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The role of diet in type 2 diabetes prevention and management – meta-evidence from epidemiological and clinical studies

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Contributions in book of abstracts: Dietary fat and incidence of type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies

SUMMARY

Type 2 diabetes is one of the most common non-communicable diseases worldwide and the prevention and management of this disease is of great public health importance. In this context, lifestyle factors, including diet, play an important role. There is an ongoing debate about which dietary factors influence type 2 diabetes prevention and management. In order to support evidence-based dietary recommendations regarding type 2 diabetes prevention and management, meta-evidence and an evaluation of the certainty of evidence are needed. Therefore, our aims were 1) to summarise, generate and evaluate meta-evidence regarding diet and type 2 diabetes prevention, and 2) to provide evidence for dietary interventions regarding type 2 diabetes management, specifically blood lipid management. To achieve these aims, we applied different methodological systematic approaches such as an umbrella review, linear and non-linear dose-response meta-analyses and network meta-analysis. Furthermore, we graded the certainty of evidence using validated tools.

In our umbrella review, we found high certainty of evidence for the association between higher intakes of whole grain products and cereal fibre with decreased type 2 diabetes incidence, and for higher intakes of red and processed meat and sugar sweetened beverages with increased type 2 diabetes incidence. Additionally, we observed an association between breakfast skipping and increased type 2 diabetes incidence in our original meta-analysis. Moreover, we found an inverse association with type 2 diabetes incidence for vegetable fat, as well as for polyunsaturated fatty acids and the plant-based alpha-linolenic acid, especially at lower intake levels in our non-linear dose-response meta-analyses. The certainty of evidence for these associations was moderate to low. In our network meta-analysis, the Mediterranean diet showed the most beneficial effect compared to other dietary interventions regarding blood lipid management in patients with type 2 diabetes, with moderate to low certainty of evidence.

In summary, a healthy dietary pattern, including high intakes of whole grain products, cereal fibre and vegetable fat, as well as low intakes of red and processed meat and sugar sweetened beverages should be recommended for type 2 diabetes prevention. Moreover, our findings suggest that the Mediterranean diet should be promoted regarding blood lipid control in type 2 diabetes. Further dietary factors are also likely to play a role, but more well-conducted prospective observational studies and randomized controlled trials are needed to strengthen the evidence. For example, additional research regarding breakfast quality is needed. Future studies should use validated dietary assessment methods and focus on food sources and dietary patterns to account for the complexity of the diet. This dissertation highlights the importance of the role of diet in type 2 diabetes prevention and management and will help to develop evidence-based guidelines.

ZUSAMMENFASSUNG

Typ-2-Diabetes ist eine der häufigsten nichtübertragbaren Krankheiten weltweit, weshalb die Prävention und das Management von Typ-2-Diabetes von großer Bedeutung ist. In diesem Zusammenhang spielen Lebensstilfaktoren, einschließlich Ernährung, eine wichtige Rolle. Es wird kontrovers diskutiert, welche Ernährungsfaktoren die Prävention und das Management von Typ-2-Diabetes beeinflussen. Um evidenzbasierte Ernährungsempfehlungen zu unterstützen, braucht es Meta-Evidenz und eine Evaluierung der Evidenz. Daher waren unsere Ziele, 1) Meta-Evidenz zusammenzufassen, zu erstellen und zu evaluieren, und 2) Evidenz bezüglich Ernährungsinterventionen für das Typ-2-Diabetes-Managment, namentlich die Blutlipidkontrolle bei Patienten mit Typ-2-Diabetes zu liefern. Hierfür wurden verschiedene methodische systematische Ansätze, wie ein Umbrella-Review, Dosis-Wirkungs-Metaanalysen und eine Netzwerk-Metaanalyse angewandt sowie die Aussagekraft der Evidenz anhand validierter Instrumente beurteilt.

In unserem Umbrella-Review fanden wir eine hohe Evidenz für die Assoziationen zwischen Vollkornprodukten und Getreidefasern mit reduzierter Typ-2-Diabetes-Inzidenz, sowie zwischen rotem und verarbeitetem Fleisch und zuckergesüßten Getränken mit einer erhöhten Typ-2-Diabetes-Inzidenz. In unserer Metaanalyse hatten Personen, die auf das Frühstück verzichteten, eine höhere Typ-2-Diabetes-Inzidenz als Personen, die regelmäßig frühstückten. Des Weiteren fanden wir in unserer Dosis-Wirkungs-Metaanalyse eine reduzierte Typ-2-Diabetes-Inzidenz für Pflanzenfette, mehrfach ungesättigte Fettsäuren und die pflanzliche alpha-Linolensäure, insbesondere in moderaten Aufnahmemengen. Die Evidenz dieser Assoziationen war moderat bis gering. In unserer Netzwerk-Metaanalyse zeigte eine mediterrane Ernährung im Vergleich zu anderen Ernährungsinterventionen den stärksten Effekt bezüglich der Blutlipidkontrolle bei Personen mit Typ-2-Diabetes, mit moderater bis geringer Evidenz.

Zusammenfassend sollte ein gesundes Ernährungsmuster, mit Vollkornprodukten und Getreidefasern und wenig rotem und verarbeitetem Fleisch und zuckergesüßten Getränken für die Typ-2-Diabetesprävention empfohlen werden. Die mediterrane Ernährung eignet sich insbesondere für die Blutlipidkontrolle bei Typ-2-Diabetes. Es ist wahrscheinlich, dass weitere Ernährungsfaktoren eine Rolle spielen. Weitere gut durchgeführte prospektive Kohortenstudien und randomisierte kontrollierte Studien sind nötig, um die Evidenz zu stärken. Diese sollten validierte Ernährungserhebungsmethoden anwenden und den Fokus auf Nahrungsquellen und Ernährungsmuster legen, um die Komplexität der Ernährung zu berücksichtigen. Diese Dissertation hebt die Bedeutung der Ernährung bei der Prävention und dem Management von Typ-2-Diabetes hervor und wird die Entwicklung von evidenzbasierten Leitlinien unterstützen.

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ABBREVATIONS

ADA	American Diabetes Association
ASA	American Statistical Association
AMSTAR	A measurement tool to assess the methodological quality of systematic reviews
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
DASH	Dietary Approach to Stop Hypertension
EPIC	European Prospective Investigation into Cancer
FFQ	Food frequency questionnaire
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HbA1C	Glycated haemoglobin
HDL cholesterol	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IDF	International Diabetes Federation
LDL cholesterol	Low-density lipoprotein cholesterol
NOS	Newcastle-Ottawa-Scale
RCT	Randomized controlled trial
ROBINS-I	Cochrane Risk of bias in Non-randomized Studies of Interventions
ROBIS	A tool to assess risk of bias in systematic reviews
TG	Triglycerides
US	United States (of America)
WHO	World Health Organisation

CHAPTER 1

General introduction

Diabetes mellitus is one of the most common non-communicable diseases worldwide, with a global prevalence of 9% in 2019 (1), and both the prevalence and incidence of diabetes are projected to rise (1). People who suffer from diabetes are at higher risk for diabetes-related complications (e.g. coronary heart disease (CHD), stroke, diabetic retinopathy, neuropathy and nephropathy) (2), other health-related comorbidities (e.g. depression or cancer) (3, 4) and premature death (5). Moreover, diabetes leads to increased health care costs, for example for medication or due to time missed at work (1). Thus, the prevention and management of diabetes is of great public health importance.

Type 2 diabetes is the most common type of diabetes accounting for 90% of all diabetes cases (1). While unmodifiable factors such as genetic predisposition and age play a role in the development of type 2 diabetes, modifiable risk factors, such as smoking, obesity and low levels of physical activity also contribute to the onset of this disease (6, 7). Moreover, diet is a key modifiable lifestyle factor that influences both the development and the progression of this disease (8-10).

Current nutritional guidelines on the prevention of type 2 diabetes recommend following an overall healthy dietary pattern, including specific dietary factors that were shown to be associated with decreased incidence of type 2 diabetes, such as whole grains, yogurt, nuts, coffee and tea, as wells as reducing intakes of red meat and sugar sweetened beverages that increase type 2 diabetes incidence (9, 11). However, additional evidence and a large body of research on dietary factors, including dietary patterns (e.g. the Mediterranean diet) and dietary behaviours (e.g. breakfast skipping), foods and food groups, beverages, alcoholic beverages, as well as macro- and micronutrients (12) is available. Moreover, the strength, the precision and the influence of potential bias of these findings remain to be assessed.

Some dietary aspects regarding the prevention of type 2 diabetes warrant further investigation. First, epidemiological evidence indicated that people who skipped their breakfast had a higher risk to develop type 2 diabetes compared to persons who ate breakfast regularly (13). Breakfast skipping is often observed as behavioural changes in order to lose weight (14). However, it is unclear if breakfast skipping leads to weight loss or, as epidemiological studies indicated, even to an increase of overweight and obesity (15), which are important risk factors for type 2 diabetes (16). Thus, the influence of the body mass index (BMI) on the association between breakfast skipping and type 2 diabetes needs to be considered when conducting a meta-analysis of prospective cohort studies. Moreover, no dose-response meta-analysis was conducted so far. Second, a particularly controversially discussed dietary aspect is the role of fat quantity and quality in the prevention of type 2 diabetes (17). In recent years, the research focus shifted from fat quantity to fat quality and therefore many current guidelines emphasise recommendations regarding single fatty acids, such as the reduction of saturated fatty acid intake (9, 10) as well as a higher consumption of monounsaturated fatty acids (10, 11) and omega-3 fatty acids (10, 12). However, epidemiological evidence regarding the association between dietary intake of single fatty acids and incidence of type 2 diabetes is inconclusive and investigations into the dose-response relationship of these associations are lacking (18-21).

Furthermore, nutrition is a corner stone of diabetes therapy (9, 22), with the aim to attain glycaemic and lipid goals in order to delay and prevent diabetes-related complications (22). Based on expert opinion, current guidelines recommend following a healthy dietary pattern, such as a vegetarian or Mediterranean diet (9, 22). However, the effects of many other dietary patterns, e.g. a low fat or a low carbohydrate diet, on glycaemic and lipid control have been investigated in clinical studies (23-26). Therefore, the question which diet offers the greatest benefit remains to be answered. In a recent network meta-analysis, this question regarding glycaemic control was addressed. A network meta-analysis allows the estimation of all possible relative effects within a network and thus, a ranking of all interventions (27, 28). The Mediterranean diet was found to be the most effective dietary approach to improve glycaemic control in individuals with type 2 diabetes (29). However, it is still unclear which dietary pattern shows the most beneficial effects regarding blood lipid control in type 2 diabetes.

To address these research gaps in a way that findings can support decision making regarding public health recommendations, meta-evidence is needed (30). Meta-evidence is an important part of evidence-based medicine (30). Many studies regarding the same research question are published continuously (31). Thus, a systematic synthesis and critical evaluation of this evidence is warranted in order to help understand the vast evidence base (30, 31). Therefore, in systematic reviews and meta-analyses, evidence from multiple studies regarding a specific research question is systematically searched, quantitatively summarised to an overall estimate and critically evaluated (30, 32).

Although a large body of research regarding the prevention of type 2 diabetes is available, a systematic overview of any existing evidence and the evaluation of its strength and validity are lacking. Additionally, investigations of the association between breakfast skipping and type 2 diabetes, and of the influence of BMI on this association, is warranted. Furthermore, many unclarities regarding the role of dietary fats and fatty acids exist. Moreover, the question, which dietary approach offers the greatest benefit regarding blood lipid control in type 2 diabetes, remains to be answered. Therefore, this dissertation includes four papers which address these research gaps regarding the role of diet in type 2 diabetes prevention and management by applying different methodological approaches, including an umbrella review, a systematic review with dose-response meta-analysis and a network meta-analysis.

Public health relevance

The International Diabetes Federation (IDF) estimates the global prevalence of diabetes to be 9% in 2019 and approximately 463.0 million adults aged 20-79 years are living with this disease worldwide (1). Diabetes is characterized by progressive loss of beta-cell mass and function, which results in a chronic state of hyperglycaemia (6, 33). According to the American Diabetes Association (ADA), diabetes mellitus can be classified into four general categories: type 1 diabetes, type 2 diabetes, gestational diabetes mellitus and specific types of diabetes (for example maturity-onset diabetes in the young) (33). A new classification into five clusters (mild age-related diabetes, mild obesity-related diabetes, severe autoimmune diabetes, severe insulin-resistant diabetes and severe insulin-deficient diabetes) has been proposed (34, 35). However, since all the included studies followed the previous categories, the terminology defined by the ADA will be used in this dissertation. Gestational diabetes refers to a state of hyperglycaemia that only occurs during pregnancy and is not due to pre-existing diabetes (33). Type 1 diabetes is an autoimmune disease, which leads to beta-cell destruction and, thus, absolute insulin deficiency (6, 33). Type 2 diabetes is the most common type of diabetes and accounts for approximately 90% of all cases (1). In type 2 diabetes, beta-cell function is lost progressively (33). An initial state of insulin resistance is compensated by a hypersecretion of insulin in the pancreatic beta-cells, ultimately leading to a depletion of the beta-cells. Thus, the body cannot cope with the insulin requirements resulting in hyperglycaemia (6, 36). Diagnostic criteria for type 2 diabetes as defined by the ADA and the World Health Organization (WHO) are a fasting plasma glucose of ≥126 mg/dL (≥7.7 mmol/L), or a 2-hour plasma glucose level of ≥200 mg/dL (≥11.1 mmol/L) during an oral glucose tolerance test using 75g glucose dissolved in water (33, 37), or a glycated haemoglobin (HbA1C) level of ≥6.5% (33).

The prevalence of type 2 diabetes strongly increased in the past forty years. Between 1980 and 2019, the age-standardised prevalence more than doubled in both men and women (1, 38). The IDF estimated that the diabetes prevalence in adults aged 20-79 years will further rise to 578.5 million people by 2030 and to 700.1 million individuals by 2045 worldwide (1). In Germany, the prevalence was estimated to be even higher than the worldwide average with 10.4% in 2019 (1). Calculations regarding the projected number of people diagnosed with type 2 diabetes in Germany predict that type 2 diabetes incidence will rise by 54-77% until the year 2040 (39).

Type 2 diabetes is associated with many health complications, comorbidities and increased mortality (5). Epidemiological evidence showed that the relative risk to develop CHD, ischaemic stroke and non-fatal myocardial infarction was doubled in individuals with type 2 diabetes compared to individuals without type 2 diabetes (40) and that increasing levels of HbA1C were associated with an increased incidence of CHD and stroke (41). Moreover, individuals with type 2 diabetes often suffer from increased levels of low-density lipoprotein cholesterol (LDL) and triglycerides (TG), as well as lower levels of high-density lipoprotein cholesterol (HDL), which is associated with a higher relative risk for cardiovascular diseases (CVD) (42) (43). Furthermore, the relative risk for incident chronic kidney disease was approximately tripled in individuals with type 2 diabetes compared to those without type 2 diabetes (44). Moreover, diabetes, including type 2 diabetes, is one of the leading causes for blindness globally (45) and a disease duration of ten or more years was associated with a two-fold relative risk for diabetic retinopathy (46). Additionally, increasing levels of HbA1C were associated with an increased relative risk for lower limp amputations (47). Furthermore, type 2 diabetes was associated with an increased incidence for non-cardiovascular diseases, such as cancer (4) and depression (3). Finally, type 2 diabetes is associated with increased mortality rates (4, 48) and is one of the leading causes of death worldwide (1).

Type 2 diabetes increases direct and indirect health care costs, such as medical costs for hospital stays or medication, and loss of production due to time missed at work, disability or increased mortality, respectively (1). The IDF estimated direct and indirect health care costs for diabetes, including type 2 diabetes, which is estimated to account for 90% of all diabetes cases (1). According to their calculations, the direct costs for diabetes have more than tripled from 232 billion US dollars to 727 billion US dollars spent worldwide between 2007 and 2017 (1). Given the expected increase in diabetes prevalence and incidence up to 2045, the IDF estimates the direct health care costs to reach 825 billion US dollars in 2030 and 845 billion US dollars in 2045 (1). A little over one third of total health care costs due to diabetes are estimated to be indirect health care costs, equalling in 454.81 billion US dollars in 2015 (1). The most recent numbers from Germany estimated that health care costs were around 16.1 billion Euro in 2010 and 1.7 times higher for individuals with type 2 diabetes than for those without type 2 diabetes (49). Furthermore, individuals with macro- and microvascular diabetic complications cause approximately three and two times higher health care costs compared to people without these complications, respectively (50, 51).

Type 2 diabetes prevention

Type 2 diabetes is a multifactorial disease with a complex pathophysiology (6, 36). Both unmodifiable and modifiable risk factors contribute to the onset of type 2 diabetes. The following chapter will take a closer look at these risk factors.

Risk factors

Increasing age (1, 33), age at menarche (52), and family history of diabetes (53-55) play a role in the development of type 2 diabetes. Furthermore, it was shown that individuals with low income and education levels were more likely to develop type 2 diabetes (56). Moreover, several lifestyle-related factors affect the onset of type 2 diabetes (6, 7). Both current and past smoking were associated with a higher relative risk for type 2 diabetes compared to non-smoking (57). Also, overweight and obesity, especially abdominal obesity, were shown to increase type 2 diabetes incidence (16). Related to that, both physical activity and diet were associated with type 2 diabetes (8-10, 58). Epidemiological evidence indicated that physical activity, even at low intensity levels, was inversely associated with type 2 diabetes incidence (58). Finally, diet is a key modifiable risk factor, which plays an important role in type 2 diabetes prevention (8-10). The current knowledge and existing research gaps regarding this aspect will be elaborated in the following chapter in more detail.

Diet and diabetes prevention

A large body of research on the role of diet in type 2 diabetes prevention is available. Recent reports summarised and evaluated the evidence on selected dietary factors and their association with incidence of type 2 diabetes (7, 59, 60). Convincing evidence was found regarding the inverse association between whole grain consumption and type 2 diabetes, as well as for the increased type 2 diabetes incidence for higher intakes of red meat (59, 60), processed meat (59, 60) and sugar sweetened beverages (7, 59, 60). There is evidence that the high content of fibre, phytochemicals, vitamins, and minerals in whole grain products beneficially influence insulin sensitivity, fasting insulin concentrations and inflammatory markers (61-63), whereas red and processed meat seem to have the opposite effect (64, 65). Epidemiological evidence also suggests that there are beneficial associations of dairy (7, 60), including yogurt (59), nuts or seeds (59, 60, 66), alcohol intake (7), dietary fibre (59, 67) and magnesium (7) with decreased incidence of type 2 diabetes. On the other hand, breakfast skipping (7), higher compared to lower intake of foods with a high glycaemic load (59) and artificially sweetened beverages (7) were associated with increased type 2 diabetes incidence. However, more research is needed to confirm these associations. More research is also needed for fruit (68) and vegetables (69), which were inversely associated with type 2 diabetes in one meta-analysis, but were not associated with type 2 diabetes in another (60).

So far, there is no comprehensive overview of any existing evidence on diet and type 2 diabetes. Additionally, differences between subgroups of foods, that may show diverse associations with type 2 diabetes incidence (70-73), remain to be investigated. Moreover, the strength, precision and influence of potential bias on the entire available evidence needs to be assessed using a validated tool. Thus, internal consistencies or inconsistencies can be examined and relevant research directions identified. Furthermore, when providing a systematic overview of evidence from meta-analyses, an assessment of the methodological quality of the included meta-analyses is necessary. Such an assessment using a validated tool is lacking so far (7, 59).

There are specific dietary aspects that warrant further investigation. First, as stated above, epidemiological evidence indicated that breakfast skipping is associated with increased insulin resistance and type 2 diabetes incidence (13, 74, 75). Up to 30% of the adult population worldwide have been reported to skip breakfast in 2010, especially in the context of behavioural changes in order to lose weight (14). However, it is unclear if breakfast skipping leads to weight loss or, as epidemiological studies indicated, even to an increase of overweight and obesity (15), which are important risk factors for type 2 diabetes(16). Thus, the influence of BMI on the association between breakfast skipping and type 2 diabetes incidence needs to be examined in prospective cohort studies. Additionally, a dose-response meta-analysis on this association is lacking.

The second particularly controversially discussed dietary aspect is the role of dietary fats and fatty acids in type 2 diabetes prevention (17). For a long time, research was focused on fat quantity. Due to its high energy density, it was believed that high fat diets mainly lead to type 2 diabetes through overweight and obesity (76). However, fatty acids vary in their chemical structures and thus, biological functions, and more recent evidence indicated that fatty acids also have an impact on metabolic pathways which influence the development of type 2 diabetes (76). Therefore, current dietary guidelines on the prevention of type 2 diabetes recommend higher intakes of vegetable fat (10), monounsaturated fatty acids and polyunsaturated fatty acids (10, 77), including omega-3 fatty acids (10, 12), as well as a lower intakes of saturated fatty acids (9) and *trans*-fatty acids (10). However, while epidemiological evidence indicated a protective association of vegetable fat intake with type 2 diabetes incidence, meta-analyses of prospective observational studies found no association for higher versus lower intake of saturated fatty acids (21), monounsaturated fatty acids (18), or omega-3 fatty acids (19, 20). However, these meta-analyses only included studies up to 2014 (18-21). Meanwhile, new prospective studies investigating dietary fats and fatty acids and type 2 diabetes incidence are available, adding to the existing evidence and the controversy (78-80). For example, a prospective analysis of an Italian cohort found an increased type 2 diabetes incidence for higher intakes of vegetable fat (78). Furthermore, an analysis within the European Prospective Investigation into Cancer (EPIC) cohort found no association between type 2 diabetes incidence and saturated fatty acids or monounsaturated fatty acids (79), while an inverse association was observed for monounsaturated fatty acids, polyunsaturated fatty acids and omega-3 fatty acids in the Teheran Lipid and Glucose Study (80). In order to summarise and analyse all existing evidence, an updated meta-analysis is warranted. Additionally, the certainty of evidence for these associations has yet to be evaluated. Moreover, most of these meta-analyses only conducted high versus low analyses (18-21).

Conducting high versus low meta-analyses leads to comparisons of different doses (30). This might lead to wrong conclusions about differences between studies as they are based on differences in doses (30). Therefore, an investigation into dose-response relationships, which eliminates this risk by comparing standardised doses and enables to investigate the natural shape of the association (30), is necessary.

Type 2 diabetes management

The main aims of type 2 diabetes management are to achieve glycaemic and blood lipid control in order to prevent and delay the onset of diabetes complications (81). Although pharmacological therapy is an option for type 2 diabetes management (especially for glycaemic control) (82), lifestyle management also plays an important role. In accordance with identified modifiable risk factors for type 2 diabetes, lifestyle recommendations include smoking cessation, increased physical activity and weight loss (9, 81). Furthermore, nutrition therapy is a corner stone in type 2 diabetes management (9, 81). Current knowledge regarding the role of diet in diabetes management and open research questions will be elucidated in the following chapter.

Diet and diabetes management

So far, little is known about the association between dietary factors and incidence of diabetes complications. According to results from a meta-analysis of prospective cohort studies, higher versus lower egg consumption was associated with increased incidence of CVD in individuals with type 2 diabetes (83). Moreover, the association between dietary factors and incidence of diabetic retinopathy was investigated in a systematic review and according to the authors conclusion, the limited evidence suggests that the Mediterranean diet, as well as fruit, vegetable and fish consumption, might be beneficial regarding the prevention of diabetes retinopathy (84).

Instead, a lot of research focused on the effects of dietary factors on glycaemic and lipid control in individuals with type 2 diabetes, and especially of dietary patterns, since there was a shift from the focus on single nutrients to dietary patterns regarding dietary recommendations (81, 85). In a systematic review, Herrera et al (2017) investigated the effects of several dietary patterns on cardiovascular health in type 2 diabetes patients and concluded that the Mediterranean diet, the vegetarian diet, the Dietary Approach to Stop Hypertension (DASH), as well as a low glycaemic index diet are potentially beneficial for glycaemic and blood lipid control in type 2 diabetes (86). Another systematic review discussed the controversy between low carbohydrate and low fat diets (87). They concluded that a broad range of carbohydrate and fat compositions in the diet offers health benefits, and thus, do not favour one dietary pattern over the other (87). Moreover, several pairwise meta-analyses of randomized controlled trials investigated the effects of different dietary interventions on glycaemic and blood lipid control. One meta-analysis found that a low carbohydrate diet compared to other diets, including a low fat diet, had beneficial effects on

HbA1C and increased HDL levels, but had little effect on LDL and triglyceride levels (23). Similarly, results from another meta-analysis favoured a low carbohydrate-high fat diet compared to a low fat-high carbohydrate diet regarding 2-hour postprandial glucose, TG and HDL levels (26). Moreover, a diet with low glycaemic index compared to control diets showed beneficial effects on HbA1C, HDL, LDL and TG levels (23). The Mediterranean diet also decreased HbA1C and TG levels compared to control diets (23). Another meta-analysis confirmed the results for the Mediterranean diet on HbA1C (24). Moreover, a vegetarian diet was shown to lower levels of HbA1C, fasting glucose and LDL compared to conventional diets (25).

Although this evidence indicates that many dietary patterns beneficially impact glycaemic and blood lipid in control in type 2 diabetes, it does not become clear which of these different dietary approaches offers the greatest benefits regarding glycaemic and blood lipid management. A recent network meta-analysis addressed this question regarding glycaemic control (29). The authors simultaneously compared nine dietary approaches (low fat, vegetarian, Mediterranean, high protein, moderate carbohydrate, low carbohydrate, low glycaemic index/low glycaemic load, Palaeolithic and control diet) and identified the Mediterranean diet as the most beneficial dietary approach to achieve glycaemic control (29). However, the question, which of these dietary regimens offers the greatest benefits regarding blood lipid management in individuals with type 2 diabetes remains to be answered.

Research aims

Given the identified gaps in research regarding the role of diet in type 2 diabetes prevention and management, four main papers will be included in this doctoral thesis, with the following aims:

1) to summarise any evidence of associations between dietary factors (dietary behaviours or dietary quality indices, food groups and foods, beverages, alcoholic beverages, macro- and micronutrients) and incidence of type 2 diabetes, and to evaluate the certainty of evidence (88) (Chapter 2).
2) to examine the association between breakfast skipping and type 2 diabetes incidence, including dose-response meta-analyses and investigations of the influence of BMI on this association (89) (Chapter 3.1).

3) to investigate the associations between dietary fat and fatty acid intake with the incidence of type 2 diabetes in dose-response meta-analyses and to evaluate the certainty of evidence of these associations (90) (Chapter 3.2).
4) to examine the effects of nine dietary approaches (low fat, vegetarian, Mediterranean, high protein, moderate carbohydrate, low carbohydrate, low glycaemic index/low glycaemic load, Palaeolithic and control diet) on LDL cholesterol, HDL cholesterol and TG levels in individuals with type 2 diabetes and to identify the most beneficial approach regarding blood lipid control (91) (Chapter 4).

In order to achieve these aims a broad spectrum of methodological approaches were used.

For the first aim, an umbrella review was conducted to provide an overview of any existing evidence on dietary factors and type 2 diabetes incidence. An umbrella review is a systematic review of meta-analyses or systematic reviews and is an innovative and helpful tool to provide a comprehensive overview of the existing evidence regarding a certain topic (92). The strength of evidence and the precision of estimates were elucidated and the certainty of evidence and the methodological quality of the included meta-analyses were evaluated using validated tools (93, 94) (88).

For the second aim, a systematic review and meta-analysis regarding the association between breakfast skipping and type 2 diabetes was performed, including dose-response meta-analyses and separate models adjusting for BMI and not adjusting for BMI in order to investigate the role of overweight and obesity as potential intermediate risk factor for this association (89).

For the third aim, an updated systematic review and dose-response meta-analyses was performed in order to investigate the association between dietary fats and fatty acids with type 2 diabetes incidence and the certainty of evidence was evaluated (90).

For the fourth aim, a network meta-analysis was conducted in order to identify the most beneficial approach regarding blood lipid control in individuals with type 2 diabetes and assessed the certainty of evidence (91).

Each research aim will be addressed and answered in the respective chapters (Chapter 2-4). Finally, the findings will be summarised and discussed in Chapter 5.

CHAPTER 2

Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies

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CHAPTER 3

Association between selected dietary factors and incidence of type 2 diabetes

CHAPTER 3.1

Breakfast Skipping Is Associated with Increased Risk of Type 2 Diabetes among Adults: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

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The Journal of Nutrition, 2018, https://doi.org/10.1093/jn/nxy194.

CHAPTER 3.2

Dietary fat and fatty acid intake and incidence of type 2 diabetes: a systematic review and updated meta-analysis of prospective observational studies

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PLoS Medicine, 2020, 17(12): e1003347, https://doi.org/10.1371/journal.pmed.1003347.

CHAPTER 4

Impact of different dietary approaches on blood lipid control in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis

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CHAPTER 5

General discussion

Key findings

This dissertation focussed on four research aims (compare Chapter 1). In summary, the findings of the thesis showed that

1) the association between dietary factors and type 2 diabetes incidence has extensively been investigated. However, out of 153 identified associations, the certainty of evidence was only high for the inverse associations between the intake of whole grain, cereal fibre and moderate alcohol consumption with type 2 diabetes incidence, as well for the association between red meat, processed meat, bacon and sugar sweetened beverages with increased type 2 diabetes incidence. For the other associations, the certainty of evidence was moderate, low or very low. However, the methodological quality of the included meta-analyses in the umbrella review was mostly high (88).
2) breakfast skipping was associated with increased type 2 diabetes incidence. This association was independent from BMI status. Furthermore, there was a non-linear dose-response association between breakfast skipping and type 2 diabetes, with the highest increase in type 2 diabetes incidence for skipping breakfast 4-5 times per week (89).
3) dietary fats and fatty acids were not or only weakly associated with type 2 diabetes incidence in linear dose-response meta-analyses. However, in non-linear dose-response meta-analyses, vegetable fat was associated with decreased type 2 diabetes incidence, as were polyunsaturated fatty acids and the plant-based alpha-linolenic acid in lower doses. Animal-based long-chain omega-3 fatty acids were associated with increased type 2 diabetes incidence, although geographical differences were observed. A harmful association for saturated fatty acids was not confirmed. However, the findings were limited by very low to moderate certainty of evidence (90) .
4) a vegetarian diet most effectively reduced LDL-levels, while a Mediterranean diet beneficially increased HDL-levels and reduced TG-levels in individuals with type 2 diabetes. For the overall blood lipid management in individuals with type 2 diabetes, the Mediterranean diet was the most beneficial dietary approach. The certainty of evidence was moderate to low (91).

The bigger picture

Our findings show that the associations and effects of nutrition regarding type 2 diabetes prevention and management, have been widely researched in observational and clinical studies, respectively (88, 91). Nutrition epidemiology is often criticised for the observational character of many nutrition studies because of their risk for confounding (31, 95). Thus, the current system of evaluating evidence in evidence-based medicine, mainly follows a hierarchy that generally places randomized controlled trials (RCTs) over observational studies (96). However, while large RCTs might eliminate risk of confounding at baseline, they do bear problems of their own for nutrition research (31). First, changing one component in diet means changing another (in isocaloric conditions) and results might depend on this substitution (31). Furthermore, if hard endpoints (such as type 2 diabetes incidence) are the outcome of interest, follow-up times of many years are necessary and it is extremely difficult to ensure compliance over such a long time period (31). Accordingly, mainly observational studies were available regarding the associations between different dietary factors and type 2 diabetes prevention, while the effect of entire dietary patterns on blood lipids as surrogate markers in type 2 diabetes were investigated in RCTs. In any case, the results need to be interpreted in the bigger context and to be combined with evidence from both clinical and epidemiological studies (31, 96).

Type 2 diabetes prevention

In general, we found that the directions of the associations for related exposures with type 2 diabetes incidence coincided. For example, a healthy dietary pattern (which is characterized for example by high intakes of whole grain products and low intakes of red and processed meat), as well as high whole grain, cereal fibre and magnesium consumption were all inversely associated with type 2 diabetes (88). Moreover, breakfast skipping, which might be associated with lower intakes of whole grain products and fibre (97), and possibly with higher intake of energy dense snacks during the day (98), increased type 2 diabetes incidence (89). Furthermore, there was indication that plant-based diets, as well as higher intake of vegetable fats, decrease the incidence of type 2 diabetes (88, 90). On the other hand, following an unhealthy dietary pattern (which is characterized for example by high intakes of red and processed meat and sugar sweetened beverages) as well as higher intakes of red and processed meat, and thus animal fat, sugar sweetened beverages, animal protein and haem iron were associated with increased type 2 diabetes incidence (88, 90).

It is possible that associations were partly mediated by overweight or obesity. Individuals with an unhealthy dietary behaviour usually have an unhealthy lifestyle in general, including higher rates of obesity (98, 99). Breakfast skipping, higher intakes of red and processed meat, as well as sugar sweetened beverages were associated with weight gain over time (100-102), while higher intakes of whole grain products were associated with weight loss (100). However, most of the primary studies included in our umbrella review and in the meta-analysis on dietary fat and fatty acids adjusted for BMI and the associations persisted (88, 90). Furthermore, in our meta-analysis on the association between breakfast skipping and type 2 diabetes incidence, we evaluated the influence of BMI and found that the association was attenuated after adjusting for BMI, but the association persisted and skipping breakfast was still associated with increased type 2 diabetes incidence (89). Furthermore, evidence from different research fields suggest that other mechanisms might play a role, as discussed below.

We found an inverse association between whole grain and cereal fibre consumption and type 2 diabetes incidence with high certainty of evidence (88). In accordance, in short-term RCTs, the intake of whole grain foods and cereal fibre compared to intakes of refined grain products lowered postprandial glucose and insulin levels (103), increased insulin sensitivity (104) and lowered fasting glucose levels (62). Moreover, a network meta-analysis of RCTs comparing the effects of different food groups on intermediate disease markers found that whole grain most effectively reduced fasting glucose, HbA1C and insulin resistance (HOMA-IR) compared to other food groups, such as refined grains, fruits and vegetables (105). However, in medium- and long-term RCTs comparing increased whole grain intake to a control diet, no effect on insulin levels and HOMA-IR were observed, but fasting glucose was reduced when excluding participants at higher risk for type 2 diabetes (103). Nevertheless, epidemiological evidence found an association between higher whole grain intake with increased insulin sensitivity (61) and lower inflammatory markers (63, 106), which might reduce type 2 diabetes incidence (107).

Moreover, we observed an association for red and processed meat products with increased type 2 diabetes incidence with high certainty of evidence (88). A recent meta-analysis of RCTs on the effects of red and processed meat and cardiometabolic outcomes, including type 2 diabetes, found no effect on type 2 diabetes (108). However, this result was based on only one large trial (the Women's Health Initiative trial) (108), which did not actually investigate the effects of red and processed meat, but rather of a low fat diet (109). There are no RCTs investigating the effect of red and processed meat on type 2 diabetes incidence or cardiometabolic risk markers (108, 110). However, in prospective cohort studies, higher intakes of red and processed meat were associated with higher fasting glucose and insulin levels (111). Moreover, *in vitro* studies showed that nitrates, nitrites and their by-products (e.g. peroxynitrites) contained in meat disrupt mitochondrial function, which plays a role in the disease process of type 2 diabetes (112). Furthermore, meat contains high amounts of heme-iron, which has pro-oxidative properties and might damage pancreas cells (113), as well as glycated end products that increase inflammatory markers (114, 115).

We also found high certainty of evidence for the association between sugar sweetened beverages and increased type 2 diabetes incidence (88). Sugar sweetened beverages usually have a high glycaemic index (116), which was associated with higher postprandial glucose levels compared to a low glycaemic index in RCTs (117). Furthermore, in long-term RCTs, diets with a low glycaemic index were associated with lower fasting insulin concentrations, but not with fasting glucose or HbA1C levels compared to diets with a high glycaemic index (118). Fructose containing beverages may have a lower glycaemic index (119). However, research regarding fructose metabolism and its health effects indicated that high fructose contents might lead to increased hepatic lipogenesis and insulin resistance (120). Moreover, consuming sugar in liquid form was shown to negatively affect the regulation of hunger and satiety compared to sugar intake in solid foods in an RCT (121).

In our investigation regarding breakfast skipping and type 2 diabetes incidence, we found that breakfast skipping was associated with increased type 2 diabetes incidence compared to regularly breakfast consumption (89). The effects of breakfast skipping on glucose metabolism and appetite were only investigated in short-term RCTs and the results were not consistent. While skipping breakfast compared to consuming breakfast led to increased postprandial glucose response and impaired insulin response after lunch in some studies (122, 123), no difference between groups regarding insulin response or appetite were found in others (124, 125). A recent meta-analysis of RCTs found that breakfast skipping was associated with weight loss compared to breakfast eating (126). However, a possible explanation for this observation is that, in the clinical setting with standardized meals, breakfast skippers had a lower energy intake than breakfast eaters (126). In cohort studies, skipping breakfast was associated with following an unhealthy dietary pattern (98), which increased type 2 diabetes incidence (127). Furthermore, eating breakfast could be associated with higher intakes of fibre, vitamins and minerals (97), which decreased type 2 diabetes incidence (128, 129). In contrast to our results, intermittent fasting has received increased attention, especially regarding its beneficial effects on weight loss (130, 131). However, a meta-analysis of RCTs showed that intermittent fasting is not superior to continuous energy restriction regarding weight loss (131). Therefore, it seems that energy restriction with regards to weight loss plays a more important role than the skipping of meals. Furthermore, studies to investigate the association between intermittent fasting and type 2 diabetes incidence are needed.

Regarding dietary fats and fatty acids, our findings indicated that especially vegetable fats and lower doses of polyunsaturated fatty acids, including the plant-based alpha-linolenic acid were associated with decreased type 2 diabetes incidence, while the animal-based long-chain omega-3 fatty acids, although geographical differences were observed (90). Accordingly, results from RCTs indicated beneficial effects of plant-derived polyunsaturated fatty acids on glucose homeostasis and insulin resistance compared to placebo or carbohydrates (132, 133). Moreover, epidemiological evidence indicated that lower levels of the plant-derived alpha-linolenic acid were associated with higher pro-inflammatory markers (134) and therefore influence inflammatory processes that are playing an important role in the development of type 2 diabetes (107, 135). However, epidemiological studies also indicate the source of the vegetable fat needs to be considered. While olive oil was associated with a decreased type 2 diabetes incidence (136), the health effects of other plant oils, such as palm oil and coconut oil, are controversially discussed (76, 137). This is also true for saturated fatty acids, for which a harmful association with type 2 diabetes could not be confirmed in our meta-analysis. In a meta-analysis of RCTs, replacing saturated fatty acids with mono- or polyunsaturated fatty acids reduced HbA1C levels and HOMA-IR, but did not affect fasting glucose or postprandial glucose and insulin levels (138). However, saturated fatty acids are a group of fatty acids with different lengths and structures and thus, different biological functions (76). Prospective cohort studies that measured saturated fatty acids as biomarkers showed that short-chain, even-chain saturated fatty acids increase the incidence of type 2 diabetes (139-141), while odd-chain saturated fatty acids, which are contained in dairy products, and circulating very long-chain saturated fatty acids, which are contained in low concentrations in peanuts, canola oil or dairy products, were associated with a decreased incidence of type 2 diabetes (139-142).

Type 2 diabetes management

In our network meta-analysis, a vegetarian diet was most effective to reduce LDL-levels, while the Mediterranean diet beneficially raised HDL-levels and decreased TG-levels compared to other dietary interventions (91). While we focussed on surrogate markers in this network meta-analyses, evidence from prospective cohort studies is available, investigating hard endpoints related to blood lipid control in type 2 diabetes. These studies found that both a vegetarian, as well as a Mediterranean diet were associated with lower rates of cardiovascular events (143) and CVD mortality (86, 143-145). The mediating effect of weight loss during the trials, especially in visceral adiposity, might partly explain the observed effects, since for example the Mediterranean diet has been shown to promote weight loss by increasing satiety and energy expenditure (146). However, also individual components of the diets seem to play a role (146), because they were also associated with blood lipids in both epidemiological as well as clinical studies (147-149). In the Mediterranean diet, consumption of monounsaturated fatty acids and omega-3 fatty acids is typically high through the intake of extra virgin olive oil and fish (150). Monounsaturated fatty acids were shown to reduce TG levels in individuals with type 2 diabetes and also omega-3 fatty acids led to small reduction of TGs and LDL (147-149). Furthermore, the anti-inflammatory and anti-oxidant compounds that are contained in the vegetarian and the Mediterranean diet (for example in fruits, vegetables, nuts and olive oil (146)), are likely to play a beneficial role, since inflammatory adipokines contribute to diabetic dyslipidaemia (151).

Assessing risk of bias and certainty of evidence in nutrition studies

Apart from discussing results in a bigger context, an assessment of risk of bias of each included study and of the certainty of evidence should be conducted. The risk of bias assessment is an important part of the certainty of evidence evaluation (152, 153), which investigates to what extent we can trust the results and if more research is needed (154). Thus, overinterpretation of the results can be avoided (155).

In our umbrella review (88), we assessed the methodological quality of the included meta-analyses using a validated tool, namely 'a measurement tool to assess the methodological quality of systematic reviews' (AMSTAR) (93). In this tool, eleven items about the conduct of a meta-analysis are investigated, including study selection, quality assessment of the included studies and statistical methods (93). More recently, an update of this tool (AMSTAR 2) was introduced (156). AMSTAR 2 provides a more comprehensive user guide, includes additional questions (e.g. about the reporting of funding sources of the included studies) and defines critical domains (156). Furthermore, a tool to assess risk of bias in systematic reviews (ROBIS) was developed. It contains four domains, each including five to six signalling questions, about the study eligibility criteria, the selection of studies, data collection and risk of bias assessment of the included studies as well as the data synthesis (157). Since both more recent tools apply stricter criteria (156, 157), it is possible that an evaluation using these tools would have led to a higher risk of bias of the included meta-analyses and that we overestimated the methodological quality of these reports.

A widely used tool to assess the quality of observational studies is the Newcastle-Ottawa-Scale (NOS) (158, 159), which we applied in our meta-analysis on breakfast skipping and type 2 diabetes incidence (89). It assesses the quality of the included studies using a semi-quantitative star system (158). However, this tool has been criticised not to be valid for the quality assessment of cohort studies (159) and that it overlooks important sources of bias (155). Moreover, the lack of a manual with detailed instruction likely leads to diverse interpretations and answers by different investigators (160). Therefore, a tool which focuses on risk of bias, including detailed instructions, was developed by the Cochrane Collaboration (Cochrane Risk of bias in Non-randomized Studies of Interventions (ROBINS-I)) (155, 160), which we applied in our more recent meta-analysis on dietary fats and fatty acids and type 2 diabetes incidence (90). ROBINS-I includes seven domains of bias, for example due to confounding or selection of participants (160). The tool was adapted from the risk of bias assessment for RCTs (160) and acknowledges that the conduct of RCTs is not always feasible and ethical, which, as described before, is often the case in nutrition epidemiology (155, 160). The evaluation of each domain is based on the mimicking of a hypothetical trial, with no restriction due to ethical reasons or feasibility (160), with bias being defined as the differences between the results of the study of interest and the hypothetical trial (160). Low risk of bias would signal equivalence with an RCT. However, since unknown and residual confounding can never be ruled out, the overall assessment can never be higher than moderate (155). This was also the case in our ROBINS-I evaluation regarding dietary fats and fatty acids and incidence of type 2 diabetes. Our assessment showed that main concerns in the included prospective cohort studies were risk of bias due to possible residual confounding, as well as exposure measurement as with the current possibilities of measuring diet via self-report and food frequency questionnaires (FFQs), measurement errors can never be ruled out (90, 161).

For RCTs, the Cochrane collaboration’s risk of bias assessment for RCTs is an established tool (162), which we applied in our network meta-analysis (91). In this tool, risk of selection bias, performance bias, attrition bias and reporting bias are assessed (162). More recently, a revised version of this tool (the RoB 2.0 tool), was introduced in order to account for identified weaknesses, such as questions about whether lack of blinding of a study automatically leads to high risk of bias and the incorporation of the risk of bias assessment in systematic reviews and meta-analyses (163). This might be of special interest in nutrition research, since blinding is often not possible for dietary interventions (31).

Regarding the certainty of evidence assessment in umbrella reviews, a method which is based solely on statistical values, such as the p value (statistical significance; $p < 0.000001$) and the 95% prediction intervals (excluding the null value) was proposed (164). However, the American Statistical Association (ASA) recommends refraining from interpreting results based on p-values (165), and thus, we judged this kind of evidence grading as critical (152). Moreover, because this approach does not account for the risk of bias of the primary studies included in the meta-analyses, we evaluated the certainty of evidence in our umbrella review using NutriGrade (88, 94). This validated tool is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines but was adapted for nutrition search (94). The GRADE assessment is well-established for the evaluation of the efficacy of clinical interventions (110, 154). However, observational studies are classified as low certainty of evidence by default due to lack of randomization, without accounting for differences between different types of observational studies and limitations of RCTs regarding long-term dietary interventions (110, 154). Thus, NutriGrade includes similar domains as GRADE, such as risk of bias of the included studies, precision, heterogeneity (inconsistency), indirectness, publication bias, effect size and dose-response gradient (94, 154), but adds several specific aspects of nutritional studies, such as dietary assessment methods and the evaluation of funding bias (94). Differences between the NutriGrade and GRADE approach were recently evident in a newly developed guideline on red and processed meat regarding different health outcomes, including type 2 diabetes (166), which found the same association between higher meat consumption and increased incidence of type 2 diabetes, but evaluated the certainty of evidence as low using GRADE and therefore concluded, that the evidence was too weak to recommend lower meat consumption (166). However, although the authors assessed the risk of bias of the included studies, which was mostly moderate, this was not considered in their grading of the evidence (166). In the meantime, an update of the GRADE assessment was published, which we applied in our newest meta-analysis on dietary fats and fatty acids. It also aims to overcome the short-comings of the original GRADE approach for observational studies by including the ROBINS-I assessment (154), which allows for a differentiation between different observational studies and accounts for the fact that well-conducted non-randomized studies might minimize the risk for selection bias and confounding. In this updated approach, the initial certainty of evidence level is also high for observational studies and a lack of randomization leads to a downgrading by two levels (to low), unless the study design reduces confounding and selection bias, as evaluated by ROBINS-I (167). The GRADE approach can also be applied to network meta-analyses, for which an extended version is available, which additionally takes into account how much of evidence comes from direct and indirect evidence (168).

Strengths and limitations

The specific strengths and limitations of each paper have been discussed in detail in chapters 2-4. In this section, general strengths and limitations will be discussed.

A general strength of this dissertation is the application of different and innovative methods, such as an umbrella review, linear and non-linear dose-response meta-analyses and a network meta-analysis. We were able to provide a broad overview of the meta-evidence regarding diet and type 2 diabetes prevention and management and we assessed risk of bias and the certainty of evidence using validated tools, such as ROBINS-I, NutriGrade and GRADE (extended for network meta-analyses). This allowed a realistic interpretation of the results, which can support decision making regarding evidence-based guidelines on diet and type 2 diabetes prevention as well as management, and help to identify future research directions (30, 155). By conducting dose-response meta-analyses, we also minimised the risk of drawing wrong conclusions about differences in study results based on different doses by comparing standardised doses and were able to provide new insights into the natural shape of relationship between breakfast skipping and intake of dietary fat and fatty acids with incidence of type 2 diabetes.

This work also has several limitations. First, all meta-evidence, apart from the network meta-analysis, was based on observational studies, which increased the risk for confounding (31). However, studies providing unadjusted estimates were excluded from our analyses, and most of the included studies in our umbrella review and meta-analyses were adjusted for age, sex, BMI, smoking status and physical activity. Family history of diabetes and education were the two relevant confounders that were most often not accounted for (in about half of the studies). In our umbrella review, we were not able to conduct subgroup analyses by adjustment status for specific confounders. However, in our own meta-analyses, subgroup analyses according to level of adjustment did not change the results substantially. Nevertheless, unknown and residual confounding can never be completely ruled out. Furthermore, habitual diet in the observational studies was assessed as self-reports using mainly FFQs. Therefore, measurement errors cannot be ruled out (95, 161). This was especially true for the measurement of dietary fatty acids as in FFQs only the main food sources for fatty acids are included and they are assessed on a food group level, which might lead to difficulties in quantifying fat and fatty acid intake. Moreover, diet was usually assessed only once at the beginning of the study, and thus, no repeated measurements were available.

Implications for public health and future research

Our findings showed that diet plays a role in diabetes prevention and management. A healthy dietary pattern with high intakes of whole grain products, cereal fibre and vegetable fat, as well as low intakes of red and processed meat and sugar sweetened beverages should be promoted for type 2 diabetes prevention. Regarding type 2 diabetes management, especially the Mediterranean diet was shown to have beneficial effects.

For the beneficial associations between higher intakes of whole grain products, and especially cereal fibre, as well as lower consumption of red and processed meat and sugar sweetened beverages with type 2 diabetes prevention, we found high certainty of evidence and results from other research fields support the plausibility of the observed associations. There was also indication with moderate certainty of evidence that higher intakes of coffee, tea, dairy products, especially yogurt, and magnesium as well as lower intakes of white rice, fast food, artificially sweetened beverages and protein, especially animal protein, might contribute to a reduction of type 2 diabetes incidence. However, more research is needed to strengthen the evidence for these findings. Regarding breakfast skipping, there was indication that a healthy breakfast, including whole grain products and with a high fibre content, might reduce type 2 diabetes incidence. However, to draw conclusion for public health recommendations, more research, especially regarding the influence of the breakfast quality, is necessary to strengthen the evidence. Furthermore, especially plant-based fatty acids seemed to have a beneficial role in type 2 diabetes incidence. However, the certainty of evidence was moderate to low. Additionally, both observational and clinical evidence indicated that health effects of different dietary fatty acids depend on their chemical structure and their food source. Therefore, more research into the influence of food sources of fatty acids is warranted. Moreover, given the complexity of the diet and the difficulty of accurately measuring single nutrients, focussing on food sources and dietary patterns rather than single nutrients in dietary recommendations should be considered. A plant-based diet, as well as the Mediterranean diet were also identified as the most beneficial approaches regarding blood lipid control in type 2 diabetes management, which is supported by epidemiological evidence. However, these results were mainly based on indirect evidence, and thus, the certainty of evidence was rated as moderate to low.

In general, some limitations in the certainty of evidence remain and some challenges in nutrition epidemiology need to be addressed in future research. Future studies should therefore account for the composition of diet and relationships between nutrients, by focussing on food groups (60), substitution analyses (169) or pattern analyses (170). Furthermore, in order to allow a better estimation of the diet, dietary assessment methods need to be improved and repeated measurements applying validated FFQs, and studies using biomarker assessments should be conducted, in order to increase the validity of the findings and reduce measurement errors (31).

Conclusions

In this dissertation, a broad overview of the meta-evidence regarding diet and type 2 diabetes prevention and management was provided. Our findings highlight the importance of the role of diet in type 2 diabetes prevention and management. A healthy dietary pattern with high intakes of whole grain products, cereal fibre and vegetable fat, as well as low intakes of red and processed meat and sugar sweetened beverages was associated with decreased type 2 diabetes incidence. Regarding blood lipid control in type 2 diabetes, the Mediterranean diet had the most beneficial effects.

However, many associations were rated with low or very low certainty of evidence and more research is needed to strengthen the evidence. Future studies should focus on food sources and dietary patterns and apply methods such as substitution analysis and pattern analysis. Furthermore, dietary assessment methods need to be improved and diet should be measured repeatedly to account for changes in dietary intake over time. In general, risk of bias and certainty of evidence should always be assessed in meta-analyses in order to allow a realistic interpretation of the results. Furthermore, the findings should be put in a bigger context with findings from different sources of evidence, and thus, can provide a valuable contribution to further insights into the role of diet and type 2 diabetes prevention.

This dissertation highlights the importance of the role of diet in type 2 diabetes prevention and management and will help to develop evidence-based guidelines.

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