tertiles of the DASH score. The mean DASH score was 24 in both groups. Compared with participants with T2D, participants with T1D were younger, had a lower BMI and received antihypertensive medication less frequently. Among people with T1D, 94% received pharmacological glucose-lowering treatment (mainly insulin: 89%), while among those with T2D, 68% received glucose-lowering treatment (metformin: 51%, insulin: 9%, other glucose-lowering drugs: 40%) and 23% only received dietary advice. None of the participants reported using glucagon-like peptide-1 receptor agonists (GLP1-RAs) or sodium-glucose co-transporter-2 inhibitors (SGLT2is) at baseline. After the 5-year follow-up, very few participants reported using GLP1-RAs (T2D, $n = 3$) and SGLT2is (T1D, $n = 2$; T2D, $n = 7$). Participants with T1D in the highest tertile of the DASH score had lower WC and were less often smokers than those in the lowest tertile. People with T2D with the highest DASH score had higher SES and the lowest proportion of current smokers compared with those with the lowest DASH score. Additionally, 83% of participants with T1D and 90% of those with T2D reported changing their diet in the last 12 months. No major differences in characteristics were detected between individuals with and without available MRI/MRS data (Table S3).

The median baseline and follow-up intake of all food groups were similar among people with T1D and T2D (Table S4).

3.2 | SAT volume

We found imprecisely estimated associations between baseline DASH score and SAT in people with T1D and T2D (ß [95% CI] for tertile 3 [T3] vs. tertile 1 [T1] of the DASH score: T1D: −1069 [−4181; 2043] cm^3, T2D: 2787 [−1447; 7021] cm^3) (Table 2). Adjustment for BMI attenuated the estimate. The association between the DASH score and SAT in those participants with T2D was linear, but an inverted *U*-shape association was observed for participants with T1D (Figure 1A).

An increase in the DASH score per 5 points over 5 years was inversely but imprecisely associated with lower SAT values in both groups (Table 3). There was an indication of a non-linear association for both groups (Figure 1B). In people with T1D, increases in the DASH score were associated with the strongest decreases in SAT, while decreases in the DASH score were not associated with such a strong increase in SAT. By contrast, in people with T2D, reduction of the DASH score was associated with the strongest SAT increase.

The mediation analysis showed that changes in BMI explained 36% of the association between changes in the DASH score and changes in SAT in people with T1D and 79% of the association in people with T2D, while changes in WC explained 61% of the association in people with T1D and 62% of the association in people with T2D. Changes in Adipo-IR explained 5% of the association between changes in the DASH score and in SAT in people with T2D (Table S5).

3.3 | VAT volume

We found an inverse but imprecisely estimated association between the DASH score and VAT in both groups at baseline (T3 vs. T1: T1D: −404 [−851; 43] cm^3, T2D: −219 [−1012; 573] cm^3) (Table 2). Adjustment for baseline BMI did not considerably change the results. In people with T1D, an inverse *U*-shaped association was evident, whereas in participants with T2D, the curve steeply increased among those with the lowest DASH score (Figure 1C).

Over 5 years, a 5-point increase in DASH score was associated with a reduction in VAT in both groups, but estimates for people with T1D were imprecise (T1D: −403 [−861; 55] cm^3, T2D: −514 [−800; −228] cm^3) (Table 3). There was no evidence for non-linearity of the association among participants with T2D. Individuals with T1D with

TABLE 1 Baseline characteristics stratified by diabetes type and tertiles of the DASH score among participants from the GDS ($n = 335$)

	Type 1 diabetes				Type 2 diabetes			
	All	DASH score T1 (<22)	DASH score T2 (22-26)	DASH score T3 (>26)	All	DASH score T1 (<22)	DASH score T2 (22-26)	DASH score T3 (>26)
N	151	52 (34)	57 (37)	42 (29)	184	62 (34)	65 (35)	57 (31)
DASH score	24 ± 5	19 ± 2	24 ± 2	29 ± 2	24 ± 5	19 ± 2	24 ± 2	29 ± 2
Women (%)	63 (42)	19 (37)	24 (42)	20 (48)	67 (36)	24 (39)	27 (42)	16 (28)
Age (y)	36.2 ± 11.4	36.2 ± 10.8	37.1 ± 12.4	35.0 ± 10.7	51.8 ± 9.0	51.8 ± 8.4	52.1 ± 10.2	51.6 ± 8.4
Body mass index categories								
<25 kg/m^2	85 (56)	30 (58)	31 (54)	24 (57)	27 (15)	10 (16)	10 (15)	7 (12)
25-30 kg/m^2	47 (31)	12 (23)	19 (33)	16 (38)	51 (28)	17 (27)	13 (20)	21 (37)
≥30 kg/m^2	19 (13)	10 (19)	7 (13)	2 (5)	106 (57)	35 (57)	42 (65)	29 (51)
Continuous	25.1 ± 4.2	25.4 ± 4.7	25.4 ± 4.2	24.2 ± 3.4	31.3 ± 6.0	30.8 ± 5.8	31.5 ± 5.6	31.5 ± 6.5
Waist circumference (cm)	86.5 ± 13.0	88.1 ± 13.7	87.7 ± 14.0	82.9 ± 10.0	104.5 ± 13.3	104.3 ± 13.3	103.9 ± 12.2	105.0 ± 14.7
Socioeconomic status[a]								
Lower	10 (7)	6 (11)	3 (5)	1 (3)	6 (3)	2 (3)	2 (3)	2 (4)
Middle	76 (50)	27 (52)	25 (44)	24 (57)	96 (52)	35 (56)	34 (52)	27 (47)
Upper	56 (37)	18 (35)	24 (42)	14 (33)	77 (42)	24 (39)	25 (39)	28 (49)
Missings	9 (6)	1 (2)	5 (9)	3 (7)	5 (3)	1 (2)	4 (6)	-
Continuous	13.9 ± 2.7	13.8 ± 3.0	13.8 ± 2.5	14.3 ± 2.4	14.3 ± 2.7	13.8 ± 2.6	14.4 ± 2.7	14.8 ± 2.9
Smoking status								
Current	39 (26)	17 (33)	15 (26)	7 (17)	47 (25.4)	17 (27)	17 (26)	13 (22)
Former	39 (26)	12 (23)	14 (25)	13 (31)	63 (34)	22 (36)	19 (29)	22 (39)
Never	73 (48)	23 (44)	28 (49)	22 (52)	73 (40)	23 (37)	28 (43)	22 (39)
Missings	-	-	-	-	1 (0.6)	-	1 (2)	-
Physical activity index[b]	5.3 ± 0.9	5.1 ± 0.8	5.4 ± 0.9	5.5 ± 1.1	5.3 ± 1.1	5.2 ± 1.0	5.2 ± 1.1	5.4 ± 1.1
Missings	11 (7)	3 (6)	6 (11)	2 (5)	29 (16)	10 (16)	10 (16)	9 (16)
Antihypertensive medication (yes)	11 (7)	3 (6)	5 (9)	3 (7)	79 (43)	23 (37)	29 (45)	27 (47)
Lipid-lowering medication (yes)	5 (3)	1 (2)	1 (2)	3 (7)	24 (13)	8 (13)	9 (14)	7 (12)
Glucose-lowering medication								
Dietary advice only	4 (3)	1 (2)	2 (4)	1 (2)	43 (23)	15 (24)	14 (21)	14 (25)
No treatment	1 (1)	0 (0)	0 (0)	1 (2)	11 (6)	5 (8)	6 (9)	0 (0)
Pharmacological treatment	143 (94)	50 (96)	53 (92)	40 (96)	125 (68)	40 (64)	42 (67)	43 (75)
Missings	3 (2)	1 (2)	2 (4)	0 (0.0)	5 (3)	2 (4)	3 (4)	0 (0)

(Continues)

TABLE 1 (Continued)

	Type 1 diabetes				Type 2 diabetes			
	All	DASH score T1 (<22)	DASH score T2 (22-26)	DASH score T3 (>26)	All	DASH score T1 (<22)	DASH score T2 (22-26)	DASH score T3 (>26)
Alcohol intake (g/day)	7.1 (1.7-17.0)	8.0 (2.0-18.6)	5.0 (1.6-16.4)	8.1 (1.6-16.4)	3.4 (0.5-11.2)	3.3 (0.9-11.2)	4.4 (0.3-12.7)	2.5 (0.7-9.6)
Change in diet during the last year (yes or partial)	125 (83)	39 (85)	49 (86)	34 (76)	165 (90)	56 (90)	54 (83)	55 (97)
M-value (mg/[kg min])	8.5 (6.4-10.5)	8.3 (6.4-11.1)	8.5 (6.5-10.4)	8.7 (7.1-10.0)	5.7 (4.4-7.4)	5.4 (4.0-7.0)	5.6 (4.2-7.7)	6.0 (4.9-7.3)
Missings	6 (4)	2 (4)	1 (2)	3 (7)	13 (7)	4 (7)	5 (8)	4 (7)
Adipo-IR (mU/[Lμmol/L])[c]	4158 (2208-8175)	4534 (2226-8735)	4392 (2622-9168)	3465 (1722-5439)	6141 (3786-11 701)	6748 (4894-12 615)	6335 (3497-12 466)	5213 (3613-9071)
Missings	18 (12)	6 (11)	7 (13)	5 (12)	24 (13)	6 (10)	13 (20)	5 (9)
NEFA (μmol/L)[d]	514 (359-665)	524 (409-617)	499 (367-666)	487 (317-706)	531 (425; 653)	513 (425-656)	548 (428-664)	522 (425-648)
Missings	1 (1)	-	1 (2)	-	-	-	-	-
Energy (kcal/day)	2342.2 ± 603.3	2469 ± 627	2283 ± 632	2264 ± 499	2158 ± 649	2243 ± 764	2127 ± 591	2103 ± 573
SAT (cm^3)[e]	16 090 (11 570-22 238)	16 170 (11 611-20 692)	16 235 (11 428-25 137)	15 824 (11 756-20 047)	23 226 (16 632-32 420)	21 322 (15 982-33 520)	24 110 (17 136-31 892)	22 444 (16 740-31 667)
Missings	7 (5)	3 (6)	3 (5)	1 (2)	34 (19)	13 (21)	8 (12)	13 (22)
VAT (cm^3)[e]	1142 (525-2304)	1223 (677-2307)	1177 (572-2784)	592 (403-1608)	3878 (2811-5085)	3849 (2986-5530)	4006 (3044-5151)	3823 (2605-4775)
Missings	8 (5)	3 (6)	4 (7)	1 (2)	34 (19)	13 (21)	8 (12)	13 (22)
HLC (%)[f]	0.3 (0-1.1)	0.4 (0-2.0)	0.5 (0-1.1)	0.2 (0-0.6)	6.3 (2.4-13.3)	7.2 (2.5-13.4)	6.7 (2.7-14.0)	4.9 (1.9-9.8)
Missings	7 (5)	4 (8)	-	3 (7)	10 (6)	2 (3)	4 (6)	4 (7)

Note: Categorical variables are presented as frequencies with percentages *n* (%), continuous normally distributed variables as means and (±) standard deviations, continuous and not normally distributed variables as median values with interquartile ranges.

Abbreviations: Adipo-IR, adipose tissue insulin resistance index; DASH, Dietary Approaches to Stop Hypertension; GDS, German Diabetes Study; HLC, hepatic lipid content; M-value, whole-body insulin sensitivity; NEFA, non-esterified fatty acids; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

[a]Socioeconomic status index: based on education, occupation and income variables (range 3-21).

[b]Physical activity index: a modified version of the Baecke Index[26,54] covering leisure and working activities (range 2.25-10).

[c]Calculated as a product of the mean of two measurements of fasting insulin (mU/L) and the mean of two measurements of plasma free fatty acids concentration (μmol/L).

[d]The mean of two measurements of plasma free fatty acids concentration (μmol/L).

[e]Assessed by magnetic resonance imaging.

[f]Assessed by magnetic resonance spectroscopy.

TABLE 2 Associations between adherence to the DASH score and SAT volume, VAT volume and HLC at baseline in individuals with type 1 diabetes and type 2 diabetes from the GDS ($n = 335$)

	Type 1 diabetes			Type 2 diabetes		
DASH score	**Model 1**	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
SAT (cm^3)						
N	144			149		
Tertile 1 (<22 points)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tertile 2 (22-26 points)	−153 (−3320; 3014)	781 (−2342; 3903)	650 (−921; 220)	1414 (−2259; 5087)	1290 (−1915; 4496)	−524 (−2237; 1188)
Tertile 3 (>26 points)	−2169 (−5580; 1242)	−1069 (−4181; 2043)	16 (−1369; 1705)	1935 (−1986; 5856)	2787 (−1447; 7021)	1061 (−1043; 3166)
P trend	.22	.58	.70	.36	.20	.25
Per 5 points	−1069 (−2525; 388)	−619 (−1845; 743)	−285 (−18 911; 343)	703 (−985; 2391)	1305 (−495; 3104)	537 (−331; 1405)
VAT (cm^3)						
N	143			149		
Tertile 1 (<22 points)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tertile 2 (22-26 points)	11 (−482; 505)	145 (−333; 625)	133 (−263; 529)	45 (−707; 797)	−56 (−739; 626)	−303 (−819; 213)
Tertile 3 (>26 points)	−554 (−1083; −26)	−404 (−851; 43)	−280 (−636; 82)	−470 (−1273; 333)	−219 (−1012; 573)	−461 (−1056; 135)
P trend	.05	.12	.20	.20	.60	.15
Per 5 points	−229 (−457; −2)	−151 (−333; 31)	−122 (−271; 28)	−252 (−597; 93)	−110 (−453; 234)	−218 (−464; 28)
HLC (%)						
N	144			173		
Tertile 1 (<22 points)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tertile 2 (22-26 points)	−0.1 (−1.4; 1.3)	−0.1 (−1.4; 1.2)	−0.2 (−1.3; 0.9)	−0.3 (−3.3; 2.7)	−0.1 (−3.0; 2.8)	−0.4 (−3.1; 2.3)
Tertile 3 (>26 points)	−1.3 (−2.8; 0.2)	−1.3 (−2.4; 0.2)	−1.1 (−2.1; −0.1)	−2.6 (−5.7; 0.5)	−1.3 (−4.2; 1.7)	−2.0 (−4.8; 0.8)
P trend	.09	.03	.05	.09	.38	.14
Per 5 points	−0.5 (−1.1; 0.1)	−0.4 (−0.8; 0.0)	−0.3 (−0.7; 0.1)	−1.8 (−3.1; −0.4)	−1.0 (−2.5; 0.1)	−1.5 (−2.7; −0.3)

Note: Results are presented as ß estimates and 95% confidence intervals. Model I: adjusted for age (y) and sex (men/women); Model II: Model I + smoking status (never smokers/current smokers/former smokers), physical activity index (continuous), socioeconomic status index (continuous), energy intake (continuous, kcal/day), alcohol intake (continuous, g/day), indicated changes in diet during the last 12 months (yes or partial/no) and treatment of diabetes (no/dietary advice/pharmacological, only in the type 2 diabetes group); Model III: Model II + body mass index (continuous, kg/m^2). SAT volume and VAT volume were assessed by magnetic resonance imaging and HLC by magnetic resonance spectroscopy.

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; GDS, German Diabetes Study; HLC, hepatic lipid content; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

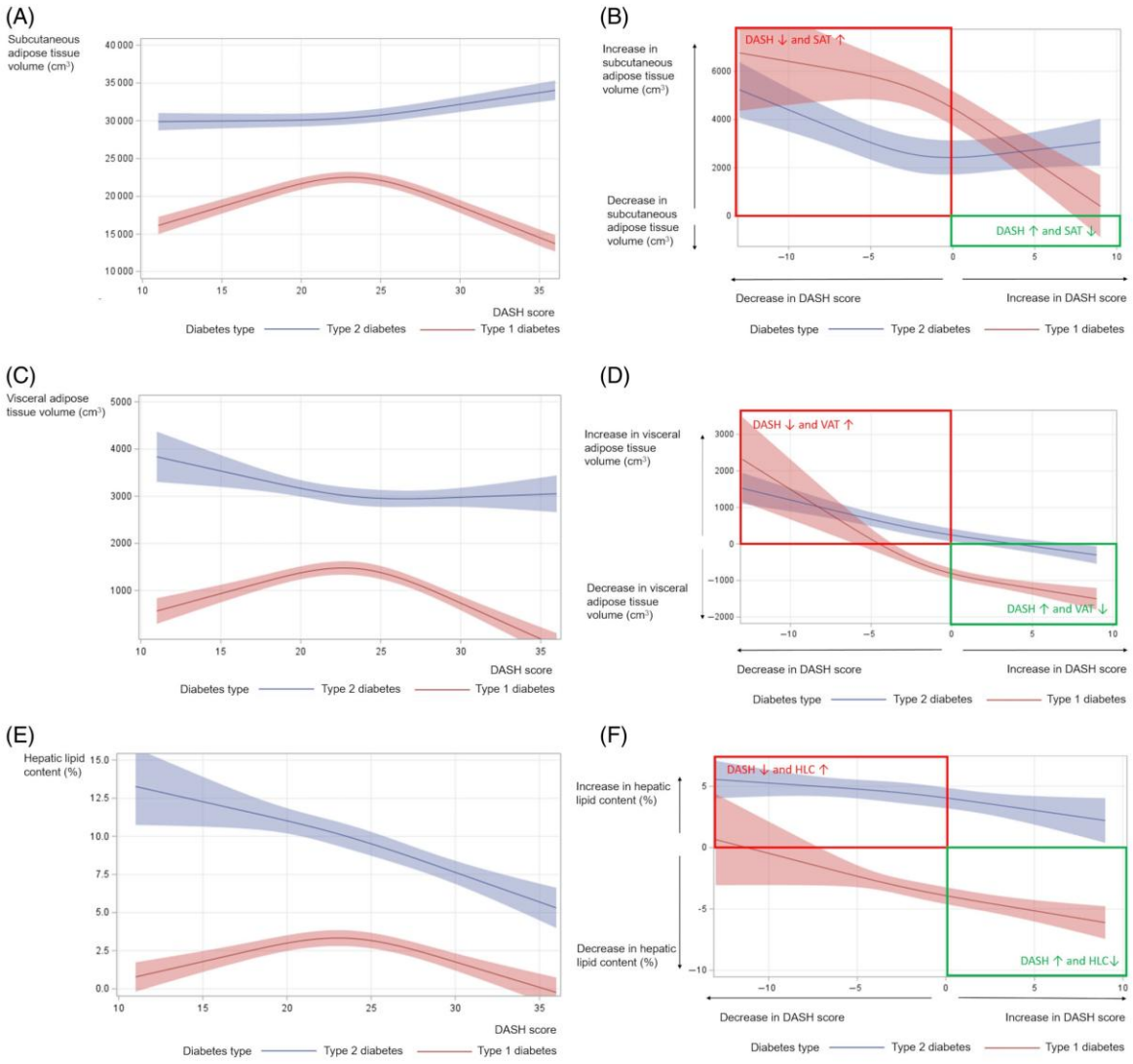

FIGURE 1 A, Associations between the baseline DASH score and MRI-determined SAT volume (cm^3) ($n = 294$); B, Associations between changes in the DASH score and changes in MRI-determined SAT volume (cm^3) over 5 years ($n = 87$); C, Associations between the baseline MRI-determined VAT volume (cm^3) ($n = 293$); D, Associations between changes in the DASH score and changes in MRI-determined VAT volume (cm^3) ($n = 87$) over 5 years; E, Associations between the baseline MRS-determined HLC (%) ($n = 318$); F, Associations between changes in the DASH score and changes in MRS-determined HLC (%) ($n = 106$) over 5 years in individuals with type 1 diabetes and type 2 diabetes from the GDS. DASH, Dietary Approaches to Stop Hypertension; GDS, German Diabetes Study; HLC, hepatic lipid content; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

decreases in their DASH scores of more than 5 points displayed the highest increases in VAT over the 5-year follow-up period (Figure 1D).

Changes in BMI explained 16% and 48% of the association between changes in the DASH score and VAT in people with T1D and T2D, respectively. The proportion mediated by a change in WC was 8% in people with T1D and 32% in those with T2D. Changes in Adipo-IR explained 2% of the association between changes in the DASH score and VAT in those with T2D (Table S5).

3.4 | Hepatic lipid content

There was an inverse association between higher baseline DASH score and HLC, especially in people with T2D (Table 2). Further adjustment for baseline BMI strengthened these associations (per 5 points, −1.5% [−2.7; −0.3]). The association was linear, while for people with T1D, a non-linear inversed *U*-shaped relationship was present (Figure 1E).

TABLE 3 Associations between changes in the DASH score and changes in SAT volume, VAT volume and HLC over 5 years of follow-up in individuals with type 1 diabetes and type 2 diabetes from the GDS ($n = 111$)

DASH score	Type 1 diabetes		Type 2 diabetes	
	Model 1	Model 2	Model 1	Model 2
SAT (cm^3)				
N	45		42	
DASH per 5 points increase	−1371 (−3535; 793)	−1329 (−3412; 754)	−316 (−1325; 695)	−493 (−1210.9; 226)
VAT (cm^3)				
N	45		42	
DASH per 5 points increase	−521 (−1043; 1)	−402 (−861; 55)	−295 (−730; 1340)	−514 (−800; −228)
HLC (%)				
N	47		59	
DASH per 5 points increase	−1.2 (−3.3; 0.9)	−0.0 (−1.2; 1.2)	−0.2 (−2.1; 1.8)	−1.3 (−2.8; 0.3)

Note: The table presents ß estimates and 95% confidence intervals. Model I: adjusted for age (y) and sex (men/women); Model II: Model I + smoking status (never smokers/current smokers/former smokers), physical activity index (continuous), socioeconomic status index (continuous), energy intake (continuous, kcal/day), alcohol intake (continuous, g/day), baseline DASH score, treatment of diabetes (no/dietary advice/pharmacological, only in the type 2 diabetes group) and baseline SAT volume/VAT volume/HLC. SAT volume and VAT volume were assessed by magnetic resonance imaging and HLC by magnetic resonance spectroscopy.

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; GDS, German Diabetes Study; HLC, hepatic lipid content; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

A 5-point increase in the DASH score over 5 years was associated with a decrease in HLC in people with T2D, but the 95% CI includes a null value (−1.3% [−2.8%; 0.3%]). No association was found among participants with T1D (Table 3). There was no evidence of non-linearity in either group (Figure 1F).

In people with T2D, BMI changes explained 67% and WC changes 54% of the association between changes in DASH score and changes in HLC. Changes in Adipo-IR mediated 47% of the association between changes in DASH score and in HLC (Table S5). Mediation analysis was not calculated for the T1D group, because no association was evident between DASH and HLC changes.

3.5 | Sensitivity analyses

We found no clear differences by sex. For T2D, there was an indication of a stronger inverse association between the baseline DASH score and HLC in women compared with men; however, the 95% CIs overlap (Table S6). Analyses of changes in single DASH-components intake indicated positive associations between increased sodium intake and increased SAT, VAT and HLC in T2D (Table S7). A 50-g increase in red and processed meat consumption was associated with an increase in SAT. Conversely, a 10-g increase in the intake of nuts and legumes was associated with decreased SAT and VAT. A 50-g increase in consumption of vegetables primarily contributed to decreased HLC in people with T2D. Additionally, a 50-g increase in whole-grain bread intake was associated with increased SAT in people with T2D.

4 | DISCUSSION

Higher baseline adherence to the DASH diet was associated with favourable body fat distribution, particularly HLC in people with T2D. Changes over time showed that decreases in DASH diet adherence were associated with increasing adipose tissue volumes. This observation was most evident for VAT changes in people with T2D. Changes in BMI, WC and Adipo-IR partly mediated associations between changes in the DASH score and SAT, VAT and HLC changes. As expected, the associations between adherence to the DASH score and SAT, VAT and HLC were stronger in individuals with T2D compared with those with T1D. Interestingly, an inverse association between baseline DASH score adherence and HLC was also present in individuals with T1D, highlighting the importance of dietary management in this group as well.

The adherence level to the DASH score in the GDS cohort was comparable with that observed in studies of the general population.[14,33,34] Participants in the GDS reported slightly higher whole-grain bread intake and lower salt intake, while their intake of energy, red and processed meat, as well as fruit and vegetables, was similar to that of the general population.[22,35–39]

Our findings align with previous studies involving diabetes-free populations. Individuals with and without metabolic dysfunction with higher DASH adherence had a 7% lower probability of visceral obesity and 0.2% lower HLC.[14,15] In another study, participants with the highest DASH scores were 30% less probable to have MASLD, although this association diminished after BMI adjustment.[40] In our cross-sectional analyses, adjustment for BMI partially influenced the associations with all outcomes. Furthermore, a randomized controlled trial

involving individuals with MASLD showed that the DASH diet led to greater HLC improvements compared with the control group.[41]

Contrary to expectations and previous studies,[42] we observed an imprecise but positive association between baseline DASH score and SAT in people with T2D. However, because 97% of participants with T2D in the highest DASH score tertile reported recent dietary changes, we suspect that this result is attributable to reverse causality. Newly diagnosed individuals who are additionally obese may have changed their diet, but the duration of the changes may not have been long enough to already affect the SAT. However, over a 5-year period, despite imprecise estimates of the results, the direction of the association between the DASH score and SAT reversed, suggesting a favourable association between the DASH score and SAT over the long term in people with T2D. On the other hand, an inverse association was found between higher baseline DASH score and HLC in people with T1D and in those with T2D. This may suggest that the recent dietary changes are most quickly noticeable in HLC. Consistent with this, a previous study showed that, after caloric restriction, hepatic triacylglycerol content decreased by 30% during 1 week and continued to decline throughout 8 weeks.[43]

A recent study on the general population found that the effect of the dietary inflammatory index on MASLD was mediated by changes in BMI by up to 89%.[44] In our study, the proportion mediated by BMI or WC changes ranged from 8% to 83%. These findings indicate that BMI and WC changes partly mediate the association between changes in DASH score and in SAT, VAT and HLC; however, other direct mechanisms might still influence these associations. In this context, our analysis showed that, in people with T2D, improved Adipo-IR mediated 2%-5% of the association between DASH and VAT and SAT changes. Also, 47% of the association between changes in DASH score and HLC could be explained by Adipo-IR changes, indicating that improvements in adipose tissue insulin sensitivity may play an important role in the investigated association.[45]

Further speculations are that stronger adherence to the DASH diet indicates adopting a healthier lifestyle, contributing to lower HLC and VAT. However, our analyses accounted for various confounders, like physical activity, smoking and alcohol intake. It is commonly hypothesized that the beneficial effects of a healthy diet are primarily a result of reduced calorie intake and subsequent weight loss. However, our analyses adjusted for energy intake and changes in BMI and WC did not fully explain the observed associations with DASH score. Several DASH diet-components can explain direct mechanisms underlying the observed associations. Whole-grain intake may positively impact SAT, VAT and HLC by stimulating gut microbiota and producing short-chain fatty acids.[46] Interestingly, our analysis in people with T2D revealed a positive association between increased whole-grain bread intake and increased SAT levels. This result is surprising, because evidence exists on the beneficial association between whole-grain bread intake and the incidence of diabetes and cardiovascular diseases.[47] Antioxidants, which are obtained from fruit and vegetables, as well as nuts and pulses, influence adiposity and liver health by inhibiting adipocyte differentiation and enhancing the oxidation of fatty acids.[48] Reduced red and processed meat consumption is related to a lower intake of saturated fat, nitrates, trimethylamine *N*-oxide and advanced glycation end products, and can reduce the accumulation of VAT and liver lipids, as well as improve insulin resistance, dysglycaemia and inflammation.[49–51] Sodium intake is associated with higher serum C-reactive protein and tumour necrosis factor-α levels and promotes endogenous fructose production.[52] SSBs containing refined sugars stimulate de novo lipogenesis and deposition of liver triglycerides, leading to hepatic steatosis.[53] Although these are all suggested mechanisms of action, it is not possible to distinguish which of the DASH components are the most important. Furthermore, future studies are warranted to confirm the beneficial health impacts of the DASH diet in people with diabetes.

Our study has several strengths. The GDS cohort includes participants with a defined diabetes duration since diagnosis who underwent comprehensive phenotyping, including non-invasive gold standard assessment of SAT, VAT and HLC by MRI and MRS. Additionally, we examined the potential mediating effects of BMI, WC and Adipo-IR on the associations of interest. However, limitations should be acknowledged. First, this was an observational study, limiting conclusions on the causality of the observed associations. Additionally, although we adjusted for important confounding factors, residual confounding cannot be excluded. Second, in the cross-sectional analyses, lifestyle changes prompted by the diabetes diagnosis may not have yet impacted the outcomes studied, potentially leading to an underestimation of the associations examined. Third, because diet was assessed via self-reports and misclassification, over- and under-reporting cannot be ruled out. Participants may have reported their intake based on diabetes-related recommendations received during medical consultations, rather than their true intake. This inference is supported by the positive association between the baseline DASH score and SAT. Fourth, because the GDS is an ongoing study, dietary follow-up and imaging data were not available for all participants. The sample size for the analyses of changes was small, which also limited possibilities for further sensitivity analyses. Furthermore, the 95% CIs for some of our results were wide, reflecting the potential limitations of our sample size. Finally, our findings may not be generalizable to all individuals with diabetes because of potential selection bias resulting from the comprehensive GDS protocol and its exclusion criteria.

In conclusion, via cross-sectional analysis, the current study shows that the DASH diet is beneficially associated with HLC in people with newly diagnosed diabetes. In the long term, people with T1D and those with T2D can derive benefits from a shift to a DASH-style diet by experiencing improvements in VAT; additionally, those with T2D may derive benefits in relation to HLC. Changes in BMI and WC partially explain these associations, and improved Adipo-IR in T2D appears to play an important role in the association between changes in the DASH diet and HLC.

AUTHOR CONTRIBUTIONS

ES, SS and MR conceptualized the idea for the analysis. VSH, YK, JS, KBB, TK, KSW, CH and MR collected and analysed the data. ES and AL conducted statistical analyses. ES, SS, YK, KBB, CH, AB, OK and MR contributed to the interpretation and discussion of the

results. ES and SS wrote the manuscript. ES is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The German Diabetes Study (GDS) group consists of M. Roden (speaker), H. Al-Hasani, B. Belgardt, G. Bönhof, G. Geerling, C. Herder, A. Icks, K. Jandeleit-Dahm, J. Kotzka, O. Kuß, E. Lammert, W. Rathmann, S. Schlesinger, V. Schrauwen-Hinderling, J. Szendroedi, S. Trenkamp, R. Wagner and their co-workers who contributed to the design and conduct of the GDS. The authors appreciate the voluntary contributions of all study participants. Furthermore, we thank the staff of the Clinical Research Centre at the Institute for Clinical Diabetology, German Diabetes Centre (DDZ), for their excellent contribution to the GDS. This work was initially exclusively supported by the German Diabetes Center (DDZ), which is funded by the German Federal Minitry of Health (BMG, Berlin, Germany) and the Ministry of Culture and Science of Northrhine-Westphalia (MKW-NRW, Düsseldorf, Germany) and as a multicenter study now receives additional funding by the German Federal Ministry of Education and Research (BMBF, Berlin, Germany) through the German Center of Diabetes Research (DZD e.V.).

CONFLICT OF INTEREST STATEMENT

MR received fees consulting, lecturing or serving on advisory boards from Astra Zeneca, Boehringer-Ingelheim, Echosens, Eli Lilly, Merc-MSD, Madrigal, Novo Nordisk, Madrigal and Target RWE and has performed investigator-initiated research with support from Boehringer-Ingelheim, Novo Nordisk and Nutricia/ Danone to the DDZ. The research of MR is supported by grants from the German Research Foundation (DFG; RTG/GRK 2576), the European Community (HORIZON-HLTH-2022-STAYHLTH-02-01: Panel A) to the INTERCEPT-T2D consortium, BMG, MKW, BMBF and the Schmutzler-Stiftung. RW received personal fees from Eli Lilly, Boehringer-Ingelheim, Sanofi Aventis and Novo Nordisk, and has been on scientific advisory boards of Eli Lilly, Novo Nordisk, Daiichi Sankyo and Akcea Therapeutics. AB received personal fees from the Editorial Board 'Nutrition' and had a leadership or fiduciary role in the scientific committee of the transnational governance of the Nutri-Score system and Scientific Advisory Council for Agricultural Policy, Nutrition and Consumer Health Protection, Federal Ministry of Food and Agriculture. The research of AB has been supported by grants from the DFG (BU 1807/3-2) and Federal Ministry for Education and Research (CarbHealth (JPI/HDHL)). No other potential conflicts of interest relevant to this article were reported by the other co-authors.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15772.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed in the current study are available from the GDS on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schaefer E, Lang A, Kupriyanova Y, et al. Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet is associated with lower visceral and hepatic lipid content in recent-onset type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab*. 2024;26(10):4281-4292. doi:10.1111/dom.15772

Online supplementary information can be accessed at the following link:
https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15772

Chapter 6

Discussion

6.1 Key findings

The projects included in this dissertation were designed to address four research aims, with the objective of providing further insights and strengthening the evidence on the relationship between dietary aspects and both prevention and management of diabetes mellitus.

In summary, findings of this thesis show that:

1. Circulating FAs play a role in the development of T2D. Our findings provide robust evidence that higher concentrations of specific SFAs (15:0, 17:0), MUFA (18:2), and PUFAs (20:3, 22:6) in PPL and RBC are associated with a lower risk of T2D. In contrast, elevated levels of MUFAs (16:1n-7, 18:1n-9) and n-6 PUFAs (γ-20:3, γ-18:3, 20:4) in PPL and RBC were linked to a higher relative risk of T2D. Thus, implicating, that consideration of specific FAs within larger FAs groups (i.e., SFAs, MUFAs or PUFAs) is crucial. Furthermore, biospecimen-specific analyses aligned with results across combined biospecimens but demonstrated stronger associations for measurements in PPL and RBC, underscoring the importance of biospecimen selection in FA-T2D risk assessment. (Chapter 2 (130))

2. The effectiveness of dietary factors on health outcomes in the population with T2D has been extensively investigated. Although a broad range of dietary factors has been evaluated, high CoE supports liquid meal-replacement strategies for clinically meaningful changes in body weight and BMI, as well as carbohydrate restriction to <26% of total energy for improvements in HbA1c and triglycerides. Beyond energy restriction, individuals with T2D can choose between plant-based, Mediterranean, low-carbohydrate, and high-protein dietary patterns based on their preferences to achieve improvements in cardiometabolic health. (Chapter 3 (131))

3. Regarding long-term health outcomes, current evidence shows that intake of fish, whole grain, fiber and n-3 PUFAs is linked to lower risk of all-cause mortality in people with T2D. Increased consumption of vegetables and plant-based protein also appears to be beneficially associated with all-cause mortality risk, although further studies are needed to confirm this. Conversely, intake of animal-based protein, and accordingly of eggs and cholesterol, should be limited. Overall, associations between various dietary factors and mortality appear to be more

pronounced in people with T2D, compared to general population, highlighting the need for further research in this population and the development of tailored, population-specific dietary guidelines. (Chapter 4 (132))

4. The DASH diet represents a promising dietary approach for managing adipose tissue distribution in both T1D and T2D. Increasing adherence to the DASH diet was particularly associated with reductions in VAT and HLC in individuals with T2D, while weaker inverse associations were observed in T1D. Notably, the improvements in HLC can occur independently of weight loss, as BMI and waist circumference changes accounted for a maximum of 67% and 54% of the observed associations, respectively. Additionally, Adipo-IR explained 47% of the DASH-HLC relationship in those with T2D, highlighting a key mechanistic pathway. (Chapter 5 (133))

6.2 Diet in prevention and management of T2D: bridging evidence and practice

Overall, we demonstrated that different dietary strategies can lead to comparable improvements across a broad spectrum of cardiometabolic risk factors. Robust evidence supports calorie reduction through meal replacement, as well as plant-based, carbohydrate-restricted, and high-protein diets. Additionally, supplementation with soy protein, probiotics, psyllium, ginger, and anthocyanins has shown beneficial effects on anthropometric measures, blood lipid profiles, glycaemic control, and blood pressure. In terms of all-cause mortality risk, robust evidence supports higher intake of fish, whole grain, fiber and n-3 PUFAs.

Among these dietary approaches, carbohydrate restriction stands out as particularly effective. This dietary pattern has been studied most extensively and provides the most robust evidence of its benefits across multiple metabolic parameters (Chapter 3). However, body of evidence is still low to support low-carbohydrate diet for all-cause mortality risk reduction (Chapter 4). The quality of carbohydrates consumed seems to be important as well, as higher whole grain and fiber intake were associated with beneficial health effects (Chapter 3 and 4). Additionally, increasing fiber consumption, and following a low glycaemic index diet appear to be a common denominator in strategies for both the prevention and management of T2D (45, 134). However, the evidence for beneficial association between overall low-cabrohydrate diet and T2D risk is very low (45).

In terms of protein intake, contrary to current diabetes management guidelines, the robust evidence in our umbrella review supporting higher protein intake for blood lipid control offers

new insights into dietary management of diabetes (Chapter 3). However, theoretically, increasing protein intake while keeping total energy intake constant could also reflect a lower carbohydrate diet. Furthermore, when recommending higher protein intake, the source of dietary protein seems to be crucial. We found beneficial associations for plant-based protein in terms of all-cause mortality, while higher risk was observed for higher egg and animal-based protein intake. Furthermore, replacing 2% energy from carbohydrates with 2% energy from plant-based protein was associated with 24% lower mortality risk, while no association was observed for replacement with animal-based protein (Chapter 4). In addition, a recently published study showed that higher adherence to a plant-based diet was linked to lower the risk of all-cause, CVD and cancer mortality in NHANES participants with diabetes (135). A consistent picture also emerged from our umbrella review, with plant-based and soy protein supplementation showing a beneficial effect on anthropometric measures and blood lipid levels (Chapter 3). Beneficial effect of plant-based protein was also evident in meta-analyses of RCTs, where replacement of animal with plant protein lowered HbA1, fasting glucose and insulin in people with diabetes (136). Also, for T2D prevention, following a vegetarian diet, increasing intake of vegetable fat and berries was associated with lower risk of T2D (45). Furthermore, higher intakes of total and animal protein, red and processed meat, eggs, and cholesterol were associated with an increased risk of T2D, while plant protein intake was inversely associated (45).

Consistently with current diabetes management guidelines (91), a low-fat diet did not appear to be the optimal approach for individuals with T2D, as it only results in minimal and clinically insignificant improvements in blood lipid profiles (Chapter 3). We also found no association between higher SFAs intake and all-cause mortality risk (Chapter 4). In contrast, fat quality seems to play a more important role. Our results suggest cardio-protective effects of n-3 PUFAs supplementation in reducing the risk of major adverse cardiovascular events, a positive effect of PUFAs supplementation on glycaemic parameter (Chapter 3) and strong evidence on beneficial association between higher n-3 PUFAs intake lower risk of all-cause mortality (Chapter 4). Although current guidelines for diabetes prevention recommend diets high in MUFAs (137), dietary intake of MUFAs and PUFAs was imprecisely but positively associated with T2D risk (138). However, our findings indicate beneficial effects of long-chain n-3 PUFAs, as we observed inverse associations between their circulating concentration and T2D risk (Chapter 2). This discrepancy may be due to confounding in dietary intake studies, such as cooking methods (e.g., deep-frying) (139). Moreover, as our study shows, specific FAs within broader FA categories (e.g., SFAs, MUFAs, or PUFAs) can have different associations with

T2D risk. This may explain why studies evaluating entire FA groups often yield weaker or imprecise associations.

In summary, a coherent picture emerges regarding optimal dietary strategies for individuals with T2D. Caloric reduction should be prioritized for those with overweight or obesity. Beyond this, individuals with T2D should focus on reducing carbohydrate intake while simultaneously paying attention to the quality of carbohydrate consumed, choosing mainly whole grain products and increasing dietary fiber consumption to lower the glycemic index of their diet. Additionally, protein intake, particularly from plant-based sources such as soy, appears to be a crucial dietary component. Given the strong evidence supporting the benefits of ginger, almonds, and anthocyanins, as well as adverse associations for animal-based protein, egg and cholesterol intake with all-cause mortality risk, a general emphasis on consuming a more plant-based diet represents a promising approach to improving metabolic health and reduce the risk of premature mortatliy among people with T2D. Additionally, focusing on fat quality instead lowering overall fat intake can be beneficial. These recommendations seem to be universal for both prevention and management of T2D. Furthermore, shifting recommendations to dietary pattern level, the DASH diet seem to be a promising approach for both T2D prevention and management (45) (Chapter 5) and potentially for premature mortlity risk reduction in people with T2D (Chapter 4). Many of its individual components - such as fruit, vegetables, nuts and legumes, dairy products and whole grains - align with the overall picture of diet for which we identified robust evidence of benefit. Additionally, its emphasis on reducing sodium intake and increasing potassium-rich foods may further contribute to improved blood pressure regulation, an essential consideration for individuals with T2D (140).

Finally, given the variety of effective dietary strategies available, individuals with T2D should select an approach that best aligns with their personal preferences and lifestyle, whether through a structured dietary pattern or a focus on macronutrient composition. Prioritizing individual preferences may enhance long-term adherence, ultimately contributing to sustainable health improvements (33, 76).

6.2.1 Limited evidence of popular dietary approaches

Despite the robust evidence supporting several dietary approaches, not all emerging diets have shown consistent benefits. For example, recent trends like the ketogenic diet and intermittent fasting have raised interest, but current evidence from systematic reviews and meta-analyses of RCTs remains insufficient to confirm their effectiveness in diabetes management. For intermittent fasting, a modest reduction in body weight of about 2 kg was observed, but there was no effect on HbA1c, with both outcomes showing very low CoE. The ketogenic diet led to

a reduction of about 3 kg in body weight, a decrease of 0.6% in HbA1c and a reduction of 0.2 mmol/mol in triglycerides. However, the CoE was ranging from low to very low. The small sample sizes in these studies (fewer than 400 participants) were a major reason for downgrading the CoE. Consequently, the low to very low robustness of evidence for both diets indicates that these estimates may change with the inclusion of future studies, making it difficult to draw firm conclusions about their benefits for diabetes management. Further research is needed to clarify their potential role.

At the same time, evidence on the health impact of well-established dietary patterns, like the Mediterranean or DASH diet, on T2D management is very limited. In our systematic review with meta-analysis, we identified three studies on Mediterranean diet adherence and two on DASH diet adherence in relation to all-cause mortality in individuals with T2D (Chapter 4). We did find inverse associations between these two dietary patterns and all-cause mortality risk; however, the CoE for these results was very low. This was mainly due to insufficient adjustment for important confounders, such as diabetes duration or treatment, and imprecise estimates. In our umbrella review, the Mediterranean diet showed no beneficial effect on body weight reduction, with the only robust finding being an improvement in triglyceride concentrations (Chapter 3). Another systematic review with meta-analysis reported inverse associations for both Mediterranean and DASH diets with cancer risk among people with T2D, although the CoE was similarly rated as low to very low (141). Notably, we did not identify any studies evaluating the health impact of vegetarian, vegan, or planetary health diets on mortality risk in individuals with T2D (Chapter 4). Understanding the health effects of these dietary patterns is increasingly important, as modern dietary recommendations must address not only health but also environmental sustainability (142). Furthermore, evidence on the associations between dietary patterns and other diabetes-related health outcomes - such as CVD or neurodegenerative disorders - is largely lacking.

A similar gap exists at the level of specific food groups. While there is a substantial body of evidence supporting the role of different foods in T2D prevention (45), evidence on their association with health outcomes in individuals with T2D is limited. We identified a sufficient number of primary studies to conduct meta-analyses and evaluate the CoE for several food groups; however, evidence regarding the intake of other important foods, such as specific dairy products (milk, yogurt, cheese), meat (white meat, red meat), legumes, white or fatty fish, and potatoes and all-cause mortality risk in T2D remains unstudied. In a recent systematic review and meta-analysis on dietary factors and cancer outcomes in individuals with T2D, no meta-analyses could be conducted for any food group or item due to the limited number of available

studies (141). Consequently, also associations for food groups and outcomes such as cancer, but also CVD, and neurodegenerative disorders in people with T2D remain unclear, underscoring a critical need for further research.

6.2.2. Does one size fit all?

Results of our systematic-review and meta-analysis consistently indicate stronger associations between dietary factors and all-cause mortality risk in people with T2D compared to general population (Chapter 4). For example, we observed a 13% lower risk of all-cause mortality per 0.1g/ day of n-3 PUFAs, whereas a 7% lower risk per 0.1g/ day of n-3 PUFAs was reported in a general population (143). Similarly, Jayedi et al. found a 14% lower risk of all-cause mortality when comparing higher vs lower fish intake in people with T2D (90), while the corresponding risk reduction in the general population was 6% (143). Furthermore, meta-analyses of RCTs also pointed to larger effects in population with T2D. In our umbrella review, a 10% reduction in carbohydrate intake led to a 1.34 kg body weight reduction after 6-12 months, whereas in the general population with overweight or obesity (Chapter 3), the same 10% reduction in carbohydrate intake resulted in a 0.64 kg body weight reduction after 6 months (144). Stronger diet-health associations in people with T2D may reflect their elevated risk profile, characterized by insulin resistance, chronic inflammation, and adiposity (2), which may allow for greater improvement when adhering to a higher quality diet. These findings underscore the importance of dietary management for treatment and secondary prevention in individuals with T2D, while also suggesting that a 'one-size-fits-all' approach may not be appropriate and that results from the general population may not always be directly applicable to this group. As a consequence, there is a need to fill this evidence gap and develop evidence-based, population-specific dietary guidelines.

Beyond the population-level differences described above, recent research has increasingly drawn attention to the substantial heterogeneity among individuals with T2D. Variability in risk factors and underlying pathophysiology contributes to differences in preclinical abnormalities, comorbidities, and complications observed at T2D onset. Disease progression and complication risk were shown to vary between individuals with T2D, even when glycaemic control levels are similar (145). Studies using clustering approaches have demonstrated differences among specific groups of people with T2D regarding their risk of developing complications (146-148). At the same time, classification based on simple clinical characteristics, such as age at diagnosis, presence of obesity, and glycaemic control (149-152), has also revealed differences in mortality, chronic kidney disease, retinopathy, cardiovascular disease, and heart failure risk (150), and could predict responsiveness to lifestyle interventions (152). Therefore, although not

implemented in this work, identifying high-risk subgroups of individuals with T2D who respond differently to lifestyle and dietary interventions is of major public health interest and should be addressed in future studies. Subgroup identification may enhance precision nutrition by targeting those most likely to benefit from specific interventions, while integrating personalised risk profiles with tailored advice could improve intervention effectiveness, support behavioural change, and promote cost-effective outcomes (153).

6.3 Complexities of dietary biomarkers

Studies examining dietary intake often point to contradictory findings compared to biomarker-based studies. Based on examples from this dissertation, higher fish consumption - a key source of n-3 PUFAs - has been linked to increased T2D risk, particularly in women, and a meta-analysis of 16 cohorts found that dietary EPA and DHA intake was associated with higher T2D risk (138, 154). In contrast, our study observed robust inverse associations between circulating long-chain n-3 PUFAs and T2D (Chapter 2). Similarly, the imprecise associations between α-linolenic acid (α-18:3) and T2D in our study contrast with findings on its dietary sources (155). Foods like walnuts and flaxseeds, rich in α-linolenic acid (α-18:3), also contain fiber, magnesium, and phenolic compounds, which may mediate the associations seen in dietary studies (156). The lack of association in our study may be due to limited endogenous conversion of α-linolenic acid (α-18:3) to long-chain n-3 PUFAs (157). Another contradiction is present for MUFAs: although intake of MUFA-rich foods (e.g., nuts, seeds, olive oil) has been inversely associated with T2D (45, 138, 158, 159), we found positive associations between circulating oleic acid (18:1) and total MUFAs and T2D. This may reflect endogenous synthesis of oleic acid (18:1) via DNL or elongation from SFAs (e.g., 16:0 and 18:0) (69, 160). These differences highlight the inherent limitations of dietary data collection.

The associations observed for self-reported dietary intake of a specific food or food compund, may be confounded by other bioactive compounds present in the same dietary source. However, also in the case of objectively measured concentration of a given biomarker, interpretation is not straightforward and their concentration may not solely reflect the dietary intake. For example, serum calcium measurement may also be influences by the albumin concentration, as a large fraction of circulating calcium is bound to albumin (161). In case of FA biomarkers, endogenous synthesis, particularly via DNL, complicates the interpretation of circulating FAs as dietary biomarkers. DNL converts dietary starch, sugar, and protein into lipids, primarily producing palmitic acid (16:0), which can be elongated to stearic acid (18:0) or desaturated to palmitoleic acid (16:1n7) and further to oleic acid (18:1) (62). Furthermore, DNL is also

influenced by various factors, including high alcohol intake, high-glycaemic carbohydrates (which promote it), and coffee or n-6 PUFA intake (which suppress it), as well as sleep, meal frequency, and physical activity (61, 62, 162-164). Similarly, odd-chain FAs, once considered good markers of dairy intake, are now known to be influenced by fiber, branched-chain amino acids, and fish oil intake (165). Therefore, it remains unclear to what extent the associations observed in our study, especially for SFAs and MUFAs, can be attributed to dietary intake or to endogenous synthesis. Perhaps a new broader perspective may be necessary - interpreting certain FA patterns as lifestyle markers. For example, elevated palmitic acid (16:0) and stearic acid (18:0) may reflect unhealthy habits like high alcohol/sugar intake and low physical activity, while higher odd-chain FAs may indicate a healthier, fiber-rich diet and distinct gut microbiota (165, 166).

Additionally, although biomarkers offer an objective assessment of dietary exposure compared to self-reported data, their reliability may be limited when based on a single measurement, as it may not adequately capture long-term dietary patterns or account for within-person variability, just as in case of self-reported data (54). Several studies have demonstrated that blood FA levels can fluctuate over time, and a single measurement may not accurately reflect long-term status. Notably, correlations between two circulating FA measurements taken three years apart were higher than those between measurements taken 15 years apart (167, 168). Moreover, even if an individual's dietary FA intake remains stable, policy-driven changes in the FAs composition of available foods can lead to shifts in circulating FAs levels over time (169). This problem is also relevant for other biomarkers, for instance serum folate concentration is rather considered an indicator for recent folate intake and cannot be used to differentiate between deficiency states (170). Similarly, urinary sodium intake is a good measure of short-term sodium intake but its excretion is as variable as intake itself and seasonal variation has been observed as well (54). This highlights the need for cautious interpretation of biomarker measurements at single time point in epidemiological studies, as well as the need for future studies taking changes in biomarker concentration over time.

Furthermore, intercorrelations among specific FAs complicate the isolation of individual FA effects on disease risk. For example, associations between trans-palmitoleic acid (t-16:1n7) and T2D risk were attenuated after adjusting for other trans-FAs, while the association between linoleic acid and T2D weakened after adjustment for DNL-related FAs (171, 172). Emerging multi-omics approaches - including lipidomics, proteomics, and integrative analyses - aim to overcome the limitations of traditional dietary assessment by capturing a broad spectrum of molecular markers. Given the complex mixture of bioactive compounds in foods that may act

synergistically, omics can offer a more nuanced understanding of dietary exposures and their biological effects. By reflecting the molecular signatures of specific foods or dietary patterns, these profiles enhance specificity and reduce misclassification (173). For instance, a recent study developed a lipidomics-derived score based on 45 lipid metabolites using data from a RCT that replaced SFAs with unsaturated fats (174). This score, reflecting lower SFA and higher plant-based unsaturated FA intake, was associated with a 20-30% reduced risk of T2D and CVD in prospective cohorts. Notably, these associations were stronger than those seen with conventional markers, suggesting greater cardiometabolic benefits from improved fat quality than previously thought. Thus, omics approaches provide deeper insights into the biological responses to diet - including absorption, metabolism, and systemic effects - and hold promise for advancing nutritional epidemiology by addressing key limitations of traditional methods (173).

6.4 Weaker dietary associations in persons with T1D

With regards to persons with T1D, DASH diet seems to be beneficially associated with adipose tissue distribution in our work (Chapter 5); however, observed associations were weaker than in persons with T2D. One could argue that this can be caused by differences in pathophysiology of these two diabetes types or by the intense insulin therapy in those with T1D. The more stable metabolic state typically seen in T2D could make diet-induced changes in fat distribution more evident in this group. Additionally, individuals with T1D may experience greater glycaemic variability, which may obscure the relationship between diet and fat distribution (175). Another possible explanation for the weak associations observed in this thesis could be the fact that participants with T1D were newly diagnosed, more than half of having a normal body weight and HLC ranging from 0.4 to 0.2%, which is within the normal range (176). As a result, no substantial improvements may have been observed with increased adherence to the DASH diet. Nevertheless, dietary approaches are still an important element of T1D management. For example, a RCT with individuals with T1D and metabolic syndrome showed that both, Mediterranean and low-fat diet were effective in improving anthropometric measures, such as waist circumference and BMI over 6 months intervention (177). Another study showed that adults with T1D meeting Canadian nutrient recommendation and Mediterranean diet score had a lower truncal fat percentage (18% vs 32%) (178). Furthermore, in a study on youth (<20 years) with T1D, an increase in DASH diet score was associated with a decrease in HbA1c levels by 0.2% (179). Finally, higher adherence to DASH, Mediterranean diet and Healthy

Eating Index score were inversely associated with incident microalbuminuria in young adults with T1D; however, associations diminished after adjustment for HbA1c levels (180).

Recently, a systematic review and meta-analysis of RCTs on dietary patterns and glucose control outcomes in T1D was published (181). Interventions focused on carbohydrate restriction and increased dietary fiber intake led to improvements in time in range - a key metric reflecting the percentage of time blood glucose levels remain within the target range - and reductions in HbA1c, both supported by moderate CoE. Interestingly, low-carbohydrate diets did not affect HbA1c levels in T1D, in contrast to the robust evidence observed for HbA1c improvements with low-carbohydrate diets in people with T2D in our study (Chapter 3). Zeng et al. suggest that the lack of effect in T1D may be due to the short duration of most interventions, with the majority lasting less than three months, which can be insufficient to detect meaningful changes in HbA1c (181). Furthermore, no effects of Mediterranean diet on HbA1c were observed in individuals with T1D, while our umbrella review pointed to 0.3% reduction in HbA1c level with this dietary pattern (Chapter 3). The absence of an effect from high-protein diets on HbA1c in T1D aligns with findings from our analyses in T2D populations. Other dietary patterns - such as higher-protein, low-glycaemic index, gluten-free, intermittent fasting, and vegan diets - also showed no impact on glucose management in T1D (181). However, the evidence supporting these findings was limited due to the small number of available studies and potential benefits may become more apparent as research expands. For example, components of the Mediterranean diet - such as its high content of unsaturated fats and antioxidants - have been shown to improve insulin sensitivity and could potentially benefit individuals with T1D as well (182, 183). Finally, recent studies have shown that overweight and obesity are also becoming a problem among people with T1D, further highlighting the need to investigate dietary interventions in this group (184).

6.5 Is it more than simply weight loss?

While the beneficial effects of lifestyle interventions are evident, the underlying mechanisms are not completely understood. A key question in this context is whether these benefits, including those from dietary changes, are primarily driven by weight loss and its consequent effects on health outcomes, or whether improvements in diet quality alone are sufficient to result in health benefits. Our study (Chapter 5) found that while changes in BMI and waist circumference explained up to 67% of the changes in VAT and HLC associated with better adherence to the DASH diet in individuals with T1D and T2D, a substantial proportion of these improvements may be driven by mechanisms beyond weight loss - particularly metabolic

adaptations such as enhanced insulin sensitivity. Specifically, changes in Adipo-IR accounted for 47% of the association between DASH adherence and HLC in individuals with T2D.

Regarding existing literature, on the one hand, evidence from large trials, including the DiRECT and the Look AHEAD trial, highlights weight loss through lifestyle interventions as the key factor in reducing the risk of diabetes complications and achieving disease remission. In the DiRECT trial, 46% of participants achieved T2D remission at 12 months, defined as HbA1c below 48 mmol/mol (6.5%) without medication, through a structured weight management programme (185). Furthermore, a reanalysis of the Look AHEAD trial showed that participants who lost at least 10% of their body weight had a 20% lower risk of CVD (33). Supporting these findings, mechanistic studies in a sub-cohort of the DiRECT trial have shown that diabetes remission is closely associated with the reduction of ectopic fat in the liver and pancreas. This fat accumulation impairs organ function and contributes to β-cell failure - both of which appear to be reversible, particularly in the early stages of T2D (43, 186). Consistent with this concept, data from the Look AHEAD trial also showed that a 5% reduction in total body fat percentage was associated with a 0.15% (95% CI 0.12; 0.18) decrease in HbA1c over the follow-up period (187).

On the other hand, not all findings align with the idea that weight loss alone is the primary determinant of diabetes or prediabetes remission. The Prediabetes Lifestyle Intervention Study (PLIS) found that participants who achieved remission and those who remained prediabetic after lifestyle treatment experienced similar weight loss. Instead, greater improvement in insulin sensitivity were observed among participants who returned to a normal glucose tolerance state (188). Similarly, also among people with T2D, remission was more closely linked to improved insulin secretion (188). These findings suggest that improvements in insulin sensitivity and β-cell function may be more central to remission than weight loss itself.

Some evidence from observational studies further supports the idea that dietary effects on metabolic health may not fully be explained by body weight changes. For instance, a study using objective sucrose biomarkers showed that BMI explained only 16% of the association between sucrose and diabetes risk (189). Likewise, data from the UK Biobank found that overweight mediated just 10% of the observed 14% reduction in diabetes risk associated with a Mediterranean diet (190). Furthermore, a systematic review and meta-analysis on interventions based on carbohydrate-restricted diets in T2D management demonstrated improvements in cardiometabolic risk factors even in the absence of caloric restriction, emphasizing the potential for weight-independent benefits of dietary composition (191). Additionally, nearly all studies included in our systematic review and meta-analysis on FA

biomarkers and T2D risk adjusted for BMI, making observed associations independent from overall adiposity (Chapter 2).

These findings highlight the complexity of the mechanisms linking lifestyle to diabetes outcomes. While weight loss clearly improves health, metabolic improvements - particularly enhanced insulin sensitivity - may be at least as important. This question has gained new relevance with the widespread use of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which have shown impressive weight-loss effects through their appetite-suppressing effect and are increasingly used both in T2D treatment and obesity management (192). However, their real-world effectiveness often falls short of clinical trial results due to limited adherence, treatment discontinuation, and the lack of representativeness of trial populations (193, 194). Moreover, weight regain typically occurs after cessation of therapy (195). Importantly, combining GLP-1 RAs with nutritional education led to greater weight loss and a higher proportion of participants achieving ≥10% body weight loss after 2 years, compared with GLP-1 RA treatment combined with standard care (196). Finally, similar effects of lifestyle interventions and GLP-1 RAs on body weight and hepatic fat have been demonstrated in RCTs in populations with MASLD (197).

In summary, although weight loss remains a critical component in diabetes prevention and remission, emerging evidence suggests that it is not the only, or always the most decisive factor. Improvements in insulin sensitivity, reductions in ectopic fat, and favourable changes in dietary quality could benefit health independently of weight loss. Therefore, as the use of pharmacological weight-loss agents increases, it is important to recognize that it may indeed be more than simply weight loss, and sustainable diabetes remission requires lasting lifestyle changes that improve metabolism.

6.6 Expanding horizons: are RCTs always the best choice?

Evidence from both observational and interventional studies was combined to answer the objectives of this doctoral thesis. This approach allowed the investigation of broad, nutrition-related questions that would have been difficult to address using a single study design.

The debate over whether both RCTs and prospective observational studies can provide reliable results for decision-making has been ongoing for years (198). Although the GBD studies and most dietary guidelines draw primarily on body of evidence from cohort studies, with RCT data playing a secondary role, nutritional epidemiology in particular has been criticized for yielding estimates of diet-related risks and benefits that may be less reliable (199). Interestingly, a recent Cochrane review pointed to very little to no differences between the effect estimates from RCTs

and observational studies addressing the same health-related study question (200). Similarly, another study systematically compared bodies of evidence from RCTs and cohort studies on nutrition-related questions and found only minor differences in effect estimates between the two designs (201). However, wide prediction intervals and substantial statistical heterogeneity across cohort studies suggest the possibility of bias or true underlying differences. Variations in effect estimates may partly stem from how exposures or comparisons are categorized as 'similar' across RCTs and observational studies, despite, meaningful differences in factors such as dosage or duration. The two study designs often also differ in terms of study populations. For example, participants in RCTs investigating supplements like selenium often already have adequate selenium levels (202, 203), whereas observational studies typically encompass individuals with a broader range of selenium status (204). Consequently, risk estimates from trials and cohorts may not be directly comparable. Notably, as shown by Schwingshackl et al., when the type of dietary intake or exposure was consistent across both study types, the effect estimates aligned closely and showed low heterogeneity (201). Comparing our results (Chapter 2) with intervention studies on omega-3 FAs supplementation illustrates this point: we observed an inverse association between circulating omega-3 FAs and T2D risk, whereas intervention studies on diabetes prevention reported no effect (50), suggesting that differences in exposure classification between study types may lead to divergent results. Comparing other results from this work, i.e., systematic reviews and meta-analyses of RCTs on dietary treatment of T2D, was not possible due to the very limited evidence available from observational studies on changes in surogate markers in this population. Similarly, meta-analyses of RCTs investigating diet and hard endpoints in people with T2D are rare, and prospective observational studies examining various dietary exposures and outcomes in this population are also limited, as described in detail in Chapter 6.2.1. Additionally, no RCT investigated effects of DASH diet on VAT, SAT or HLC in people with T1D or T2D.

Typically, a common argument in favour of RCTs is that, due to the randomization process accounting for unknown confounding factors causal effects can be established. Additionally, RCTs are less prone to systematic errors and are therefore considered the gold standard. Random allocation of participants into treatment arms reduces selection bias, blinding helps prevent bias in outcome assessment, and the standardization of procedures and protocols across intervention and control groups ensures consistency in how participants are treated. On the other hand, observational studies evaluate the effectiveness of an exposure in real-world, non-experimental settings at the population level and are generally considered to have a higher risk

of bias - mainly due to unmeasured confounding or inadequate adjustment for known factors (68).

However, depending on the question being studied, RCTs have limitations and observational studies can be used to give an indication of the effectiveness of an intervention (205). This is particularly relevant in the field of nutritional epidemiology (96). Studies investigating long-term outcomes, such as the impact of an intervention on the incidence of T2D or its complications, require prolonged follow-up periods or large study samples - both of which are often challenging, resource-intensive, and financially unfeasible within the setting of an RCT. For instance, in this thesis (Chapter 3), we identified only two meta-analyses of RCTs that examined the effects of dietary factors on the incidence of complications or adverse events in individuals with T2D (76, 206). Withouth involving evidence from prospective observational studies, it would have not been possible to investigate associations on dietary factors and all-cause mortality risk in T2D population (Chapter 4). On the other hand, when it comes to the effects of diet on surrogate or clinical markers, RCTs offer a more feasible approach, as they do not require large cohorts or prolonged follow-up and can provide results within a shorter timeframe. However, in nutritional studies, participants' awareness of being in a trial - even when blinded, can lead to changes in lifestyle-associated behaviours. Additionally, fixed dietary protocols or intensive follow-up schedules, may limit the generalizability of findings to real-world settings. For dietary pattern or food-based interventions, double-blinding is not possible because participants are aware of the dietary changes they need to make. Furthermore, creating a true placebo group is challenging. If the intervention group is instructed to eat more vegetables, it would be unethical to require the control group to avoid them entirely. Another example is when the intervention group receives PUFA supplements - completely eliminating these FAs from the diet of the control group is difficult, which may dilute the observed effect. The fact that nutrients and foods are not consumed in isolation makes choosing a control group even more challenging. Reducing one often leads to an increase in another in order to maintain caloric balance. For example, lowering fat intake typically results in higher carbohydrate consumption, and vice versa (96).

6.6.1 Balancing evidence from RCTs and observational studies

Although observational studies have their limitations, if well-conducted can significantly contribute to current evidence. In fact, much of the current evidence in nutritional research is derived from cohort studies (91). Therefore, findings from both RCTs and observational studies should be considered for integration into clinical guidelines. Applying state of the art approaches during evidence synthesis, as done in this work, enables direct comparison between

observational and interventional study findings and facilitates the complementary integration of evidence in contexts where a single study design may be insufficient. Due to the rigorous assessment of study quality, presence of inconsistency and imprecision in the results, a moderate CoE from observational studies is considered equivalent to a moderate CoE from intervention studies.

As outlined in the introduction, the revised evidence hierarchy also reflects this perspective. It emphasizes that systematic reviews and meta-analyses should not judge the validity of an effect estimate solely based on study design. Instead, they should critically assess methodological quality, risk of bias, and the overall certainty of the body of evidence (117). Correspondingly, the new GRADE approach applied in this thesis addresses this issue suggesting a way to balance and enable direct comparison of evidence from both RCTs and observational studies. When considering evidence from non-randomized studies, the ROBINS-I tool should be used to assess these studies' risk of bias (118). A newer version of this tool, ROBINS-E, has since been developed specifically for evaluating non-randomized studies of exposures (207), but it was not yet available when project described in Chapter 2 and 4 began. ROBINS-I tool encourages reviewers to consider how the study would have been conducted in an ideal randomized setting. If a non-randomized study is deemed to have a low risk of bias, it may be considered equivalent to a well-conducted RCT. If ROBINS-I tool was used, initial starting point of CoE can be rated as high, similar to meta-analyses based on RCTs. However, because residual confounding cannot be entirely ruled out, meta-analyses of observational studies should generally be downgraded at least by one level in the risk of bias domain (123). Nonetheless, if there is evidence of a large effect size or a clear dose-response relationship, the CoE may be upgraded. The rationale is that the larger the observed effect, the more unlikely it is that residual confounding alone could explain it (123). This nuanced approach enables, at least theoretically, the integration of evidence from both RCTs and observational studies in a single systematic review. The GRADE Working Group has also provided guidance on when evidence from non-randomized studies should be incorporated into guideline development (205). These include situations where RCTs are unfeasible or unethical, when addressing questions related to exposures (rather than interventions), when serious indirectness is expected from RCTs, or in the case of urgent public health questions. In the context of this work, RCTs are often not feasible for investigating long-term dietary effects on diabetes risk, its complications or mortality risk; however, they can provide valuable insights when assessing effects on clinical biomarkers. Moreover, when the available RCT evidence is of low or very low certainty, high-quality observational data may strengthen the overall body of evidence.

In fields such as nutrition and public health - where long-term exposures or complex behaviours often limit the feasibility of RCTs - a rigorous yet flexible approach to evidence synthesis is essential. Therefore, evidence coming from observational studies on diet and diabetes prevention and management should not be inevitably subject to criticism or considered as lower-quality evidence, as these studies provide valuable insights in areas where RCTs are not implementable or realistic. Embracing tools such as ROBINS-I/E and updated GRADE methods offer a path forward, enabling more balanced and transparent guideline development that reflects the full spectrum of available evidence.

6.6.2 Clinical relevance of effect sizes in nutritional studies

Observed effect sizes also influence the overall CoE assessment. As mentioned above, large effect sizes observed in the meta-analyses of observational studies can theoretically lead to an upgrade of the CoE by one level (123). However, if a threshold for the minimal important difference/ effect/ association is included within the 95% CI, the CoE should be downgraded by one level for imprecision. This is because the CI does not exclude the possibility of a clinically unimportant effect, making it difficult to determine whether an association truly exists.

A large proportion of the evidence presented in this thesis has been downgraded due to the inclusion of minimal important difference in the 95% CIs. At the same time, various dietary strategies discussed above, were not punished for issues associated with imprecision, and demonstrated robust effectiveness in improving cardiometabolic risk factors. However, despite being rated as robust evidence, many of these results can be criticised for their clinical relevance, or rather, their lack thereof. For instance, a body weight reduction of 5% has been generally accepted as clinically meaningful for achieving health improvements. For individuals weighing 80 to 100 kg, this corresponds to a weight loss of 4 to 16 kg. At this level of weight reduction, improvements in glycaemic control have been observed (208), while changes in blood lipids appeared after a 16% body weight reduction (209). In contrast, the Look AHEAD trial, which included participants with existing diabetes, showed improvements in glycaemic control already after body weight loss of 2-5% (210). Body weight reduction of 2.4 kg after dietary interventions of duration between 12-52 weeks (211) or 1.3% percentage decrease in HLC over 5-year follow-up period reported in this thesis may be perceived as minor. Especially when compared to the reductions seen with GLP-1 RAs, which showed a 14 kg difference in body weight over 12-78 weeks, compared to the placebo group (212). However, in this context it is crucial to consider the nature of the comparator groups in nutritional studies. The control groups in intervention studies or comparator groups in observational research are not entirely

free from dietary factors that are included in the intervention or considered as an exposure, as would be the case in drug studies. This often reduces the observed differences between groups and leads to weaker effects or associations. Furthermore, because nutrition represents a lifelong exposure, even modest changes can accumulate over time and result in substantial long-term health benefits. What may appear to be small effect sizes in short-term studies should be interpreted within the broader context of chronic disease prevention and management. Even small changes in body weight, and consequently lipid profiles, or glycaemic control, when sustained over time, can lead to long-term health benefits, thus calling for a more comprehensive perspective when evaluating these effect sizes.

6.7 Strengths and limitations

A key strength of this doctoral thesis is the integration of multiple levels of evidence, encompassing an umbrella review, systematic reviews with meta-analyses, and a clinical cohort study. This thesis employed diverse study designs, including meta-analyses of both RCTs and observational studies, while also incorporating advanced methodologies, such as mediation analysis in a primary observational study. Mediation analysis allowed us to investigate which mechanisms or metabolic pathways contribute most to observed associations. In the context of T2D prevention, this thesis demonstrates that using specific biospecimens for FAs measurement, such as PPL and RBC, can strengthen the validity of biomarker-based findings. Moreover, rigorous evaluation of dietary interventions for T2D management, through critical appraisal and comprehensive evidence synthesis, ensures that the conclusions drawn are both reliable and applicable in clinical practice, supporting the development of evidence-based recommendations. Furthermore, we summarized studies on the whole range of dietary factors and all-cause mortality risk among people with T2D for the first time, thereby adding substantial evidence on diet and long-term health outcomes. Additionally, we provide novel insights into the role of dietary approaches, such as the DASH diet, in managing both T1D and T2D, expanding the current understanding beyond weight loss alone.

However, several methodological limitations must be acknowledged. First, causal inferences can only be derived from observational data under certain assumptions. Although most of the important confounders has been considered, residual confounding cannot be ruled out. Additionally, substantial proportion of studies on dietary factors and all-cause mortality in T2D did not adjust for crucial confounders, such as diabetes duration, medication or energy intake. Regarding exposure assessment, although validated dietary assessment tools were used, self-reported data are inherently susceptible to biases such as underreporting, social desirability bias,

and recall bias. Furthermore, although objective biomarkers for FA assessment circumvent some limitations of self-reporting, their concentrations are influenced not only by dietary intake but also by endogenous metabolic processes, thereby complicating the interpretation of associations. Selection bias is another potential concern. Individuals who voluntarily participate in both intervention and observational studies tend to be healthier and may not be fully representative of the general population, which limits the generalizability of the results. Furthermore, a key limitation of systematic reviews is its dependence on the quality and comprehensiveness of the included studies. Finally, as discussed in Chapter 6.6, the design of dietary intervention studies presents inherent challenges, particularly with respect to randomization and blinding, which can introduce methodological limitations.

6.8 Implications for public health and future research

From a public health and T2D prevention perspective, our findings highlight the need to account for differences in the associations between specific FAs within the same group, such as SFAs, when shaping prevention strategies for T2D. Furthermore, since higher concentrations of odd-chain FAs, linoleic acid, and long-chain n-3 PUFAs - which partially reflect dietary intake - were beneficially associated with T2D risk, the general recommendation to lower total fat intake for T2D prevention no longer seems accurate. On the other hand, the complex interpretation of circulating FAs as biomarkers of dietary fat intake raises questions about direct integration of these findings into dietary prevention guidelines of T2D. Thus, our results open a new perspective and support shifting away from a reductionist focus on individual nutrients and adopting a more comprehensive, systems-based approach that considers metabolic pathways, overall dietary quality, and lifestyle factors in disease risk assessment and prevention.

With regard to dietary management of T2D, there is a range of evidence on the effectiveness of various dietary approaches on cardiometabolic markers in this population. Persons with existing T2D, beyond approaches focusing on energy restriction like liquid meal replacement diet, can choose between dietary approaches like plant-based, Mediterranean, low-carbohydrate, and high-protein diet. In terms of long-term health effects, like all-cause mortality, current evidence supports higher intake of fish, whole grain, fiber and n-3 PUFAs. Overall, the available evidence presents a consistent picture of what constitutes a healthy diet for both the prevention and management of T2D. However, evidence on the associations between diet and various long-term outcomes in individuals with diabetes - such as the incidence of diabetes-related complications - and the health impacts of additional dietary patterns, including the Nordic diet, Planetary Health Diet, or specific food groups (e.g., dairy products, legumes, meat, sugar, and

artificially sweetened beverages) remains limited. To address these gaps, future long-term studies conducted specifically in people with T2D are needed. Importantly, it is essential to look beyond RCTs, as well-conducted observational studies, considering all potential confounding factors and using validated tools, are also crucial for capturing real-world dietary exposures and long-term associations. Finally, since diet is a key component in the management of T1D as well, more research is needed in this area, especially with regard to the onset of long-term complications.

Furthermore, the DASH diet, which can be seen as marker for higher dietary quality, shows promise as another effective strategy for managing diabetes. Importantly, these benefits were only partly due to weight loss, suggesting that improving dietary quality can have independent positive effects on metabolic health. This highlights that adopting a healthy diet offers advantages beyond simply losing weight, supporting its role as a valuable approach in diabetes management alongside medical treatments. From a public health standpoint, emphasizing the broad benefits of dietary improvements may encourage greater acceptance and motivation for lifestyle changes. Future research should explore how diet quality and weight loss interact in diabetes care, helping to refine guidelines and promote sustainable, holistic management strategies.

6.9 Conclusions

Understanding the impact of diet on T2D requires a multifaceted approach - this doctoral thesis integrates evidence from biomarker studies, RCTs and observational studies to inform strategies for both prevention and management of the disease.

The findings highlight the relevance of FA biomarkers in the association with T2D risk and enhance our understanding of the distinct role of individual FAs. Several dietary approaches with robust evidence offer health benefits in people with T2D. Energy-restricted, plant-based, Mediterranean, DASH, low-carbohydrate, and high-protein diets have been shown to improve cardiometabolic markers, while higher intakes of fish, whole grains, fiber, and n-3 PUFAs have been associated with lower all-cause mortality risk. However, while the body of evidence for prevention of T2D through diet is relatively large and robust, more high-quality, long-term data on dietary strategies for sustained dietary T2D and T1D management are still needed, as well as on whether dietary recommendations for people with diabetes should differ from those for the general population. Importantly, the findings also suggest that improvements in metabolic health trough diet may not solely dependent on weight loss and that quality of the diet also

matters. Emphasizing diet quality rather than calorie restriction can provide a more motivating message for people with diabetes.

Taken together, this work highlights the crucial role of various dietary factors in the health of people at risk of, or living with, T2D or T1D, and emphasizes the importance of integrating evidence from intervention and observational study designs to inform dietary recommendations.

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Acknowledgments

First and foremost, I would like to thank PD Sabrina Schlesinger for giving me the opportunity to pursue my PhD, for conceptualising all four PhD projects, and for her invaluable mentorship throughout the entire journey. She introduced me to the world of science, opened my eyes to new perspectives, encouraged me to aim higher, and was always available to answer questions or discuss doubts. Her openness to new ideas, combined with constructive criticism, taught me a lot and ensured that my PhD experience was both positive and life-changing.

I would also like to thank Prof. Oliver Kuss for giving me the opportunity to undertake my PhD, for his support, as well as for the pleasant and instructive time at the Institute for Biometrics and Epidemiology of the German Diabetes Center. Furthermore, I would like to thank Prof. Regina Ensenauer for agreeing to be the second supervisor of this work.

I am also especially thankful to my colleague, Dr. Alexander Lang, for his constant support during the long hours at the office, and for cheering me up and lifting my spirits during challenging moments. I greatly appreciated the opportunity to share experiences, as well as the wonderful times during business trips, which turned colleagues into friends. Additionally, I want to thank Dr. Janett Barbaresko for the constructive and enjoyable teamwork and professional exchange.

Next, I would like to express my heartfelt gratitude to my parents, Dorota and Krzysztof, for doing everything they could to give me the best possible start in life and support my development. I am especially thankful for the freedom they always gave me to make my own choices and shape my path, and I am also deeply aware of the many sacrifices - both material and personal - they made to make this possible. I would also like to thank them - and my sister, Dominika - for being a steady presence in my life, providing reassurance and space, which allowed me to focus on my career.

I am also especially thankful to my friends, Daga, Daria, and Kasia, for always encouraging me to dream big, believe in myself, and for inspiring me from an early age through their own choices and actions. Having friends like them is something I don’t take for granted. Their presence has lifted me in ways they probably don’t even realize.

Finally, and most importantly, I would like to thank my husband, Philipp, for being a constant in my life. His encouragement, his presence through all the ups and downs, and the way he stands by me in moments of doubt - always reminding me of what truly matters - have given me the resilience, comfort, and motivation to keep going and to aim high every day. His steady support has been a quiet yet powerful source of strength for me.