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Olsson, Kjell

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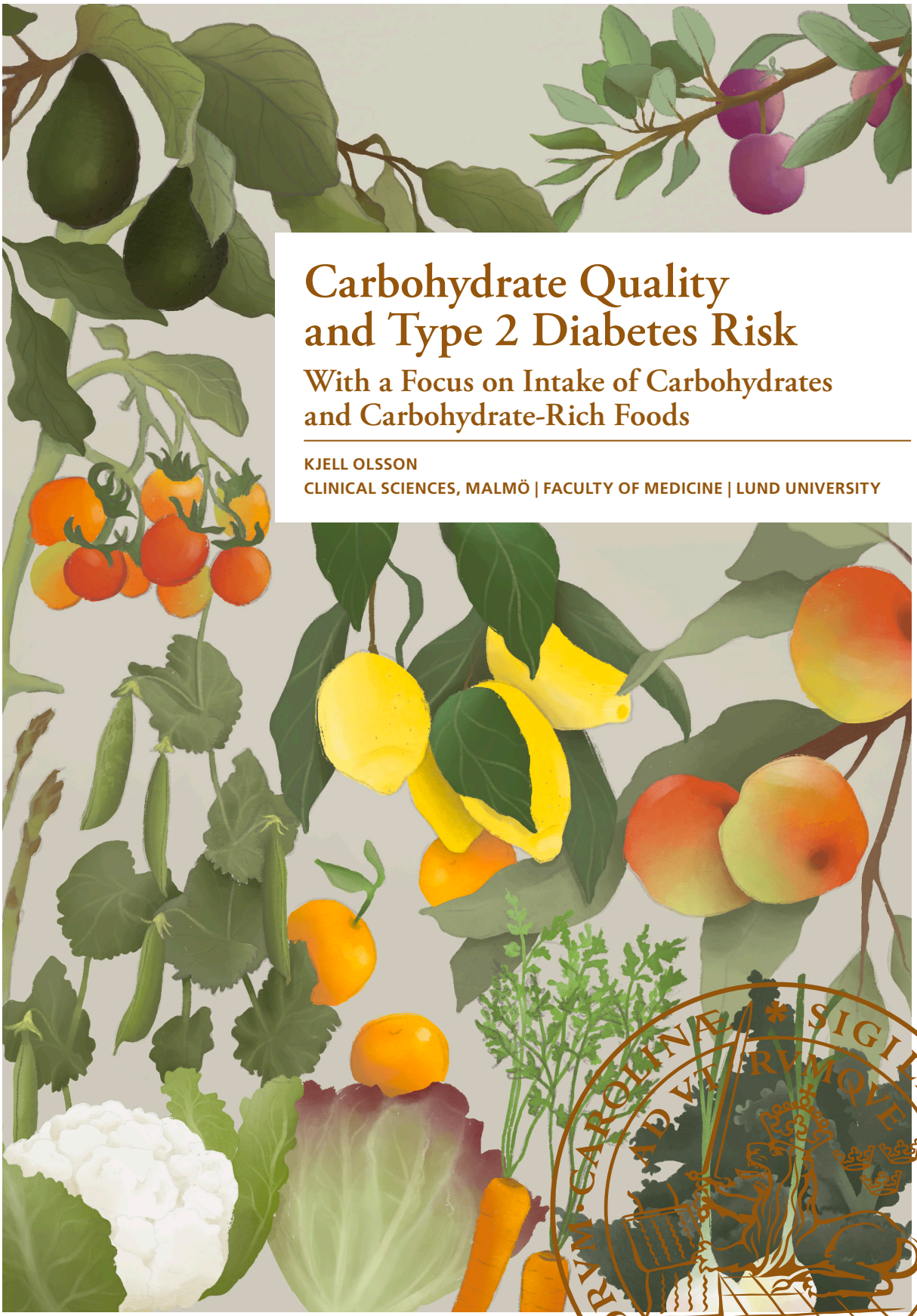

Carbohydrate Quality and Type 2 Diabetes Risk

With a Focus on Intake of Carbohydrates and Carbohydrate-Rich Foods

KJELL OLSSON
CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

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Kjell Olsson

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Mai-Lis Hellénius, Professor
Department of Medicine, Solna, Karolinska Institutet

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Abstract

In 2021, about 500 million adults worldwide were estimated to be living with diabetes, of which over 90 % are living with diabetes mellitus type 2. Intake of carbohydrates and carbohydrate-rich foods have been associated with risk of type 2 diabetes due to their effect on postprandial glucose levels, insulin resistance, obesity, and other potential causes. However, the quality of carbohydrates might play a more important role for type 2 diabetes risk than the quantity. The aim of this thesis was to study the association between carbohydrate quality and the risk of developing type 2 diabetes.

The study population consisted of nearly 30 000 participants in the Malmö Diet and Cancer Study, a prospective cohort in the city of Malmo, Sweden. Baseline examinations, including dietary assessment, were performed in 1991-1996. Type 2 diabetes cases were assessed in regional and national registers.

In study I, we analysed associations between carbohydrates and carbohydrate-rich foods with type 2 diabetes risk. We found a reduced risk with intake of monosaccharides and fruits, and an increased risk with intake of disaccharides and sweets. We also identified sex-specific associations.

In study II, we analysed associations between clusters of carbohydrate-rich foods and type 2 diabetes risk. We identified that a dietary pattern with a high intake of fruits was associated with a lower risk.

In study III, we investigated associations between four different carbohydrate quality indices and the risk of type 2 diabetes. We identified that a higher intake of dietary fibre and a lower intake of free sugar in relation to total carbohydrate intake might be associated with a lower risk.

In study IV, we investigated associations between the EAT-Lancet diet and risk of type 2 diabetes. We identified that greater adherence to the diet was associated with a lower risk, independent of genetic risk.

In study V, we investigated associations between sub-types of fruits and vegetables and type 2 diabetes risk. Higher intakes of green leafy vegetables and dried fruits were associated with a lower risk, while a higher intake of cruciferous vegetables was associated with a higher risk. Sex-specific associations were also identified.

In conclusion, promoting a higher intake of fruits and vegetables (especially green leafy vegetables), and plant-based dietary patterns with a focus on carbohydrate quality, with a higher dietary fibre intake and limited free sugars, has the opportunity to reduce type 2 diabetes incidence. This is likely to benefit all populations while also benefitting overall planetary health.

Key words: Carbohydrates, carbohydrate-rich foods, cohort study, diet, dietary patterns, epidemiology, nutrition, prevention, risk factors, type 2 diabetes.

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Faculty of Medicine
Department of Clinical Sciences, Malmö

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To my wife, Iram

"Human knowledge is never contained in one person. It grows from the relationships we create between each other and the world, and still it is never complete."

(Paul Kalanithi, When Breath Becomes Air)

Table of Contents

Abstract

In 2021, about 500 million adults worldwide were estimated to be living with diabetes, of which over 90 % are living with diabetes mellitus type 2. Intake of carbohydrates and carbohydrate-rich foods have been associated with risk of type 2 diabetes due to their effect on postprandial glucose levels, insulin resistance, obesity, and other potential causes. However, the quality of carbohydrates might play a more important role for type 2 diabetes risk than the quantity. The aim of this thesis was to study the association between carbohydrate quality and the risk of developing type 2 diabetes.

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Populärvetenskaplig sammanfattning

Typ 2-diabetes utgör en av våra vanligaste folksjukdomar och orsakar stort mänskligt och ekonomiskt lidande över hela världen. Förekomsten fortsätter att öka snabbt, inte minst i låg- och medel-inkomstländer, och behovet av förebyggande åtgärder är omfattande.

Våra levnadsvanor har stor betydelse för vår risk att insjukna i typ 2-diabetes. Ohälsosamma matvanor, låg fysisk aktivitet, stillasittande, rökning, snusning, hög alkoholkonsumtion, stress och otillräcklig sömn har alla kunnat kopplas till en ökad risk. Den goda nyheten är att det i stor utsträckning är riskfaktorer som vi själva har möjlighet att påverka. Idag finns dessutom möjlighet att få stöd av hälso- och sjukvården för att kunna förändra en eller flera ohälsosamma levnadsvanor.

Kunskapen om hur våra matvanor påverkar vår hälsa har med hjälp av forskning expanderat enormt de senaste årtiondena. Tydliga samband har kunnat påvisas med flera av våra vanligaste kroniska sjukdomar, inklusive obesitas, hjärt-kärlsjukdom, cancer, och diabetes typ 2. Både vad vi väljer att äta och att dricka har betydelse. Forskning har kunnat påvisa att såväl olika näringsämnen, som enskilda livsmedel och hela kostmönster kan knytas till vårt välmående. Trots det fortsätter våra matvanor att försämras, år efter år.

Syftet med denna avhandling var att utforska samband mellan kostens kolhydratkvalitet och risken att insjukna i typ 2-diabetes. Mer specifikt har vi studerat hur olika typer av kolhydrater, kolhydratrika livsmedel och kostmönster påverkar risken att bli sjuk. Till vår hjälp har vi haft insamlade data från närmare 30 000 Malmöbor från första halvan av 1990-talet. Vi har sedan kunnat följa deras sjukdomsutveckling med hjälp av ett flertal etablerade regionala och nationella register.

I vår första studie undersökte vi om en rad olika kolhydrater och kolhydratrika livsmedel kunde knytas till risken att utveckla typ 2-diabetes. Vi kunde se att ett högre intag av en typ av sockerarter, monosackarider, och ett högre intag av frukt kunde kopplas till en lägre risk, medan ett högre intag av en annan sockerart, disackarider, och av sötsaker kunde kopplas till en ökad risk. Vissa fynd var könsspecifika, där ett högre intag av grönsaker samt honung och syltprodukter sågs vara skyddande enbart hos män, medan ett högre intag av choklad kopplades till ökad risk enbart hos kvinnor.

Ett dilemma i denna typ av studie är att intag av olika livsmedel korrelerar starkt med varandra; om vi äter mycket av ett visst livsmedel så äter vi också mer eller mindre av andra livsmedel. Vilket också kan påverka vår hälsa och som vi inte kan korrigera till fullo för. I nästa studie ville vi därför utforska om vi kunde fastställa tydliga kostmönster utifrån de kolhydratrika livsmedel som studiedeltagarna åt, samt om detta kunde kopplas till risken att utveckla typ 2-diabetes.

Med hjälp av en specifik analysmetod, klusteranalys, delade vi in deltagarna i ett av fem olika kostmönster som alla karaktäriserades av ett högre eller mindre intag av specifika kolhydratrika livsmedel. Därefter utforskade vi om dessa kostmönster kunde kopplas till en högre eller lägre risk för typ 2-diabetes. Efter genomförd analys så kunde vi fastslå att enbart ett av dessa kostmönster kunde kopplas till risken att utveckla typ 2-diabetes; en lägre risk hos de individer som följde ett kostmönster som karaktäriserades av ett högre fruktintag. Återigen kunde vi därmed koppla ett högt fruktintag till en minskad risk för typ 2-diabetes.

I vår tredje studie ville vi studera betydelsen av kolhydratkvalitet i mer detalj genom att utforska om fördelningen av vårt intag av kolhydrater, socker och kostfiber har betydelse för risken att insjukna i typ 2-diabetes. Till vår hjälp använde vi oss av fyra olika index som tagits fram för att ge vägledning till hälsosamma livsmedelsval. Vi kunde därmed dela in deltagarna efter huruvida de uppfyllde kriterierna för dessa index eller inte. Enbart två av fyra index påvisade ett samband med diabetesrisk, och enbart efter att vi uteslutit deltagare som angett att de tidigare har gjort väsentliga förändringar i sin kost, eller som misstänkts ha felrapporterat sitt energiintag. Resultaten gav trots detta en indikation om att en relativt hög andel kostfiber i kosten i förhållande till socker och kolhydrater, samt en lägre andel socker, kan minska risken för typ 2-diabetes.

I fjärde studien fortsatte vi att utforska samband mellan kostmönster och typ 2-diabetes. År 2019 publicerade en lång rad forskare från olika expertområden en artikel som fick stor medial uppmärksamhet. De var alla del av den så kallade EAT-Lancet kommissionen vars uppgift var att presentera ett kostmönster som tar hänsyn både till vår hälsa och planetens ekologiska hållbarhet. Denna kost blev känd som EAT-Lancetdieten, även omtalad som en planetär hälsodiet. I vår studie delade vi in deltagarna i olika nivåer av följsamhet till EAT-Lancetdieten med hjälp av ett index, där deltagarna poängsattes utifrån intag av olika livsmedelsgrupper. Vi fann att de deltagarna med högst poäng, och således högst följsamhet, hade en lägre diabetesrisk än de med lägst poäng. Vi ville även utforska om sambandet skiljde sig åt beroende på nivå av ärftlighet för typ 2-diabetes, vilket vi inte kunde se.

Med utgångspunkt från våra resultat från de två första studierna så valde vi att i den femte och sista studien gå vidare med att utforska hur olika typer av frukter och grönsaker påverkar risken för typ 2-diabetes. Vi kunde då se att ett högre intag av gröna bladgrönsaker, torkad frukt och rotgrönsaker (hos män) var skyddande, medan högre intag av kålgrönsaker och bär (hos kvinnor) innebar en ökad risk.

Sammanfattningsvis har vi kunnat påvisa att ett högre intag av frukt och grönsaker (framförallt gröna bladgrönsaker) tycks minska risken för typ 2-diabetes, vilket stöds av tidigare forskning. Ett i huvudsak växtbaserat kostmönster, med fokus på kolhydratkvalitet, högre andel kostfiber och lägre andel socker, kan förbättra vår hälsa, minska risken för typ 2-diabetes och samtidigt bidra till ekologisk hållbarhet.

Popular Science Summary

Type 2 diabetes is one of our most common chronic diseases and causes great human and financial suffering worldwide. The prevalence continues to increase rapidly, not least in low- and middle-income countries, and the need for preventive measures is extensive.

Our lifestyle has a significant impact on our risk of type 2 diabetes. Unhealthy eating habits, low physical activity, sedentary behaviour, smoking, snus use, high alcohol consumption, stress, and insufficient sleep have all been linked to an increased risk. The good news is that these are modifiable risk factors that we ourselves have the opportunity to influence. Nowadays, there is also the opportunity to get support from health care to change unhealthy lifestyle habits.

Due to research, our knowledge of how our eating habits affect health has expanded enormously in recent decades. Clear associations have been demonstrated for several of our most common chronic diseases, including obesity, cardiovascular disease, cancer, and type 2 diabetes. What we choose to eat and drink matters. Research has been able to show how different nutrients, individual foods, and entire dietary patterns can all be linked to our well-being. Despite all this, our eating habits have continued to deteriorate, year after year.

The overall aim of this thesis was to study the association between carbohydrate quality and the risk of developing type 2 diabetes. More specifically, we have studied how different types of carbohydrates, carbohydrate-rich foods, and dietary patterns affect type 2 diabetes risk. We had access to dietary and other data collected from nearly 30 000 Malmö residents in the first half of the 1990s and could follow their disease development over time through several established regional and national registers.

In our first study, we investigated whether a large selection of carbohydrates and carbohydrate-rich foods could be linked to the risk of developing type 2 diabetes. We could see that a higher intake of one type of sugar, monosaccharides, and a higher intake of fruit was linked to a lower risk, while a higher intake of another type of sugar, disaccharides, and sweets was linked to an increased risk. Some findings were sex-specific; a higher intake of vegetables, and honey, marmalade, and jam, were seen to be protective in men only, while a higher intake of chocolate was linked to an increased risk in women only.

A challenge with this type of study is that intake of foods correlates strongly with each other; if we eat a lot of a certain food, it also relates to intake of other foods. These foods may also affect our health, something we cannot fully adjust for. Hence, in the next study, we wanted to explore whether we could establish specific dietary patterns based on the carbohydrate-rich foods the participants ate, and whether these could be linked to risk of type 2 diabetes.

With the help of a specific analysis method, cluster analysis, we divided the participants into one of five different dietary patterns, all characterized by a higher or lower intake of specific carbohydrate-rich foods. We then explored whether these dietary patterns could be linked to a higher or lower risk of type 2 diabetes. After performing our analysis, we could determine that only one of these dietary patterns was associated with the risk of developing type 2 diabetes; a lower risk in individuals who followed a dietary pattern characterized by a higher fruit intake. Again, we could thus link a high fruit intake to a reduced risk of type 2 diabetes.

In our third study, we wanted to study carbohydrate quality in more detail by exploring whether the ratio of carbohydrates, sugar, and dietary fibre in our diets plays a role in our risk of developing type 2 diabetes. To achieve this, we applied four different indices specifically developed to provide guidance for healthy food choices. We then split the participants according to whether they met the criteria for these indices or not. Only two of four indices showed a correlation with diabetes risk, and only after we excluded participants who responded that they had made significant changes in their diet in the past, or who were suspected of misreporting their energy intake. Still, the results indicated that a high proportion of dietary fibre in the diet relative to sugar and carbohydrates, and a low proportion of sugar, can reduce the risk of type 2 diabetes.

In our fourth study, we continued to explore the relationship between dietary patterns and type 2 diabetes. In 2019, several researchers from different scientific fields published an article that received great media attention. They were all part of the EAT-Lancet Commission with the task of presenting a dietary pattern that would consider both human health, as well as the planet's ecological sustainability. This diet became known as the EAT-Lancet diet, also referred to as the planetary health diet. In our study, we divided participants into different levels of adherence to the EAT-Lancet diet using an index, where the participants were scored based on the intake of different food groups. We found that the participants with the highest score, and thus the highest adherence, had a lower type 2 diabetes risk than those with the lowest score. We also wanted to explore whether the relationship differed depending on the level of heredity for type 2 diabetes, which we could not see.

In the fifth and final study, based on our results from the first two studies, we chose to explore how sub-types of fruits and vegetables affect the risk of type 2 diabetes. We found that a higher intake of green leafy vegetables, dried fruit, and root vegetables (in men) was protective, while a higher intake of cabbage and berries (in women) entailed an increased risk.

In conclusion, we found that a higher intake of fruit and vegetables (especially green leafy vegetables) may reduce the risk of type 2 diabetes, which is also supported by previous research. A plant-based dietary pattern with a focus on carbohydrate quality, with a higher proportion of dietary fibre and lower of sugar, can improve our health, reduce type 2 diabetes risk, and contribute to ecological sustainability.

List of Papers

This doctoral thesis is based on the following five original papers;

I. **Olsson K**, Ramne S, González-Padilla E, Ericson U, Sonestedt E. Associations of carbohydrates and carbohydrate-rich foods with incidence of type 2 diabetes. **Br J Nutr**. 2021 Oct 14;126(7):1065-1075.

II. **Olsson K**, González-Padilla E, Janzi S, Stubbendorff A, Borné Y, Ramne S, Ericson U, and Sonestedt E. Clusters of carbohydrate-rich foods and associations with type 2 diabetes incidence: a prospective cohort study. **Nutr J**. 2023 Dec 18;22(1):71.

III. Ramstedt M, Janzi S, **Olsson K**, González-Padilla E, Ramne S, Borné Y, Ericson U, Sonestedt E. Comparisons of Different Carbohydrate Quality Indices for Risk of Type 2 Diabetes in the Malmö Diet and Cancer Study. **Nutrients**. 2023 Sep 5;15(18):3870.

IV. Zhang S, Stubbendorff A, **Olsson K**, Ericson U, Niu K, Qi L, Borné Y, Sonestedt E. Adherence to the EAT-Lancet diet, genetic susceptibility, and risk of type 2 diabetes in Swedish adults. **Metabolism**. 2023 Apr;141:155401.

V. **Olsson K**, Janzi S, Stubbendorff A, Borné Y, Ericson U, and Sonestedt E. Associations between intake of sub-types of fruits and vegetables with incident type 2 diabetes in a cohort in southern Sweden. **Manuscript**.

Author´s Contribution to the Papers

I. Formulated the aim and the design of the study together with Emily Sonestedt. Performed the statistical analysis, interpreted the findings and drafted the manuscript. Shared the primary responsibility for the final content with Emily Sonestedt.

II. Formulated the aim and the design of the study together with Emily Sonestedt. Performed the statistical analysis, interpreted the findings and drafted the manuscript. Shared the primary responsibility for the final content with Emily Sonestedt.

III. Assisted in reviewing and editing the manuscript together with the other authors. Read and agreed to the published version of the manuscript.

IV. Assisted in methodology and in reviewing and editing the manuscript together with the other authors. Read and agreed to the published version of the manuscript.

V. Formulated the aim and the design of the study together with Emily Sonestedt. Performed the statistical analysis, interpreted the findings and drafted the manuscript. Shared the primary responsibility for the final content with Emily Sonestedt.

List of Papers Not Included in the Thesis

I. Ramne S, Alves Dias J, González-Padilla E, **Olsson K**, Lindahl B, Engström G, Ericson U, Johansson I, Sonestedt E. Association between added sugar intake and mortality is nonlinear and dependent on sugar source in 2 Swedish population-based prospective cohorts. **Am J Clin Nutr**. 2019 Feb 1;109(2):411-423.

II. González-Padilla E, A Dias J, Ramne S, **Olsson K**, Nälsén C, Sonestedt E. Association between added sugar intake and micronutrient dilution: a cross-sectional study in two adult Swedish populations. **Nutr Metab (Lond)**. 2020 Feb 11;17:15.

Abbreviations

BMI	Body mass index
CI	Confidence interval
DASH	Dietary Approach to Stop Hypertension
E%	Percent of energy
FOS	Fructo-oligosaccharides
GOS	Galacto-oligosaccharides
HbA1c	Haemoglobin A1c
HOMA-IR	Homoeostatic Model Assessment of Insulin Resistance
HR	Hazard ratio
LADA	Latent autoimmune diabetes in adults
MET	Metabolic equivalent of task
SCFA	Short-chain fatty acids

Introduction

"Let food be thy medicine and medicine be thy food."

- Hippocrates *(attribution disputed)*

Historical mentions of a disease with symptoms known today to be associated with diabetes can be traced back more than 3000 years, to ancient Egypt [1, 2]. The well-known medical papyrus Ebers Papyrus describes patients suffering from "excessive thirst" and "copious urination" with treatments including a diet of herbs, oils, honey, beer, wheat, Juniper berries, dates, grapes, and bread sops [1, 3, 4]. Almost a 1000 years later, in the 5th century BC, the Indian physician Sushruta describes diabetes by the term Madhumeha, "honey-like urine", in the Sanskrit text Susruta [1, 2, 5]. The text, an important ancient document within Ayurveda, describes the condition as caused by "excess intake of rice, cereals, and sweets". Sushruta was among the first to describe two types of diabetes, one prevalent in youth and the other in overweight individuals. Early references to a diabetes-like condition can also be found in ancient Chinese medicine.

The term diabetes would, however, not be introduced until centuries later in ancient Greece, in the 2nd century AD [2, 3]. The Ancient Greek meaning of the word refers to a condition where "the fluid runs through", referring to the symptom known today as polyuria, defined as an excessive production or passage of urine. The physician Aretaeus of Cappadocia suggested that the illness could be treated by "the consumption of cereals, milk, and wine".

In the latter part of the 18th century, the English physician Matthew Dobson identified that the sweet taste was due to sugar in the urine (glycosuria), and two decades later the Scottish military surgeon John Rollo added the term "mellitus" to "diabetes" [2, 3]. The term referred specifically to the sweet taste of the urine and was derived from the Latin word "mellītus", meaning "honey-sweet". This helped differentiate between diabetes mellitus and diabetes insipidus, a distinction that German physician Johann Frank had been the first to describe. The latter being a condition where the excess urine is due to an antidiuretic hormone deficiency, with no presence of glycosuria, and thus dubbed "insipidus" (Latin for "tasteless").

In the 19th century, a couple of French researchers would make important contributions to the understanding of the pathophysiology of diabetes mellitus.

Claude Bernard identified the role of the liver in the metabolism and storage of glucose as glycogen, and the secretion of glucose into the blood [1]. However, Bernard wrongly believed that excess secretion of glucose from the liver was the cause of diabetes mellitus. Later, Édouard Laguesse would discover the endocrine role of the islets of Langerhans and name them after their discoverer, German anatomist Paul Langerhans [2, 6]. Laguesse's discovery would, along with discoveries by Oskar Minkowski and Joseph von Mering of the role of the pancreas in diabetes, go on to be very important for the future discovery of the role of insulin.

The big breakthrough would come in the 1920s, when for the first time in history it would actually be possible to control the disease [3]. In May of 1921, Canadian surgeon Frederick Banting started collaborating with the medical student Charles Best at the University of Toronto. They would create an extract from the pancreatic glands of dogs that they would later inject into diabetic dogs. Two hours after injection they found that the blood glucose in the dogs had dropped considerably. The method of extraction and purification would continuously be improved by their colleague, James Collip, who was a chemist. The extracted substance was named "insulin" by Banting's supervisor, Professor John MacLeod. A year later, the first successful human trial was conducted with the treatment of the 14-year-old Leonard Thompson, who would go on living with diabetes until dying of pneumonia at age 27 [2]. In 1923, Frederick Banting and John MacLeod were both awarded the Nobel Prize in Physiology or Medicine. However, Banting was infuriated that MacLeod was sharing the prize with him and not Charles Best, as he saw MacLeod's contribution as miniscule compared to Best and would go on to share half of his prize money with Best.

Ever since the first descriptions of the condition, the role of diet in the cause and treatment of diabetes has been pivotal. However, rigorous research into the association between dietary intake and risk of developing diabetes could not be conducted until the introduction of epidemiology in the 19th century, and larger cohort studies that started exploring the association between diet and health outcomes did not commence until the mid-20th century.

Carbohydrates

Definition and Composition

"Any compound of carbon, hydrogen, and oxygen in the which the last two elements occur in the same proportion as in water."

- The Oxford English Dictionary

Carbohydrates are defined in the Oxford English Dictionary as "any compound of carbon, hydrogen, and oxygen in the which the last two elements occur in the same proportion as in water" [7]. It often refers to carbohydrates present in foods, which can also be referred to as "dietary", "food", or "food-sourced" carbohydrates. "Carbohydrates" is considered a mass noun rather than a count noun, as any amount of carbohydrates is referred to as "X grams of carbohydrates", instead of "X carbohydrates".

Carbohydrates can be divided into four main groups based on their size (i.e. molecular weight): monosaccharides, disaccharides, oligosaccharides, and polysaccharides [8].

Mono- and disaccharides are often referred to as "sugars" or "simple carbohydrates" [8]. Common monosaccharides include glucose, fructose and galactose, and constitute the underlying components from which all other carbohydrates are constructed [9]. Honey, fruits, and berries are common sources of monosaccharides. Meanwhile, disaccharides are made up of two monosaccharides where sucrose (glucose and fructose), lactose (glucose and galactose) and maltose (glucose and glucose) are among the most common. Sucrose, or white sugar, is abundant in many foods today, often added to enhance the sweetness of the food. Lactose, or milk sugar, is found in dairy products such as cow's milk but also in the milk from other mammals, such as sheep, goat, camel, and water buffalo. Maltose is found in malted grain, which is used to produce beer, whisky, and malted milk, among other foods.

Oligosaccharides are made up of three to ten monosaccharides. The most common oligosaccharides in food are fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), which are both regarded as prebiotics [10]. FOS are mainly found in fruit and vegetables, but also some grains, while GOS are found in breast

milk [11]. Both FOS and GOS are considered prebiotics as they stimulate growth of healthy bacteria in the colon [10, 12].

Polysaccharides can be divided into starch and non-starch polysaccharides [8]. Starch polysaccharides consist of a long chain of the monosaccharide glucose and can in turn be divided into amylose (linear polymer of glucose) and amylopectin (branched polymer of glucose) [13]. A higher amylose to amylopectin ratio in the diet has been shown to improve postprandial glycaemic control and reduce the insulin response [14]. Non-starch polysaccharides provide the structural support of the cell walls of plants and constitute the majority of all dietary fibres consumed [15]. Common non-starch polysaccharides in the diet include cellulose, pectin and β-glucans.

Carbohydrates can also be divided into glycaemic carbohydrates (digested and absorbed in the small intestine) and non-digestible carbohydrates (passing to the large intestine) [8]. Non-digestible carbohydrates are also known as dietary fibre [15]. Dietary fibre, according to the European Food Safety Authority (EFSA) and the International Carbohydrate Quality Consortium (ICQC), includes all non-starch polysaccharides, lignin, resistant oligosaccharides, and resistant starch [16, 17]. Lignin, the only non-carbohydrate dietary fibre, is a phenolic polymer and important for cell wall structure in plants [18].

For sugars, the terms “added sugar” and “free sugar” are often used in literature and recommendations [8]. This is to differentiate these sugars from intrinsic sugars, also referred to as naturally occurring sugars, which are present in foods such as intact fruits and vegetables and milk [19]. “Added sugar”, in contrast, refers to mono- and disaccharides that are added during food manufacturing and preparation, such as in sweets, pastries, and sugar-sweetened beverages, or at home, such as in table sugar [8, 20]. “Free sugar” includes all added sugars with the addition of sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.

Digestion and Metabolism

Even before food enters the mouth the body is triggered by the sight, smell, and expectation of food, and several physiological processes begin to prepare for the digestion of the food, including production of saliva and gastric juices, and the secretion of insulin [21, 22].

The digestion of carbohydrates begins in the mouth by chewing (mechanical action) and with the help of salivary amylase (chemical action), an enzyme that is produced in the salivary glands and excreted in the oral cavity [23-26]. Amylase breaks down starch into smaller molecules in several steps, ultimately resulting in the disaccharide maltose, trisaccharide maltotriose, and limit dextrin [25]. However,

salivary amylase has relatively short time for interacting with the food before it is swallowed, and the acidic gastric environment inhibits most of its activity [24]. Thus, digestion largely occurs in the duodenum through the action of pancreatic amylase. Further digestion into monosaccharides is carried out by brush border enzymes in the intestinal lining of the small intestine, for example sucrase, maltase, and lactase [8].

Glucose and galactose are actively absorbed into small intestinal cells with the help of the sodium-glucose cotransporter 1 (SGLT1) [23]. Glucose absorption is also facilitated by passive transport via the GLUT2 transporter. Similarly, fructose is passively absorbed through facilitated diffusion via the GLUT5 transporter [27].

Once absorbed, the monosaccharides enter the bloodstream and via the portal vein are transported to the liver [8]. In the liver, the monosaccharides undergo different processes. Glucose constitutes the greatest proportion of the monosaccharides and either enters into the bloodstream to maintain blood glucose homeostasis or undergoes glycogenesis to be stored in the liver as glycogen [28]. Glucose can also be stored as glycogen in muscles. For galactose, the majority is retained in the liver and stored as glycogen, while the rest is transported to other organs and tissues of the body to be used in the production of amino acids [29]. In lactating women, galactose is transported to the mammary glands in lactating women to produce lactose for the breast milk. Fructose is converted into glucose in the liver and used as energy or stored as glycogen [28]. Excess fructose intake can also generate lipogenesis and the production of triglycerides in the liver, ultimately leading to excess fat in the liver and insulin resistance.

Dietary fibre, predominantly non-digestible carbohydrates, avoid digestion and absorption in the small intestine and instead passes to the colon [15]. However, dietary fibres differ in size, structure, function, and other properties, including solubility, viscosity, and fermentability [15, 30].

Soluble fibres, such as pectin and β-glucans, generally have medium to high viscosity, increasing the resistance to flow, and high fermentability, being metabolized to a high degree by colonic bacteria [30, 31]. These fibres dissolve in water which creates swelling and a gel-like substance. This, in turn, slows down digestion and gastric emptying and increases satiety [15]. Fermentation by colonic bacteria supports the growth of beneficial bacteria and promotes healthy gut microbiota [31, 32]. During fermentation, large amounts of short-chain fatty acids (SCFA) are produced as a by-product [15, 32]. The SCFAs have anti-inflammatory and immunomodulatory properties, enhance cellular repair, strengthen the colonic epithelium, regulate appetite, and positively affect glucose and lipid metabolism [15, 30, 31]. Moreover, some viscous fibres, mainly β-glucans (primarily found in oats), have a unique ability to bind to bile acids in the small intestine and reduce their reabsorption [32]. This forces the liver to compensate by increasing the production of bile acids. Since cholesterol is needed for bile acid production, the

levels of circulating total cholesterol and LDL cholesterol in the blood are lowered [15, 30, 32].

Insoluble fibres, including cellulose and lignin, are non-viscous and generally have low fermentability [30]. They provide bulk to the stool and help promote regular bowel movements, which prevents constipation and reduces risk of colorectal cancer [15]. Fibre-rich foods often contain several different dietary fibres, with different properties, and it may thus be difficult to categorize foods based on the characteristics of one type of dietary fibre [15, 30].

Carbohydrates and Type 2 Diabetes Risk

Intake of carbohydrates have been associated with risk of developing type 2 diabetes due to several important factors. Since carbohydrates are degraded into glucose, primarily during digestion and metabolism, and enter the bloodstream, a postprandial increase in blood glucose levels will result. Higher intakes of foods containing carbohydrates that are rapidly digested and absorbed will lead to a greater glycaemic load in the body [33]. Both glycaemic index and glycaemic load are measurements of the impact on postprandial blood glucose levels from carbohydrate-rich foods and have been associated with type 2 diabetes risk [34]. A higher glycaemic index corresponds to a greater and more rapid postprandial increase in blood glucose, and thus is an indicator of carbohydrate quality, whereas glycaemic load also takes into account the quantity of carbohydrates in the specific food [8, 35].

A great and rapid increase in blood glucose levels after food consumption triggers a similarly strong insulin response, leading to the transport of glucose from the blood into cells [34]. Over time, an exaggerated insulin response may lead to insulin resistance as cells in the body may become less responsive to the hormone. Reduced insulin sensitivity will force the β-cells in the pancreas to compensate by producing and releasing more insulin to maintain blood glucose homeostasis. Eventually, the β-cells, in genetically susceptible individuals, may fail to compensate sufficiently, thus β-cell dysfunction evolves (β-cell dysfunction is mainly caused by cellular dysfunction, and less by the loss of β-cell mass) [36]. In short, β-cell dysfunction in insulin resistant individuals leads to sustained elevation of blood glucose levels first observed as prediabetes and, in a large proportion of people, progressing to manifest type 2 diabetes.

A higher intake of added and free sugars increases the risk of obesity [8, 37]. Obesity in turn increases the risk of type 2 diabetes by causing systemic inflammation and increase of adipose tissue in the body, consequently leading to insulin resistance, reduced insulin sensitivity, and accelerated β-cell dysfunction [36]. Conversely, a higher intake of dietary fibre and whole grains have been associated with a lower

risk of type 2 diabetes [38-40]. The association seems to be stronger for insoluble rather than soluble fibres, suggesting other mechanisms than the influence on postprandial glucose levels [39]. However, dietary fibre has been proven to indirectly affect the postprandial glucose response by its effect on gut microbiota, specifically the production of SCFA [41, 42]. Increased satiety, glycogen synthesis, and fatty acid oxidation, and improved glucose uptake in muscle and fat issues have all been associated with higher levels of SCFA. However, based on recent evidence, both intake of dietary fibre and of whole grains may constitute better indicators for carbohydrate quality than glycaemic index and glycaemic load [38].

Overall, in the prevention of type 2 diabetes and other chronic diseases, the quality of carbohydrates seems to play a more important role in cardiometabolic health than the quantity or proportion of carbohydrates [43-45].

Carbohydrate-Rich Foods

Carbohydrate-rich foods refer to foods that contribute to a large proportion of total carbohydrate intake, and where a high proportion of the energy content is provided by carbohydrates, regardless of total carbohydrate content or quality [46].

Several carbohydrate-rich foods have been independently associated with a lower or higher risk of type 2 diabetes, specifically fruits, green leafy vegetables, and foods rich in whole grains [38, 40, 47-50].

While some studies have found no association between a higher fruit intake and type 2 diabetes risk, recent studies have identified clear inverse associations [47-53]. The association is likely to be non-linear with no additional benefit of intakes above 200-300 grams per day [47, 49, 50, 54]. The health benefits from fruits are likely due to the low energy and high nutrient density, including micronutrients, phytochemicals, and dietary fibre. As mentioned, dietary fibre provides a range of health benefits directly associated with lower type 2 diabetes risk [39]. In addition, dietary fibre provides satiety and reduces the risk of weight gain. Phytochemicals, including polyphenols, are mainly non-essential nutrients, but are still believed to provide a range of health benefits and has been associated with a lower type 2 diabetes risk with several suggested mechanisms [55, 56]. Moreover, micronutrients found in fruits, including antioxidants, have also been suggested as a possible explanation for the lowered type 2 diabetes risk [57]. However, micronutrient supplements have failed to show similar effects [58].

Associations between a higher vegetable intake and lower type 2 diabetes risk have been less conclusive [48, 49, 53, 54, 57]. However, a higher intake of green leafy vegetables, specifically, have shown clear inverse associations [48, 53, 59]. While the exact mechanism is still unknown, plausible explanations relate to the relatively

high content of magnesium and inorganic nitrate in green leafy vegetables [60-65]. Magnesium has been found to have an essential role in insulin secretion and sensitivity, as well as in reducing low-grade inflammation and oxidative stress that might lead to insulin resistance [66]. Inorganic nitrate, on the other hand, is believed to reduce type 2 diabetes risk through multiple metabolic effects enabled by the nitrate-nitrite-NO pathway [63].

A higher intake of whole grains has also been repeatedly associated with a lower type 2 diabetes risk [38, 40, 47, 67]. The association has been found to be non-linear, with possibly no further risk reduction beyond 60 grams per day [40, 47]. There are several plausible reasons why whole grains may contribute to a lower risk. Since whole grains are high in dietary fibre, and findings related to lower type 2 diabetes risk have been similar for whole grains and dietary fibre, it is likely that the dietary fibre in whole grains might explain some, if not most, of the health benefits [38, 40]. However, just as for green leafy vegetables, whole grains are also high in magnesium, which have been linked to lower type 2 diabetes risk [40, 66]. Moreover, other micronutrients and phytochemicals might also be contributing to the reduced risk [68]. Overall, substituting refined grains for whole grains has been suggested as a health promoting recommendation [38].

Some carbohydrate-rich foods have also been associated with an increased risk of type 2 diabetes. In particular, sugar-sweetened beverages have repeatedly been associated with an increased risk [47, 69-71]. There are several possible mechanisms linking sugar-sweetened beverages to increased type 2 diabetes risk [72]. One explanation is that liquid sugars provide less satiety than other foods and may thus lead to over-consumption of energy and subsequent increased risk of obesity and type 2 diabetes [73-75]. Another plausible mechanism might be the postprandial glycaemic load generated by sugar-sweetened beverages, subsequently leading to a high insulin response [72]. Thirdly, excess consumption of fructose (found both in sucrose and high-fructose corn syrup (a common sweetener in e.g. the United States)) has been shown to trigger lipogenesis (mainly in the liver), which could lead to dyslipidaemia and insulin resistance, and to trigger increased uric acid production, all of which have been linked to type 2 diabetes [76]. Lastly, there might be addictive qualities to sugars that could trigger over-consumption and subsequent negative health effects. However, more research is needed to support and quantify the risk of addiction [72].

On the other hand, consumption of 100 % fruit juice seems to have no association with type 2 diabetes risk [77]. However, some results have been conflicting and there might be some concerns regarding associations with weight gain prompting the need to limit fruit juice consumption [78-80].

Although diets that limit intake refined grains are often associated with lower type 2 diabetes risk, this may be due to health benefits from substituting refined grains

for whole grains, rather than a direct negative effect of refined grains [38, 47, 67, 81].

Dietary Patterns

In epidemiological research, health outcomes related to dietary patterns are mainly studied using one of two different approaches [82]. One method is to apply an a priori approach, with the purpose of confirming the health benefits of an already established dietary pattern, such as the Mediterranean diet or the Dietary Approach to Stop Hypertension (DASH). This is often conducted by applying an index, or a score, developed to establish the level of adherence to a specific diet and group participants accordingly.

Carbohydrate-rich foods constitute key components of most established dietary patterns associated with lower type 2 diabetes risk [83]. These include the Mediterranean diet, DASH, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), Healthy Eating Index (HEI), low glycaemic index, Healthy Nordic diet and EAT-Lancet diet [84-91].

The other method is to apply an a posteriori approach, which is an exploratory approach as dietary patterns are discovered through analysis of the available data [82, 92]. Common a posteriori approaches include principle component analysis, factor analysis and cluster analysis. Findings from a posteriori studies confirm the association between a healthy dietary pattern and a reduced type 2 diabetes risk [93-95].

As confirmed in both a priori and a posteriori studies, healthy dietary patterns emphasize both limiting and increasing intake of carbohydrate-rich foods, specifically recommending a higher intake of fruits, vegetables, legumes, and whole grains, while limiting the intake of refined grains, sugar-sweetened beverages, and all foods high in added and free sugars [81, 84, 93, 96, 97].

Type 2 Diabetes

"Lifestyle changes are the best way to prevent or delay the onset of type 2 diabetes."

- The World Health Organization

Overview

Diabetes mellitus is a serious and increasingly prevalent condition that contributes to almost 7 million deaths yearly [98]. In 2021, about 500 million adults worldwide were estimated to be living with diabetes, constituting 1 in 10 of the total adult population [98, 99]. The global prevalence is estimated to have more than doubled since 2007 [98]. The overwhelming majority (over 90 %) are living with diabetes mellitus type 2, of which more than 80 % live in low- and middle-income countries [98, 100].

Overall, the global prevalence is slightly higher in men than in women, albeit with large regional differences, and global health expenditures due to diabetes are expected to exceed 1 trillion US dollars by 2030 [98, 99]. By 2045, almost 800 million people are estimated to have diabetes, with other estimates expecting the prevalence to reach over 1.3 billion by 2050, an increase of close to 60 % from 2021 [98, 99].

Pathophysiology

Type 2 diabetes mellitus develops due to impaired insulin secretion, insulin resistance, or a combination thereof [98, 100, 101]. Insulin is an essential hormone produced in the pancreas and necessary for blood glucose to enter the cells of the body in order to provide energy or to be stored. Type 2 diabetes often develops due to insulin resistance leading to hyperinsulinaemia and subsequent decline in pancreatic β-cell function and impaired insulin secretion [98, 100]. This, in turn, leads to increased blood glucose levels (hyperglycaemia), the diagnostic indicator

of diabetes that can be identified by elevated plasma glucose or haemoglobin A1c (HbA1c) levels.

However, type 2 diabetes is a multifaceted disease and the pathophysiology involves a complex interplay of beta-cell dysfunction, insulin resistance, abnormal glucose metabolism, adipose tissue dysfunction, and chronic inflammation [100, 102]. Genetics, environmental factors (including diet and physical activity) and epigenetics are all important underlying factors [103-106].

The pathophysiology differs somewhat between men and women, based on biological, behavioural, and psychosocial factors [107]. Recently, it has also been proposed that adult-onset diabetes can be divided into five different subtypes, due to differences in age at onset, disease progression, clinical characteristics, response to treatment, and the risk, type, and severity of complications [108].

Recent developments in proteomics and metabolomics have identified novel potential biomarkers for early detection of type 2 diabetes [109-112]. This might have wide-reaching future implications in earlier detection of disease risk, understanding of metabolic pathways and disease subtypes, development of precision medicine, and identification of novel and individually tailored treatments for type 2 diabetes.

Epidemiology, Risk Factors, and Prevention

The prevalence of type 2 diabetes is increasing worldwide, due to unhealthy diets, more sedentary lifestyles, and increased prevalence of overweight and obesity [98, 113]. However, it is also caused by ageing populations, as well as early detection and better treatments leading to longer survival. Other lifestyle factors have also been associated with type 2 diabetes risk, including tobacco use, alcohol consumption, and sleep duration, as well as environmental factors, including air pollution and noise levels [114-116].

In the prevention of type 2 diabetes, there seem to be clear benefits to focusing on multiple factors rather than one single lifestyle factor [114, 117]. While general screening for type 2 diabetes is not recommended, primary prevention initiatives, such as diabetes prevention programmes and structured health dialogues, can have significant effects on fasting blood glucose, disease prevention, and disease progress [118-120].

Genetics

A large number of genetic loci have been identified to be associated with type 2 diabetes [100, 121]. Moreover, epigenetics - regulation of the genome that does not require changes to the DNA sequence, has also been identified as an important factor in type 2 diabetes development [121].

Advances in scientific research into genomics and metabolomics have opened up the opportunity for precision nutrition in type 2 diabetes prevention, individually tailoring the dietary intervention to each individual's needs [122]. Information on genetic risk scores could help identify high-risk individuals and populations who may benefit the most from dietary interventions [123]. However, several studies have shown no difference in associations between healthy diets and type 2 diabetes risk across genetic risk score groups [124-126].

Aims

General Aim

The overall aim of this thesis was to study the association between carbohydrate quality and the risk of developing type 2 diabetes.

Specific Aims

The specific aims of the thesis and the included papers were:

I. To analyse the associations between intake of different types of carbohydrates and carbohydrate-rich foods with incidence of type 2 diabetes.

II. To identify clusters of carbohydrate-rich food intake and analyse associations with incidence of type 2 diabetes.

III. To investigate the association between four different carbohydrate quality indices with various amounts of fibres and free sugars in relation to total carbohydrates and the risk of developing type 2 diabetes.

IV. To investigate the association between the EAT-Lancet diet and risk of type 2 diabetes and assess whether the association differs by the genetic predisposition to type 2 diabetes.

V. To investigate the associations between intake of sub-types of fruits and vegetables with incidence of type 2 diabetes.

Methods

Malmö Diet and Cancer Study

An application for the ethical approval for "Diet and cancer - A prospective study in Malmö" was submitted in January of 1990, and approved a month later. The main objective of the study was to study whether diet, as part of a lifestyle pattern, may play a role in the development of certain cancers. It was believed that a Western diet (high in energy and fat, and low in dietary fibre and vitamins) could cause up to 35 % of all cancers, in particular, breast, colorectal, pancreatic, ovarian, uterine, and prostate cancer. Incidence of cancer cases was planned to be followed for 10 years in different national and regional registers.

Initially, all individuals born between 1926 and 1945, residing in Malmö Municipality, Sweden, on 1 January 1991 were invited to participate (*n* 53 325) [127]. The cohort was updated every three months identifying individuals who had moved to and from Malmö, or who had deceased. In 1995, the cohort was extended to include men born between 1923 and 1945, and women born between 1923 and 1950. The reason for including younger women was to be able to investigate breast cancer in premenopausal women. All in all, the included birth cohorts encompassed 74 138 potential participants.

Recruitment was carried out from 1 January 1991 to 25 September 1996, using both passive and active forms of recruitment [128]. Passive recruitment, through community-directed invitations, was carried out by the placement of posters and pamphlets in public areas, including banks, pharmacies, libraries, primary care centres, and in hospital wards, as well as advertisements on public buses, mainly during the years 1992-1994. In addition, a number of organizations were approached, and face-to-face recruitment was carried out during the one-week city festival in 1992 and 1993. Media was also encouraged to report on the study, resulting in newspapers, as well as local radio and TV, drawing attention to the study. In total, 5505 individuals responded to the passive recruitment, of which 5082 ultimately participated in the study [127].

Active recruitment was carried out through personal mail invitations, with one or two follow-up invitations. Follow-up phone calls were later introduced to reach out to non-responders to the mail invitations. Altogether, 23 016 participants were actively recruited to the study.

The final study population of 28 098 participants had responded to invitations, deemed eligible to participate, and completed the baseline examinations [127]. The only exclusion criteria for the study were the inability to accurately respond to the baseline questionnaires, either due to inadequate Swedish proficiency or intellectual disability. Compared to participants, non-participants in the study had higher overall mortality during the recruitment and follow-up period.

During the first baseline visit, participants were guided in groups of six to eight. They were instructed on how to register the meals in the food record and how to fill out the food frequency questionnaire, as well as filling out the questionnaire covering socio-economic and lifestyle factors, current health, medications, medical history, and family history of disease. The project nurses administered blood samples, as well as blood pressure and anthropometric measurements. The food record and both questionnaires were all completed in time for the second visit, generally two weeks later [129].

Since 1993, the Malmö Diet and Cancer Study has been part of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large European study into relationships between diet and chronic diseases with over half a million participants [130].

Dietary Assessment

In 1984, a methodological study was carried out in Malmö with 206 participants, 50-69 years old [131-134]. The purpose of the study was to determine the best way to conduct a dietary assessment. The study compared responding to an extensive 250-item food frequency questionnaire (method A) with a combined method of a shorter, 130-item food frequency questionnaire and a 14-day food record (method B). Each method was compared to an 18-day food record conducted over a one-year period, with six occasions of three-day food recording on consecutive days. When studying the correlation of method A and B with the reference method, in both men and women, the authors concluded that the shorter food frequency questionnaire combined with the 14-day food record (method B) provided the most accurate assessment, with good ranking validity and good reproducibility. The energy-adjusted Pearson correlation coefficients for men and women, respectively, was 0.66 and 0.70 for total carbohydrates, 0.74 and 0.69 for dietary fibre, and 0.60 and 0.74 for sugar, compared to the reference method [134].

The initial plan for the Malmö Diet and Cancer Study was thus to assess food intake with a combined method of a food frequency questionnaire and 14-day food record, as described in the ethical application submitted and approved by the Regional Ethics Committee (LU 90-51). However, the final approach being implemented was

a combination of a 168-item food frequency questionnaire, a 7-day food record, and a 60-minute food interview [127, 135].

The questionnaire and the food record were developed to complement each other. For the 7-day food record, participants were asked to register the intake of the cooked meals consumed (generally lunch and dinner), cold beverages, and nutritional supplements. The recording was conducted for seven consecutive days in a specific booklet. Participants were asked to provide as much information as possible regarding cooking method, specific types of food, e.g. meat, fish, and vegetables, fat content in e.g. cheese and milk, the food brand, the volume of cold beverages consumed, and the name, brand, and amount of supplements consumed.

In the food frequency questionnaire, participants were asked to register the intake of food items regularly eaten at all other times of the day, as well as all hot beverages (specifically coffee, tea, and chocolate). Participants registered the frequency of intake of 168 food items and were helped by a 48-item portion guide to estimate portion sizes. The reference period for the food frequency questionnaire was the preceding year.

Both the food record and the food frequency questionnaire were distributed during the first visit and handed in two weeks later during the second visit. At the second visit, a trained interviewer would conduct a 60-minute interview during which both the food record and the food frequency questionnaire were checked according to predefined rules. Portion sizes of the meals registered in the 7-day food record were assessed with the help of an extensive portion guide during the interview and converted into grams in the computer software. Recipes for the registered meals could be identified in the software and altered if needed. New recipes could be added if required. The interviewer also ensured that the recorded food intake did not overlap between the two methods.

A total of 17 trained interviewers participated in the study during the 6-year baseline period [135]. Several measures were incorporated to ensure a standardized dietary data collection, including regular training of interviewers, standardized data entry and coding of data in the computer software, an extensive set of coding rules, and a quality control program of the collected data by the two head nutritionists. Extreme and median values were routinely reviewed through a monthly quality control routine. Values were either verified or, if erroneous, attended to and corrected.

Due to an unexpected reduction in funding announced in 1993, there was a sudden need to examine approaches to shorten the interview time [135]. It was identified that about half of the interviewer's time was spent on examining the 7-day food record and only 25 percent on the food frequency questionnaire. Thus, changes in coding routines of the 7-day food record were implemented in September of 1994 after analysing the correlation of energy and nutrient intake, as well as the ranking of individuals, with the previous routine. Specifically, the option to add new, individual recipes to the computer software was removed, and fewer recipes were

allowed to be altered, relying to a larger degree on the use of standard recipes already present in the computer software when registering the food intake.

The change in coding routines was proven to substantially reduce interview time and meant that interview could be shortened from 60 minutes to about 45 minutes [135]. Moreover, these changes did not require any alterations to the booklet used for the food recording nor did they require any changes to the food frequency questionnaire.

When tested, the new method showed strong correlations with the old method for both energy intake as well as for all examined nutrients [135]. There were no significant differences in mean energy or nutrient intake, and no major effect on the ranking of individuals on dietary intakes.

Clinical Measurements

Anthropometric examinations and blood sampling were conducted during the first visit to the study centre [136]. Blood pressure was measured twice in the right arm after five minutes of rest, with the participant in a recumbent position. Height, waist, and hip were measured to the nearest cm, and weight to the nearest 0.1 kg, without shoes and trousers. Body fat and lean body mass were measured using bioelectrical impedance analysis [137]. Blood samples of 45 ml were drawn from all participants and stored in a biological bank [136].

A random sub-sample of half of the participants in the Malmö Diet and Cancer Study (*n* 12 445), entering the study between November 1991 and February 1994, were invited to also participate in the Malmö Diet and Cancer – Cardiovascular Cohort [138]. The purpose was to study the epidemiology of carotid artery disease. Participants who accepted the invitation (*n* 5540) were invited to provide additional blood samples, on average 8 months after the initial baseline examination. These samples, in fasting individuals, included blood glucose, insulin and HbA1c. The Homoeostatic Model Assessment of Insulin Resistance (HOMA-IR) could then be calculated using the formula: fasting insulin (mU/l) × fasting glucose (mmol/l)/22.5.

Ascertainment of Type 2 Diabetes Cases

The first event of type 2 diabetes during follow-up was identified through one of twelve sources (Table 1). Eight of the sources were local and national registers, and four of the sources were through rescreening of participants participating in different cohorts. While cases were often registered in more than one source, person-time was only contributed until the first documented date of diagnosis.

Diabetes could be classified as either type 1 diabetes, type 2 diabetes, latent autoimmune diabetes in adults (LADA), gestational diabetes, secondary diabetes, other diabetes, or unknown diabetes. During follow-up until 31 December 2016 in our study population there was a total of 162 participants of type 1 diabetes, 13 cases of LADA, no case of gestational diabetes, 2 cases of secondary diabetes and 10 cases of other diabetes. Since the focus of this thesis was on type 2 diabetes specifically, only participants registered with type 2 diabetes or of unknown type were categorized as type 2 diabetes cases. Participants with diabetes of unknown type were assumed to be of type 2 due to the high likelihood.

The Diabetes 2000 Registry, currently known as the Scania Diabetes Registry, is a local register for the region of Scania and has been active since 1996 [139]. In the register, diabetes was diagnosed in the clinic, in accordance with established diabetes criteria. Patients were then asked to participate in the register. Type 2 diabetes cases required a diagnosis by a physician in accordance with the established diagnostic criteria, with either a fasting plasma glucose concentration of $\geq$ 7.0 mmol/L, or a fasting whole blood concentration of $\geq$ 6.1 mmol/L, on two different occasions.

The same diagnosis criteria was used in the Swedish National Diabetes Register [140]. This register was also introduced in 1996 and is currently deemed to be the largest diabetes register in the world and holds 85 % of all adult diabetes cases in Sweden. Registration of new entries occurs either through a form on the website or through direct transfer from the electronic medical records.

A large number of cases in this thesis were identified through the HbA1c register at Clinical Chemistry, Skåne University Hospital, Malmö [141]. In the register, diabetes cases were identified as having at least two HbA1c values $\geq$ 6.0 % (on different days) and were all deemed to be of unknown type.

Four of the registers were controlled by the National Board of Health and Welfare in Sweden [142]. These included the National Cause of Death Register, the National Patient Register (the National Hospital-based Outpatient Care Register and the National Inpatient Register) (ICD-10 codes E10 and E14), and the National Prescribed Drug Register (ATC code A10) [143-145].

Lastly, diabetes cases were also identified through the re-examination of participants in the Malmö Diet and Cancer Study (1992–1994, 1997–2001, and 2007–2012) and in the Malmö Preventive Project (2002–2006) [146]. The Malmö Preventive Project was a primary prevention initiative that ran between 1974 and 1991, with 18 000 participants attending a re-examination in the early 2000's.

Table 1. Sources of type 2 diabetes outcome
Individuals who developed type 2 diabetes, or unknown diabetes, during follow-up (until 31 December 2016) in the Malmö Diet and Cancer cohort (*n* 26 622). Source of first event.

SOURCE	TYPE 2 DIABETES	UNKNOWN
Diabetes 2000	162	29
Swedish National Diabetes Register	838	71
HbA1c register, Clinical Chemistry, SUS, Malmö	0	1276
National Inpatient Registry	233	53
Hospital-based Outpatient Care	149	26
Cause-of-Death Register	8	6
Swedish Prescribed Drug Register	402	66
ANDIS (Alla Nya Diabetiker I Skåne) Registry	110	2
MPP rescreening	19	288
MDC baseline screening cardiovascular cohort	0	113
MDC 5-year rescreening	18	59
MDC cardiovascular rescreening	1	117
Total	1940	2106

Other Variables

Level of physical activity was assessed in the baseline questionnaire and was recorded as time spent on 17 different leisure-time activities per week in each season (spring, summer, autumn, winter) [147]. There was also the option of adding an activity. The intensity level for each activity was determined by the metabolic equivalent intensity factor. Eleven of the activities were regarded as moderate intensity activities (walking, table tennis, recreational gymnastics, golf, badminton, cycling, folk dancing, ballroom dancing, gardening, digging, and manual lawn mowing), and six of the activities were regarded as vigorous intensity activities (jogging, swimming, tennis, football, orienteering, and walking the stairs). Time spent on each activity was multiplied by the metabolic equivalent intensity factor for each activity to obtain the metabolic equivalent of task hours (MET-hours) per week. The sum of all MET-hours per week for all activities constituted each individual's level of leisure-time physical activity.

Level of alcohol consumption was assessed in the seven-day food diary. The consumption was divided into non-consumers and sex-specific quintiles of intake and combined into one variable. Non-consumption for the past year was confirmed by questions on alcohol consumption in the baseline questionnaire.

Smoking habits were assessed in the baseline questionnaire under questions on tobacco consumption. The variable on smoking was categorized into current smokers, former smokers, and never smokers. The questionnaire did not ask to specify what tobacco product was used, but in the early 1990's the great majority would have used cigarettes.

Level of education was assessed in the baseline questionnaire by one single question asking for the highest level of education achieved. The six different options were used as categories in the variable on education.

Eating habits were likely to differ due to foods varying in their availability and affordability during specific seasons of the year. The variable season was determined by the screening date for each participant and was divided into four categories: winter (December-February), spring (March-May), summer (June-August), and fall (September-November).

Due to the minor changes in coding routines of dietary data that was introduced in September 1994, a new variable was introduced to be able to adjust for this. The variable thus has two categories, old and new, corresponding to whether data collection was conducted before or after the change in routines.

To be able to adjust for the possibility that some participants may have under- or overreported their energy intake, a variable was created to identify these participants. Potential misreporters of energy intake were identified as having a ratio of reported energy intake to basal metabolic rate outside the 95% confidence interval of their reported level of physical activity [129, 148]. Participants were categorized as under, adequate, or over.

In the baseline questionnaire, participants were asked if they had made significant changes to their diet, due to illness or other reason, to which they could respond yes or no [149]. Just as for the variable on potential misreporting, the variable allowed for performing sensitivity analyses in the Malmö Diet and Cancer population.

Statistical Analysis

For the baseline characteristics in all studies, continuous variables were presented in means, with 95 % confidence interval or standard deviation. In study I, II, and V, some adjustment for known confounders were made in the general linear model. In study IV, some values of the continuous variables were presented as medians with interquartile range due to skewed distribution. The categorical variables in all studies were presented in percentages.

For the main analysis, participants in study I were divided into quintiles for six types of carbohydrates and 13 carbohydrate-rich foods based on their level of intake. In study II, K-means clustering was applied to divide participants into five different clusters based on the consumption of 21 carbohydrate-rich foods. In study III, participants were dichotomized into adherence or non-adherence to four different carbohydrate quality indices. In study IV, participants were divided into five groups by applying a newly developed index to score the participants based on their level

of adherence to the EAT-Lancet diet. In study V, participants were divided into cutoffs for 12 fruit and vegetable variables based on their daily intake.

In all studies, the Cox proportional hazards model was used to analyse the associations between the exposure and incident type 2 diabetes. In study I, II, IV and V, four different multivariate models were used, with an increasing number of covariates added in each model. In study III, three multivariate models were used.

All studies adjusted for age, sex, dietary method, season, and total energy intake in the first model, with further adjustment for leisure-time physical activity, smoking habits, alcohol consumption and level of education in the second model. In study I, II, III, and V, body mass index (BMI) was added to the third model. In study I, II, and V, further adjustment for different dietary variables was added in the fourth model. In study IV, adjustment for family history of diabetes, lipid-lowering medication, hypertension at baseline, history of cardiovascular disease and cancer was added in the third model, with further adjustment for BMI in the fourth model.

All studies included sensitivity analyses to assess the robustness of the main findings by excluding individuals who are likely to have under- or overreported their energy intake and individuals who reported having made substantial changes to their diets, due to illness or other reasons. Additional sensitivity analyses were performed by using sex-specific quintiles (study I), by using energy-adjusted food variables (study I), by using interaction terms to analyse effect modifications by sex (all studies) and BMI (study III), by excluding participants who developed diabetes within two years (study II and IV) or four years of follow-up (study IV), or non-type 2 diabetes at any time during follow-up (study IV), by excluding participants with cardiovascular disease or cancer prevalent at baseline (study IV), and by censoring participants at 5, 10, 15, 20, and 25 years of follow-up (study IV).

Cubic splines were constructed in study IV and study V to study dose-response and nonlinear associations, adjusting for the same variables as in the fully-adjusted model for each study. In study IV, the population attributable risk was calculated to estimate how many cases of type 2 diabetes that would be prevented if all participants adopted the highest adherence to the EAT-Lancet diet. In study I and V, correlation matrices were added to explore correlations between the studied variables using Spearman correlation. In study IV, additional analyses were carried out to study associations between the EAT-Lancet diet and type 2 diabetes risk across three levels of polygenic risk score (low, intermediate, high).

In study I, II, III, and V, the main statistical analyses were performed using IBM SPSS Statistics (version 24.0, 26.0, 27.0 and 29.0; IBM Corp., Armonk, New York, USA). In study V, cubic splines were developed using R Statistical Software (version 4.3.2; R Core Team 2023) with the CRAN rms-package [150]. In study IV, statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R Statistical Software (version 4.1.3; R Core Team 2023).

Results

Study I

During 18 years of follow-up, a larger proportion of men (18.8 %) than women (12.9 %) developed type 2 diabetes. Participants who developed type 2 diabetes had a higher BMI, waist circumference, and percentage of body fat at baseline. They were also more likely to report a low level of leisure-time physical activity and non-consumption of alcohol (Table 2).

Table 2. Baseline characteristics of cases and non-cases of type 2 diabetes during follow-up
Participants in the Malmö Diet and Cancer cohort (*n* 26 622).

Baseline variable	Men (*n* 10 315)		Women (*n* 16 307)	
	T2D cases	Non-cases	T2D cases	Non-cases
n	1936	8379	2110	14 197
% within sex	18.8	81.2	12.9	87.1
BMI (kg/m^2)	28.0 (27.8, 28.1)	25.7 (25.7, 25.8)	27.9 (27.7, 28.0)	24.9 (24.9, 25.0)
Waist circumf (cm)	98.4 (97.9, 98.8)	92.2 (92.0, 92.4)	84.7 (84.3, 85.1)	76.4 (76.3, 76.6)
Body fat (%)	22.4 (22.2, 22.6)	20.2 (20.1, 20.3)	33.3 (33.1, 33.5)	30.3 (30.2, 30.3)
LTPA, <7.5 (%)	13.1	9.3	12.7	8.7
Alcohol, zero (%)	4.7	4.3	9.5	6.8

The main findings of study I were that higher intakes of monosaccharides (hazard ratio (HR) of highest vs. lowest quintile 0.88; 95 % CI 0.79, 0.98; P_{trend} = 0.02) and fruit (P_{trend} = 0.03) were associated with a lower type 2 diabetes incidence, while higher intakes of disaccharides (HR 1.17; 95 % CI 1.04, 1.30; P_{trend} = 0.002) and sweets (P_{trend} = 0.02) were associated with a higher incidence (Table 3).

Higher intakes of vegetables (HR 0.85; 95 % CI 0.73, 0.98) and marmalade, honey, and jam (HR 0.82; 95 % CI 0.72, 0.94; P_{trend} < 0.001) were associated with a lower type 2 diabetes incidence in men only, while a higher intake of chocolate (HR 1.26; 95 % CI 1.09, 1.46; P_{trend} < 0.001) was associated with a higher incidence in women only.

For all other carbohydrates and carbohydrate-rich foods, associations with type 2 diabetes incidence were non-significant in the fully adjusted model.

Table 3. Associations between carbohydrates and carbohydrates-foods and type 2 diabetes incidence
Hazard ratios (95% CI) of incident type 2 diabetes by quintiles of nutrients and foods in participants in the Malmö Diet and Cancer cohort (*n* 26 622).

Variable	*n* total/*n* cases/ person-years	Basic model[a]	Extended model excl. BMI[b]	Extended model incl. BMI[c]	Extended model incl. diet & BMI[d]
Monosaccharides (E%)					
Q1 (0.4-5.0)	5324/938/93 041	1.00	1.00	1.00	1.00
Q2 (5.0-6.4)	5325/849/97 290	0.90 (0.82, 0.99)	0.96 (0.87, 1.05)	0.95 (0.87, 1.05)	0.96 (0.88, 1.06)
Q3 (6.4-7.8)	5324/801/98 700	0.84 (0.77, 0.93)	0.93 (0.84, 1.02)	0.92 (0.83, 1.01)	0.94 (0.85, 1.03)
Q4 (7.8-9.6)	5325/763/99 222	0.83 (0.75, 0.91)	0.93 (0.84, 1.03)	0.91 (0.82, 1.01)	0.93 (0.84, 1.03)
Q5 (9.6-39.8)	5324/695/100 933	0.75 (0.68, 0.83)	0.85 (0.77, 0.95)	0.86 (0.77, 0.95)	0.88 (0.79, 0.98)
P_{trend}		<0.001	0.004	0.004	0.02
$P_{interaction}$[e]		0.09	0.14	0.08	0.16
Disaccharides (E%)					
Q1 (1.1-9.7)	5324/811/98 133	1.00	1.00	1.00	1.00
Q2 (9.7-11.7)	5325/781/100 131	0.99 (0.90, 1.09)	0.99 (0.90, 1.09)	0.99 (0.90, 1.09)	1.00 (0.91, 1.11)
Q3 (11.7-13.6)	5324/799/98 650	1.07 (0.97, 1.18)	1.06 (0.96, 1.17)	1.08 (0.98, 1.19)	1.10 (0.99, 1.22)
Q4 (13.6-16.0)	5325/817/97 784	1.11 (1.00, 1.22)	1.07 (0.96, 1.18)	1.07 (0.96, 1.18)	1.10 (0.99, 1.22)
Q5 (16.0-41.1)	5324/838/94 486	1.18 (1.07, 1.30)	1.07 (0.97, 1.19)	1.10 (1.00, 1.22)	1.17 (1.04, 1.30)
P_{trend}		<0.001	0.06	0.02	0.002
$P_{interaction}$[e]		0.02	0.01	0.11	0.19
Fruits (g/d)					
Q1 (0.0-92.1)	5324/899/94 184	1.00	1.00	1.00	1.00
Q2 (92.1-144.0)	5325/820/96 545	0.93 (0.84, 1.02)	0.98 (0.89, 1.08)	0.94 (0.86, 1.04)	0.96 (0.87, 1.05)
Q3 (144.1-203.6)	5324/791/97 681	0.91 (0.82, 1.00)	0.98 (0.88, 1.08)	0.93 (0.84, 1.02)	0.94 (0.85, 1.04)
Q4 (203.6-285.0)	5325/754/100 185	0.87 (0.79, 0.96)	0.96 (0.86, 1.06)	0.87 (0.79, 0.97)	0.89 (0.80, 0.98)
Q5 (285.0-2782.2)	5324/782/100 590	0.90 (0.82, 1.00)	1.00 (0.91, 1.11)	0.89 (0.80, 0.98)	0.91 (0.82, 1.01)
P_{trend}		0.02	0.88	0.01	0.03

$P_{interaction}$[e]		0.83	0.84	0.90	0.91
Sweets (g/d)[f]					
non-consumers	8803/1384/157 673	1.00	1.00	1.00	1.00
T1 (0.1-2.6)	5779/768/108 542	0.85 (0.78, 0.93)	0.87 (0.79, 0.95)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)
T2 (2.7-8.0)	6148/942/114 355	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)	1.00 (0.92, 1.09)	1.01 (0.93, 1.10)
T3 (8.0-349.0)	5892/952/108 615	1.14 (1.05, 1.24)	1.10 (1.01, 1.20)	1.08 (0.99, 1.18)	1.09 (1.00, 1.19)
P_{trend}		0.001	0.009	0.03	0.02
$P_{interaction}$[e]		0.70	0.71	0.53	0.48

[a]adjusted for sex, age, diet-method version, season, and total energy intake.

[b]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, and education.

[c]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, and BMI.

[d]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, coffee, meat, whole grains, sugar-sweetened beverages, and BMI.

[e]*P* for interaction with sex.

[f]divided into non-consumers and tertiles of consumers, with non-consumers as reference.

Study II

Five clusters were deemed the optimal K number of clusters in the K-means cluster analysis, as this created clearly distinct clusters while also maintaining a good distribution of participants between clusters.

Four of the five clusters were clearly defined by the intake of only one or a few specific foods, while the fifth and largest cluster encompassed roughly half of all participants and was mainly defined by having a low intake of fruits and vegetables and a high intake of pastries and low-fibre bread (Table 4). This cluster was labelled *high refined carbohydrates/low fruit & vegetables* and was used as the reference.

A total of 4046 participants developed type 2 diabetes during a mean follow-up of 18 years. In the main analysis of study II, the *high fruit* cluster (HR 0.86; 95 % CI 0.78, 0.94) was associated with a lower type 2 diabetes incidence compared to the reference cluster (Table 5). No significant associations were identified for the *high vegetables/low added sugar*, *high sugar-sweetened beverages*, or *high juice* clusters. The *high fruit* cluster had the highest mean age and the lowest proportion of participants who reported being current smokers and having a low level of physical activity, compared to all other clusters.

Table 4. Cluster characteristics in clusters of carbohydrate-rich foods
Baseline characteristics in participants in the Malmö Diet and Cancer cohort (*n* 26 622). Mean (95% CI).

Cluster variable	High refined carbs/ Low fruit & veg	High vegetables/ Low added sugar	High sugar-sweetened beverages	High juice	High fruit
Potato, boiled or baked	48.2 (47.8, 48.7)	41.7 (40.5, 42.8)	44.1 (43.0, 45.3)	43.4 (42.6, 44.3)	44.4 (43.6, 45.2)
Potato, deep-fried + fried	8.41 (8.22, 8.60)	5.52 (5.04, 6.00)	8.07 (7.60, 8.53)	7.24 (6.89, 7.60)	6.58 (6.27, 6.89)
Fruits	61.0 (60.3, 61.8)	142.8 (140.9, 144.6)	77.8 (76.0, 79.6)	88.4 (87.1, 89.8)	170.8 (169.6, 172.0)
Vegetables	68.4 (67.8, 69.0)	192.7 (191.2, 194.2)	71.8 (70.3, 73.3)	81.5 (80.4, 82.7)	87.2 (86.2, 88.2)
Juice	11.2 (10.7, 11.8)	22.2 (20.8, 23.5)	23.0 (21.6, 24.4)	113.8 (112.8, 114.9)	17.7 (16.8, 18.6)
Sugar-sweetened beverag	20.2 (19.5, 20.9)	14.8 (13.1, 16.6)	196.9 (195.2, 198.7)	21.9 (20.6, 23.2)	20.4 (19.2, 21.5)
Pastries	17.8 (17.6, 18.0)	13.5 (13.0, 14.0)	16.3 (15.8, 16.8)	16.2 (15.8, 16.6)	16.3 (16.0, 16.7)
Chocolate	3.80 (3.72, 3.88)	2.64 (2.44, 2.83)	3.23 (3.04, 3.43)	3.19 (3.04, 3.34)	3.14 (3.01, 3.26)
Sweets	3.01 (2.92, 3.10)	1.88 (1.66, 2.11)	3.27 (3.05, 3.49)	2.49 (2.32, 2.65)	2.45 (2.30, 2.59)
Table sugar	4.48 (4.39, 4.58)	2.54 (2.30, 2.78)	4.56 (4.32, 4.80)	3.69 (3.51, 3.87)	3.21 (3.06, 3.37)
Ice cream	4.96 (4.83, 5.09)	5.94 (5.60, 6.28)	5.76 (5.43, 6.09)	5.45 (5.20, 5.71)	6.16 (5.94, 6.38)
Marmalade/honey/jam	7.59 (7.46, 7.72)	6.13 (5.81, 6.45)	7.29 (7.00, 7.61)	7.46 (7.22, 7.70)	7.35 (7.15, 7.56)
Ketchup	0.87 (0.84, 0.89)	0.79 (0.73, 0.85)	0.84 (0.78, 0.90)	0.83 (0.79, 0.88)	0.75 (0.71, 0.79)
Flour	3.41 (3.35, 3.46)	3.58 (3.44, 3.71)	3.16 (3.03, 3.30)	3.55 (3.45, 3.65)	3.63 (3.54, 3.72)
Grains/cereals, <10% fiber	4.50 (4.39, 4.61)	5.77 (5.50, 6.04)	3.89 (3.62, 4.16)	5.00 (4.79, 5.21)	5.40 (5.22, 5.58)
Grains/cereals, ≥10% fiber	0.05 (0.04, 0.06)	0.08 (0.05, 0.11)	0.06 (0.03, 0.08)	0.04 (0.02, 0.06)	0.06 (0.04, 0.08)
Soft bread, <4.5% fiber	30.5 (30.2, 30.9)	19.3 (18.4, 20.2)	28.1 (27.2, 29.0)	23.7 (23.0, 24.4)	22.3 (21.7, 22.9)
Soft bread, ≥4.5% fiber	16.3 (16.0, 16.6)	18.8 (18.0, 19.6)	13.4 (12.6, 14.2)	16.8 (16.2, 17.5)	17.9 (17.3, 18.4)
Crisp bread, <10% fiber	2.32 (2.26, 2.38)	2.30 (2.15, 2.45)	2.45 (2.30, 2.60)	2.21 (2.10, 2.33)	2.31 (2.21, 2.41)
Crisp bread, ≥10% fiber	4.98 (4.87, 5.09)	7.25 (6.97, 7.52)	4.55 (4.28, 4.82)	5.54 (5.33, 5.75)	6.32 (6.14, 6.50)
Rice/pasta	5.09 (4.99, 5.19)	6.93 (6.68, 7.19)	4.96 (4.71, 5.21)	5.38 (5.19, 5.57)	5.55 (5.38, 5.72)

Table 5. Associations between clusters of carbohydrate-rich foods and type 2 diabetes incidence

Hazard ratios (95% CI) of incident type 2 diabetes by clusters of carbohydrate-rich foods in participants in the Malmö Diet and Cancer cohort (*n* 26 622).

Cluster membership	*n* total/*n* cases/person-years	Model 1[1]	Model 2[2]	Model 3[3]	Model 4[4]
High ref carb/Low fruit & veg	13,622/2193/246,436	1.00	1.00	1.00	1.00
High veg/Low added sugar	2168/334/42,289	1.02 (0.90, 1.15)	1.12 (0.99, 1.26)	0.98 (0.87, 1.11)	0.99 (0.88, 1.12)
High sugar-sweetened bever	2119/355/36,715	1.13 (1.01, 1.27)*	1.08 (0.96, 1.21)	0.98 (0.87, 1.09)	0.97 (0.86, 1.08)
High juice	3682/498/68,606	0.91 (0.83, 1.01)	0.96 (0.87, 1.06)	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)
High fruit	5031/666/95,138	0.87 (0.80, 0.96)*	0.93 (0.84, 1.01)	0.85 (0.78, 0.93)*	0.86 (0.78, 0.94)*

[1]adjusted for age, sex, diet-method version, season, and total energy intake.

[2]adjusted for age, sex, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, and education.

[3]adjusted for age, sex, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, and BMI.

[4]adjusted for age, sex, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, coffee, red meat, and BMI.

*$P<0.05$

Study III

In 26 622 participants (61.3 % women), the mean intake was 244 g (45.2 percent of energy (E%)) for carbohydrates, 20.1 g for fibre, and 61.9 g (11.0 E%) for free sugar, respectively (Table 6). Fibre intake was significantly higher among participants adhering to any of the four carbohydrate quality indices.

The index with the highest adherence was the *10:1 carbohydrates:fibre* index (19.9 % of the population), followed by the *10:1 & 1:2 carbohydrates:fibre & fibre:free sugar* index (14.6 %), the *10:1:2 carbohydrates:fibre:free sugar* index (12.1 %), and the *10:1:1 carbohydrates:fibre:free sugar* index (1.9 %).

The main analysis, after full adjustment for potential confounders, was carried out both for all participants and after exclusion of potential misreporters of energy intake and diet changers (excluding n = 9530 (36 %) of participants).

The main findings of study III were inverse associations for both the 10:1 & 1:2 (HR 0.84; 95 % CI 0.72, 0.97) and the 10:1:2 (HR 0.82; 95 % CI 0.70, 0.97) indices with lower incidence of type 2 diabetes, after full adjustment and exclusion of potential misreporters and diet changers (Table 7).

Table 6. Baseline characteristics within each carbohydrate quality index group

Baseline characteristics for participants in the Malmö Diet and Cancer cohort (*n* 26 622). Mean (SD) (except for Females, *n* (%)).

Baseline variable	10:1 CHO:FI[1]		10:1:1 CHO:FI:FS[2]		10:1:2 CHO:FI:FS[3]		10:1&1:2 CHO:FS&FS:FI[4]	
	No (*n* 21 328)	Yes (*n* 5294)	No (*n* 26 118)	Yes (*n* 504)	No (*n* 23 399)	Yes (*n* 3223)	No (*n* 22 732)	Yes (*n* 3890)
Females (%)	12 238 (57.4)	4069 (76.7)	15 912 (60.9)	395 (78.4)	13 853 (59.2)	2454 (76.1)	2974 (58.7)	2974 (76.5)
Total energy (kcal/day)	2345 (658)	2015 (559)	2290 (651)	1742 (527)	2324 (653)	1955 (555)	2333 (654)	1967 (551)
Carbohydrate intake (E%)	45.1 (5.9)	45.9 (6.5)	45.2 (6.0)	45.0 (7.4)	45.2 (6.0)	45.3 (6.6)	45.2 (6.0)	45.5 (6.6)
Fiber intake (g/1000kcal)	8.4 (1.9)	13.0 (2.6)	9.2 (2.7)	13.9 (3.5)	8.8 (2.3)	13.1 (2.8)	8.7 (2.1)	13.2 (2.8)
Free sugar intake (E%)	11.7 (4.5)	8.3 (3.4)	11.2 (4.4)	3.2 (1.1)	11.7 (4.3)	6.3 (2.0)	11.7 (4.4)	6.9 (2.4)

[1]A total of ≥1g fibre per 10 g of carbohydrates.
[2]A total of ≥1 g fibre and <1 g free sugars per 10 g of carbohydrates.
[3]A total of ≥1 g fibre and <2 g free sugars per 10 g of carbohydrates.
[4]A total of ≥1 g fibre per 10 g of carbohydrates, and with each 1 g of fibre <2 g free sugars.

Table 7. Associations between four carbohydrate quality indices and risk of type 2 diabetes

Hazard ratios (95% CI) of incident type 2 diabetes by clusters of carbohydrate-rich foods in participants in the Malmö Diet and Cancer cohort (*n* 26 622).

	10:1 CHO:FI		10:1:1 CHO:FI:FS		10:1:2 CHO:FI:FS		10:1&1:2 CHO:FS&FS:FI	
	No	Yes	No	Yes	No	Yes	No	Yes
N/cases	21 328/3290	5294/756	26 118/3956	504/90	23 399/3587	3223/459	22 732/3501	3890/545
Basic model[1]	1.00	0.94 (0.86–1.02)	1.00	1.26 (1.02–1.56)	1.00	0.94 (0.85–1.03)	1.00	0.91 (0.83–1.00)
Multivariable model[2]	1.00	1.00 (0.92–1.08)	1.00	1.27 (1.03–1.56)	1.00	0.99 (0.89–1.09)	1.00	0.96 (0.88–1.06)
Multivariable model + BMI[3]	1.00	0.99 (0.91–1.08)	1.00	1.08 (0.87–1.34)	1.00	0.95 (0.86–1.05)	1.00	0.93 (0.85–1.02)
Excl diet changers + misreport								
N/cases	14 512/2055	2580/297	16 918/2332	174/20	15 610/2191	1482/161	15 312/2154	1780/189
Multivariable model + BMI[3]	1.00	0.89 (0.79–1.01)	1.00	0.79 (0.51–1.23)	1.00	0.82 (0.70–0.97)	1.00	0.84 (0.72–0.97)

[1]Adjusted for age, sex, dietary method, season, and energy intake.
[2]Adjusted for age, sex, dietary method, season, energy intake, alcohol consumption, smoking habits, leisure-time physical activity, and education.
[3]Adjusted for age, sex, dietary method, season, energy intake, alcohol consumption, smoking habits, leisure-time physical activity, education, and BMI.

Study IV

In 24 494 participants (61.5 % women), 4197 individuals (17.1 %) developed type 2 diabetes during a median follow-up of 24 years. Participants with a higher score on the EAT-Lancet index were more likely to be women, to have a university degree, to report a high level of leisure-time physical activity, and to be non-smokers. They also reported a lower total energy intake (Table 8).

Table 8. Baseline characteristics according to categories of the EAT-Lancet diet index
Participants in the Malmö Diet and Cancer cohort (*n* 24 494).

	Categories of the EAT-Lancet diet index				
	≤13	14-16	17-19	20-22	≥23
N participants	2379	5846	8727	5566	1976
Sex, men (%)	60.6	47.2	37.0	28.0	21.5
University degree (%)	9.8	12.8	14.5	16.6	20.1
LTPA, high (%)	42.6	49.2	53.4	57.9	62.4
Smoking, never (%)	23.3	33.3	39.8	43.6	43.4
Total energy (kcal/d)	2572	2328	2160	2029	1934

The main finding in study IV was a significant association between a higher adherence to the EAT-Lancet diet and a lower type 2 diabetes incidence in the fully adjusted model (HR highest vs. lowest EAT-Lancet index score 0.82; 95 % CI 0.70, 0.96; $P_{trend} < 0.01$) (Table 9). The association was linear with a clear dose-response analysis shows that the EAT- Lancet diet index had a linear association with type 2 diabetes risk ($P_{overall\ association} = 0.01$ and $P_{non\text{-}linear} = 0.70$). The population attributable risk of type 2 diabetes incidence for low adherence to the EAT-Lancet diet index (<23 points) was 12.9 % (95 % CI 1.83 %, 22.1 %).

Participants with a high type 2 diabetes polygenic risk score had a higher risk of type 2 diabetes when compared to participants with a low score (HR 2.39; 95 % CI 2.15, 2.66). No significant associations between the EAT-Lancet index score and type 2 diabetes incidence could be identified in a subgroup analysis of participants with a low or high type 2 diabetes polygenic genetic risk score (Figure 1). However, there was a significant inverse association in participants with a medium risk score (HR 0.95; 95 % CI 0.91, 0.99). Participants with a high genetic risk and a low adherence to the EAT-Lancet diet had a significantly higher risk of type 2 diabetes compared to participants with a low genetic risk and a high adherence to the EAT-Lancet diet (HR 1.79; 95 % CI 1.63, 1.96) (Figure 2).

Table 9. Associations between EAT-Lancet diet index and risk of type 2 diabetes

Hazard ratios (95% CI) of incident type 2 diabetes by EAT-Lancet diet index category in participants in the Malmö Diet and Cancer cohort (*n* 24 494).

	EAT-Lancet diet index categories					*P* for trend
	≤13	14-16	17-19	20-22	≥23	
N participants	2379	5846	8727	5566	1976	-
N cases	447	1107	1448	919	276	-
Person-years	45 483	114 875	177 674	115 826	42 990	-
Incidence per 1000 person-years	9.83	9.64	8.15	7.93	6.42	-
Model 1	1.00 (ref)	1.01 (0.90, 1.13)	0.86 (0.77, 0.96)	0.86 (0.76, 0.96)	0.70 (0.60, 0.82)	<0.0001
Model 2	1.00 (ref)	1.09 (0.98, 1.22)	0.98 (0.88, 1.10)	1.00 (0.89, 1.13)	0.84 (0.72, 0.99)	0.01
Model 3	1.00 (ref)	1.07 (0.96, 1.20)	0.96 (0.86, 1.07)	0.97 (0.86, 1.10)	0.84 (0.72, 0.98)	<0.01
Model 4	1.00 (ref)	1.04 (0.93, 1.16)	0.90 (0.81, 1.01)	0.94 (0.83, 1.06)	0.82 (0.70, 0.96)	<0.01

Model 1: adjusted for age, sex, dietary assessment version (method), season, and total energy intake.
Model 2: adjusted for variables in model 1 plus leisure-time physical activity, alcohol consumption, smoking status, and educational level.
Model 3: adjusted for variables in model 2 plus family history of diabetes, lipid-lowering medication, hypertension at baseline, history of cardiovascular disease and cancer.
Model 4: adjusted for variables in model 3 plus body mass index.

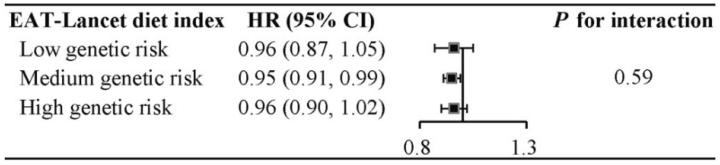

Figure 1. Association between the EAT-Lancet diet index and risk of type 2 diabetes according to the polygenic risk score.

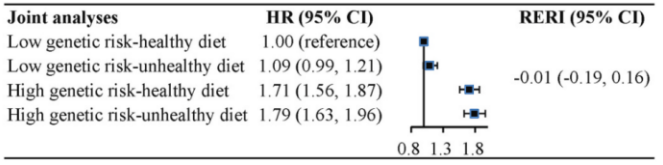

Figure 2. Joint association of the EAT-Lancet diet index and genetic susceptibility with risk of type 2 diabetes.

Study V

During 18 years of follow-up, 3723 out of 24 631 participants (15.1 %) developed type 2 diabetes. Participants who developed type 2 diabetes were more likely to be male and to have a higher BMI, waist circumference, and percentage of body fat. They also had a higher HbA1c, plasma glucose, and HOMA-IR (Table 10).

Table 10. Baseline characteristics of cases and non-cases of type 2 diabetes during follow-up
Participants in the Malmö Diet and Cancer cohort (*n* 24 631)[1].

Baseline variable	Type 2 diabetes cases	Non-cases
n	3723	20 908
% female	52.4	63.2
BMI (kg/m^2)	27.9 (27.8, 28.0)	25.2 (25.2, 25.3)
Waist circumference (cm)	91.2 (90.8, 91.5)	82.1 (82.0, 82.2)
Body fat (%)	28.2 (28.0, 28.3)	26.6 (26.5, 26.6)
HbA1c (%)	5.11 (5.07, 5.15)	4.76 (4.75, 4.78)
High p-glucose, >5.6 mmol/L (%)	80.2	37.7
HOMA-IR	2.24 (2.13, 2.35)	1.50 (1.46, 1.54)

[1]*n* 24 597 for BMI, *n* 24 586 for waist circumference, *n* 24 490 for body fat, *n* 4 663 for HbA1c, n 4 672 for high plasma glucose, and *n* 4 301 for HOMA-IR

The main findings of study V were that higher intakes of green leafy vegetables (HR highest vs. lowest cutoffs 0.84; 95 % CI 0.78, 0.98) and dried fruits (HR 0.82; 95 % CI 0.69, 0.98; P_{trend} = 0.02) were significantly associated with a lower incidence of type 2 diabetes in the fully adjusted model. Conversely, the highest intakes of cruciferous vegetables (HR 1.14; 95 % CI 1.01, 1.28) and berries (HR 1.16; 95 % CI 1.01, 1.34; P_{trend} = 0.03) were both positively associated (Table 11). For berries, after stratification by sex, there was a positive association with type 2 diabetes in women only (HR 1.26; 1.05, 1.51; P_{trend} = 0.01). For root vegetables, there was a significant trend of an inverse association for a higher intake of root vegetables in men only (P_{trend} = 0.03).

For all fruits and vegetables, and for total fruits only, there was a tendency of a lower type 2 diabetes incidence with higher intakes. The findings indicated an optimal daily intake of fruits and vegetables of around 300-500 grams daily, with optimal intake of fruits of about 200-300 grams daily.

Table 11. Associations between sub-types of fruits and vegetables and type 2 diabetes incidence
Hazard ratios (95% CI) of incident type 2 diabetes by cut-offs of fruits and vegetables in participants in the Malmö Diet and Cancer cohort (*n* 24 631).

Variable	*n* total/*n* cases/ person-years	Basic model[a]	Extended model excl. BMI[b]	Extended model incl. BMI[c]	Extended model incl. diet & BMI[d]
Cruciferous vegetables (g/d)					
0.00-9.99	14712/2206/266 149	1.00	1.00	1.00	1.00
10.00-19.99	3300/470/61 223	0.94 (0.85, 1.04)	0.96 (0.87, 1.06)	0.97 (0.88, 1.07)	0.97 (0.88, 1.08)
20.00-34.99	3258/500/59 483	1.03 (0.94, 1.14)	1.06 (0.96, 1.16)	1.02 (0.92, 1.12)	1.02 (0.93, 1.13)
35.00-49.99	1678/246/30 800	0.97 (0.85, 1.11)	0.99 (0.87, 1.14)	0.96 (0.84, 1.10)	0.97 (0.85, 1.10)
50.00-	1683/301/30 385	1.18 (1.05, 1.34)	1.21 (1.07, 1.37)	1.14 (1.01, 1.29)	1.14 (1.01, 1.28)
P_{trend}		0.07	0.02	0.18	0.19
$P_{interaction}$[e]		0.68	0.55	0.21	0.17
Green leafy vegetables (g/d)					
0.00-9.99	11504/1854/200 939	1.00	1.00	1.00	1.00
10.00-19.99	5027/739/93 749	0.90 (0.83, 0.98)	0.99 (0.90, 1.08)	1.00 (0.92, 1.09)	1.01 (0.92, 1.10)
20.00-34.99	4589/654/86 348	0.87 (0.80, 0.95)	0.97 (0.89, 1.07)	0.96 (0.88, 1.05)	0.97 (0.88, 1.06)
35.00-49.99	2006/281/37 938	0.86 (0.76, 0.97)	0.99 (0.87, 1.13)	0.99 (0.87, 1.12)	0.99 (0.87, 1.13)
50.00-	1505/195/29 065	0.77 (0.66, 0.89)	0.89 (0.77, 1.04)	0.84 (0.72, 0.97)	0.84 (0.72, 0.98)
P_{trend}		0.001	0.23	0.06	0.07
$P_{interaction}$[e]		0.64	0.74	0.78	0.82
Berries (g/d)					
0.00-4.99	22 369/3387/406 507	1.00	1.00	1.00	1.00
5.00-9.99	266/34/5101	0.81 (0.58, 1.14)	0.92 (0.65, 1.29)	0.94 (0.67, 1.32)	0.94 (0.67, 1.32)
10.00-14.99	470/63/8868	0.86 (0.67, 1.11)	0.91 (0.71, 1.17)	1.01 (0.79, 1.30)	1.02 (0.79, 1.31)
15.00-19.99	144/24/2614	1.09 (0.73, 1.63)	1.17 (0.78, 1.75)	1.19 (0.80, 1.79)	1.17 (0.78, 1.76)
20.00-	1382/215/24 949	1.05 (0.92, 1.21)	1.15 (1.00, 1.32)	1.15 (1.00, 1.33)	1.16 (1.01, 1.34)
P_{trend}		0.69	0.08	0.04	0.03

$P_{interaction}$[e]		0.13	0.15	0.03	0.05
Dried fruits (g/d)					
0.00-2.49	21465/3370/387 773	1.00	1.00	1.00	1.00
2.50-4.99	963/103/18 357	0.68 (0.56, 0.82)	0.74 (0.61, 0.90)	0.85 (0.69, 1.03)	0.86 (0.71, 1.05)
5.00-7.49	608/80/11 613	0.83 (0.66, 1.03)	0.89 (0.71, 1.11)	1.00 (0.80, 1.25)	1.01 (0.81, 1.26)
7.50-9.99	346/39/6607	0.70 (0.51, 0.97)	0.75 (0.54, 1.02)	0.87 (0.64, 1.20)	0.87 (0.64, 1.20)
10.00-	1249/131/23 689	0.65 (0.55, 0.78)	0.70 (0.58, 0.83)	0.81 (0.67, 0.96)	0.82 (0.69, 0.98)
P_{trend}		0.001	0.001	0.01	0.02
$P_{interaction}$[e]		0.21	0.18	0.44	0.44

BMI, body mass index.

[a]adjusted for sex, age, diet-method version, season, and total energy intake.

[b]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, and education.

[c]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, and BMI.

[d]adjusted for sex, age, diet-method version, season, total energy intake, physical activity, alcohol habits, smoking, education, coffee, red meat, whole grains, sugar-sweetened beverages, and BMI.

[e]*P* for interaction with sex.

Discussion

The main topic for the thesis was to explore the associations between carbohydrate quality and incidence type 2 diabetes in order to gain a deeper understanding of exposures that may increase or reduce the risk of developing type 2 diabetes. In study I-III we applied different approaches to explore how intake of carbohydrates and carbohydrate-rich foods may differ in their association with type 2 diabetes risk. In study IV we explored how a more environmentally sustainable dietary pattern, with an emphasis on plant-based foods, may be associated with type 2 diabetes risk. Finally, in study V, we expanded upon earlier findings by exploring in detail the associations between sub-types of fruits and vegetables with type 2 diabetes risk.

Carbohydrate Quality

Study I provided a foundation for the exploration of associations between carbohydrates and carbohydrate-rich foods and type 2 diabetes risk within the Malmö Diet and Cancer Study. The results provided additional evidence to support earlier findings of associations with type 2 diabetes risk.

The inverse association of a higher fruit intake with a reduced risk of type 2 diabetes in study I was further substantiated by the findings in study II and explored in more detail in study V. The association between a higher intake of monosaccharides and lower incidence of type 2 diabetes is likely explained by a higher intake of fruits (which are high in fructose), as there was a strong correlation between a higher monosaccharide intake and a higher fruit intake. Furthermore, other studies have found that the specific food source of fructose has been found to mediate the effect of fructose on glycaemic control [151, 152].

The increased risk of type 2 diabetes from a higher intake of disaccharides and sweets in study could possibly be explained by negative health effects related to a higher added sugar or sucrose intake [8]. This was further supported by our findings in study III, where we identified a possible reduced type 2 diabetes risk by limiting intake of free sugars relative to intake of total carbohydrates and dietary fibre. However, there is low certainty of a positive association between dietary sugar and type 2 diabetes risk in scientific literature [8, 37]. Moreover, we found no significant associations for neither sucrose intake nor for added sugar in study I, as well as for

refined grains, sugar-sweetened beverages, and table sugar. This suggests caution when interpreting the findings, as the associations with type 2 diabetes incidence might have been affected by strong correlations with intake of other foods. Specifically, we were surprised to find no association between a higher intake of sugar-sweetened beverages and type 2 diabetes risk, as this has been clearly observed in previous studies [47, 69-71]. However, one of the suggested mechanisms for the association between sugar-sweetened beverages and type 2 diabetes risk is due to over-consumption of energy and subsequent weight gain [72-75]. In our study, we identified a positive association with type 2 diabetes before adjusting for BMI, supporting the plausible mechanism of increased risk due to weight gain.

Despite plenty of evidence suggesting a protective effect, we could not identify any associations for intake of dietary fibre or whole grains with type 2 diabetes incidence in our main model in study I [38-40, 47, 67]. In study III, however, we identified a possible inverse association with type 2 diabetes risk for a high intake of dietary fibre relative to total carbohydrate and free sugar intake. It is likely that both absolute and relative intakes of dietary fibre and whole grains are worth considering when assessing carbohydrate quality in the diet [15, 38, 40, 67].

The EAT-Lancet Diet

In study IV we identified that a higher adherence to the EAT-Lancet diet was linearly associated with a lower risk of type 2 diabetes, independent of genetic susceptibility. Assuming a causal relationship, and that all participants had adhered to the EAT-Lancet diet (≥23 points), roughly 1 in 8 (12.9%) cases could have been prevented.

In the study, we explored the associations with type 2 diabetes risk for a dietary pattern proposed by the EAT-Lancet Commission in 2019, and previous studies have also shown an inverse association between the EAT-Lancet diet and type 2 diabetes risk [85, 153-155]. However, in our study we used a new EAT-Lancet diet index with a gradual scoring criterion, rather than a binary score, to better explore adherence to the reference diet [91].

The EAT-Lancet diet is considered a plant-based diet as it emphasizes the intake of plant-based foods while recommending limiting the intake of most animal-derived foods [85, 91]. Adherence to plant-based dietary patterns has previously shown associations with a lower type 2 diabetes risk [156, 157]. Similarly, dietary patterns associated with reduced type 2 diabetes risk generally promote dietary intake of fruits, vegetables, and legumes, and limiting the intake of red and processed meat, important features of a plant-based and sustainable diet. Generally, what is beneficial for human health is also beneficial for the health of our planet, providing

the opportunity for nutrition recommendations to combine both aspects, prominently demonstrated by the Nordic Nutrition Recommendations 2023 [158].

Our finding that genetic risk does not seem to affect dietary risk for type 2 diabetes has also been demonstrated previously in the Malmö Diet and Cancer cohort [126]. Multiple other studies have similarly shown that genetic risk and dietary risk are independently associated with type 2 diabetes risk [124, 125, 159, 160]. Hence, it could be seen as encouraging that a healthy diet could help reduce the risk of type 2 diabetes within all genetic risk groups. Some studies have, however, observed gene-diet interactions in association with type 2 diabetes risk [123, 161, 162]. As the fields of genetics and gene-lifestyle interactions are rapidly evolving, future studies will likely provide a deeper understanding of this complex relationship [163].

Fruits and Vegetables

In study I, we identified an inverse association between a higher intake of fruits and a lower risk of type 2 diabetes. This was further supported by our findings in study II. In study I we also identified a significant inverse association between a higher intake of vegetables and a lower incidence of type 2 diabetes in men specifically.

The beneficial properties of fruits and vegetables can be attributed to the low energy density and the high content of fibre, micronutrients, and phytochemicals [55, 57, 164-166]. A comprehensive systematic review discovered a non-linear inverse relationship between the risk of type 2 diabetes and polyphenols, a common type of phytochemical in fruits and berries, but they concluded that further research is required [55]. The correlation between the consumption of fruits and vegetables and a decreased risk of other noncommunicable diseases, as well as overall mortality, is already well-documented.

Our findings from study I prompted the need to analyse the intake of sub-types of fruits and vegetables to explore if there are differences in their association with type 2 diabetes risk. Thus, study V explored associations for sub-types of fruits and vegetables with type 2 diabetes risk. The study found that a higher intake of green leafy vegetables and dried fruits correlated with lower incidence, while higher intakes of cruciferous vegetables and berries (in women only) correlated with higher incidence. For root vegetables, an inverse association was found in men only.

Previous studies and meta-analyses have also identified inverse associations between intake of green leafy vegetables and type 2 diabetes risk [48, 53, 59]. The mechanism is unknown but might be due to their high content of magnesium and inorganic nitrate [60-64].

The intake of dried fruits in the Malmö Diet and Cancer Study in the early 1990's is likely to have consisted mostly of raisins. Both raisins and grapes have previously

been associated with lower diabetes incidence [54, 80]. However, a recent study concluded that there was limited evidence of an association between dried fruits and type 2 diabetes incidence [167]. Overall, dried fruits are nutrient-dense, rich in antioxidants, potassium, and dietary fibre, and contribute to better glycaemic control. Dried fruits are also high in monosaccharides, specifically fructose, which have a lower glycaemic index than disaccharides and were found to be associated with a lower type 2 diabetes incidence in study I.

An inverse association between a higher intake of root vegetables and lower type 2 diabetes incidence has also been identified previously [48]. Cooper et al (2012) found a 13 % reduction in incident type 2 diabetes for the highest versus lowest quartile of intake, but the finding was not replicated in a meta-analysis presented in the same article. In a Danish randomised controlled trial, root vegetables were found to have a positive effect on insulin sensitivity, body fat mass, and blood pressure in participants with type 2 diabetes [168]. The suggested explanation was a higher content of nutrients and phytochemicals, specifically, compared to other vegetables.

The positive associations with type 2 diabetes incidence for cruciferous vegetables and berries were unexpected. It could possibly be explained by how these foods are consumed in Sweden, especially in the early 1990s. For example, cabbage is a frequently consumed cruciferous vegetable in Sweden and is a popular side dish to pizza, while other cruciferous vegetables are frequently used in dishes high in saturated fats, such as pies and stews. A recent meta-analysis by Halvorsen et al (2021) identified positive associations with type 2 diabetes risk for three common cruciferous vegetables (Brussels sprouts, cabbage, and cauliflower) when comparing high versus low intake, and for Brussels sprouts and cauliflower when analysing the dose-response relationship, but no associations were identified for total intake of cruciferous vegetables [54]. Conversely, a recent Danish prospective study, with collection of dietary data roughly concurrent in time with our cohort, identified an inverse association between cruciferous vegetables and type 2 diabetes risk [59]. Thus, findings regarding cruciferous vegetables remain inconclusive.

For berries, it is likely that a high proportion of the intake may have consisted of strawberries, which are frequently consumed with whipped cream or ice cream. In the meta-analysis by Halvorsen et al (2021) the authors found different associations for blueberries, strawberries, and overall berries intake, with type 2 diabetes risk, where only blueberries demonstrated a significant inverse association [54].

Our findings in study I, II, and V, suggest a non-linear inverse association for fruits with an optimal intake of at least 200-300 grams per day, and of total fruit and vegetable intake of 300-500 grams per day. These are very similar to previous findings in other studies [47, 54].

Methodological Considerations

The included studies are all prospective cohort studies based on the same population cohort, the Malmö Diet and Cancer Study. The type of observational study and the methods applied to collect, register, and analyse data all have their strengths and weaknesses.

Prospective cohort studies are commonly used in nutritional epidemiology to investigate associations between diet and disease [169]. Some of the major strengths are the clear temporal sequence between exposure and disease outcome (limiting the risk of reverse causation), the opportunity of long follow-up (enabling following participants for an extended time until onset of disease), and the opportunity to study multiple different outcomes within the same cohort. Compared to retrospective cohorts, prospective cohorts generally experience less recall bias as the time from dietary exposure to assessment is shorter.

Study Population

The large study population and long follow-up time in the Malmö Diet and Cancer Study provided the opportunity of studying a large sample of the population, with a relatively large number of cases, increasing the statistical power and the prospect of identifying true associations, thus reducing the risk of type II errors. The limited number of exclusion criteria and the extensive and reliable registers to identify type 2 diabetes outcome also helped reduce selection bias.

The study population was compared to participants in a 1995 health survey that was mailed to a random sample of individuals in three of the same birth cohorts as in the Malmö Diet and Cancer Study, with a higher response rate of 75 % [127]. Participants in the Malmö Diet and Cancer Study were found to have the same socio-demographic structure, and prevalence of smoking and obesity, but were also found to have better self-reported health and fewer participants born outside of Sweden compared to the health survey. Compared to non-participants of the study, participants were also found to have lower mortality during both recruitment and follow-up.

Overall, while some limitations might be present (also due to a less diverse population and potential differences in eating habits compared to present-day Malmo), the study can still be considered to have good generalizability as the population constituted a large, socio-demographically representative sample of the background population.

Dietary Assessment

A major strength of the Malmö Diet and Cancer Study is the dietary assessment method applied, which was proven to have good validity and reproducibility [133,

134]. Combining a food record with a food frequency questionnaire was found to be superior to solely relying on a more extensive food frequency questionnaire.

However, the reliance on self-reported dietary data will always risk introducing systematic errors. The food frequency questionnaire relies on the participant accurately remembering the habitual intake of a large number of food items, which may introduce recall bias and the risk of under- or overreporting dietary intake. Both the food record and the food frequency questionnaire can introduce social desirability bias and lead to misreporting, as the respondent may report what they believe to be more socially acceptable rather than what they actually consumed. In all studies, however, we conducted additional analyses where potential misreporters of energy intake were excluded, thus confirming the robustness of our findings. The added assessment method of a dietary interview also reduced the risk of misclassification of exposure (including food, energy, and nutrient intake), as food items, cooking methods and recipes could be accurately assessed.

Furthermore, dietary data was only collected at one point in time, which may fail to identify potential temporal changes in eating habits, especially considering the long follow-up time of the study. However, we did try to attenuate this risk by conducting sensitivity analyses were participants reporting having changed their diets in their past were excluded. Furthermore, as seasonal variation in dietary habits is common, adjustment for season was consistently conducted in our studies.

The lack of available data on sub-types of mono- and disaccharides and sub-types of dietary fibre prevented the opportunity to study these exposures in more detail. Moreover, due to software limitations in the computing of fruit and vegetable intake prior to 1992, participants with baseline examinations in 1991 were excluded from study IV due to lack of separate data on legume intake, and from study V due to lack of separate data on sub-types of fruits and vegetables.

Covariates

The extensive baseline questionnaire allowed for the collection of data on a large number of possible confounders and allowed for ample adjustments in the main model. Still, residual confounding due to unknown factors cannot be ruled out.

Additionally, besides the data collected from anthropometric measurements and blood sampling, all covariate data was self-reported and thus introduce similar risk of systematic errors as mentioned for the dietary assessment.

Assessment of Outcome

Ascertainment of type 2 diabetes cases through a large number of reliable registers minimizes the risk of misclassification of outcome. However, some misclassification may still be present as all diabetes cases registered as unknown type were presumed to be type 2 diabetes. Nevertheless, despite more than half of all cases being registered as unknown, it is highly likely that the great majority of

these cases are accurately categorized as type 2 diabetes, due to the age of the participants and the overall large proportion of type 2 diabetes among all diabetes cases. Removal of these cases would have greatly reduced the power of the study.

Although prevalent cases at baseline were removed from the study population, there might always be a risk of reverse causation. Hence, we conducted sensitivity analyses in study II, IV, and V, where incident cases during early follow-up were removed.

Statistical Analysis

In study I and V, we conducted analyses on a large number of dietary variables. Due to the comprehensive statistical analyses, there is a possibility that some significant findings might have occurred solely by chance. Furthermore, we observed significant correlations between many of the dietary variables, complicating the deduction of the true causal impact of any individual nutrient or food on type 2 diabetes risk.

In nutrition research, focus has shifted more towards examining health outcomes associated with adherence to specific dietary patterns, rather than the intake of individual nutrients or foods [96, 170, 171]. When studying dietary patterns in epidemiological research, it is common to use either an a priori or an a posteriori approach [82, 92, 172]. Both of these have strengths and weaknesses but differ profoundly in their approach.

In study III and IV we applied an a priori approach, which is a deductive approach where the dietary pattern (the exposure) has already been established in previous studies. Adherence to the dietary pattern is often calculated using an index where the level of intake of specific foods or food groups is scored, and participants are categorised according to their summary score [173]. Limitations of this approach include decisions regarding cut-offs and scoring of different food groups, as well as differences in intake of food groups, and specific foods within a food group, across populations [174]. This could make it hard to compare and generalize findings from different studies and study populations.

In study II we applied an a posteriori approach, which is an inductive approach where the dietary pattern is not known beforehand but explored within a specific dataset. A frequently applied clustering algorithm using this approach is the K-means cluster analysis [92]. When using K-means, the dietary patterns are derived from differences in mean dietary intake of the included variables, separating individuals into non-overlapping clusters. However, certain more or less subjective decisions to be made, including deciding the exact number of clusters, how many and what variables to include in the analysis, and whether certain variables should be merged into a larger variable, such as foods into a larger food group [92, 175]. Furthermore, decisions also need to be made regarding as whether to energy-adjust

and standardise the dietary variables, and what cluster to assign as the reference cluster in the analysis. All of these decisions might introduce biases and errors.

In all five studies, we performed survival analysis in our main analysis by using the Cox proportional hazards regression model [176]. This model is widely used in epidemiological research, and one of its major strengths is its ability to handle right-censored data, that is when the event of interest has not occurred at the end of the follow-up period, or when a participant is lost to follow-up [177]. The model is contingent on the proportional hazards assumption not being violated. Hence, that the effect of the exposure on the hazard rate for the outcome does not change over time.

Conclusions

What we choose to eat and drink has clear implications for our future health. Carbohydrate quality is likely to be of much greater importance than carbohydrate quantity, as carbohydrate-rich foods differ in their association with type 2 diabetes risk. A higher intake of fruits and vegetables (especially green leafy vegetables), while limiting the intake of foods high in free sugars could help reduce type 2 diabetes risk.

Overall, promoting plant-based dietary patterns with a focus on carbohydrate quality, emphasizing a higher dietary fibre intake while limiting free sugar intake, has the opportunity to improve cardiometabolic health in the population and reduce the incidence of type 2 diabetes. This is likely to benefit everyone in the population, independent of genetic risk, while also benefitting overall planetary health.

Study I

In study I we identified that higher intakes of monosaccharides and fruits were associated with a lower incidence of type 2 diabetes. Conversely, higher intakes of disaccharides and sweets were positively associated with type 2 diabetes incidence. After stratification by sex, higher intakes of vegetables and marmalade/honey/jam were associated with a lower incidence in men, and a higher intake of chocolate with a higher incidence in women.

Study II

In study II we identified that a dietary pattern defined by a high intake of fruit was associated with a lower incidence of type 2 diabetes. The findings provided additional evidence of the potential protective effect from fruit intake in reducing type 2 diabetes risk.

Study III

In study III we identified that a diet with a high intake of dietary fibre and a moderate intake of free sugar in relation to total carbohydrate intake might be associated with

a lower incidence of type 2 diabetes. The results were only significant after the exclusion of potential misreporters of energy intake and diet changers.

Study IV

In study IV we identified that greater adherence to the EAT-Lancet diet was associated with a lower incidence of type 2 diabetes across all levels of genetic risk. The findings supported the EAT-Lancet Commission's recommendations for adherence to a sustainable diet.

Study V

In study V we identified that higher intakes of green leafy vegetables and dried fruits were associated with a lower incidence of type 2 diabetes. Conversely, a higher intake of cruciferous vegetables was associated with a higher incidence. After stratification by sex, a higher intake of berries was associated with a higher incidence in women, while a higher intake of root vegetables was associated with a lower incidence in men.

Future Perspectives

The field of nutrition is ever evolving, and there are currently multiple promising developments occurring simultaneously. On-going research into precision nutrition, personalized diets, metabolomics, gut microbiota, sustainable and plant-based diets, ultra-processed foods, molecular basis of food preferences, and artificial intelligence (AI), all carry with them the promise of helping us reduce the risk of future chronic disease, including type 2 diabetes.

Coinciding with the introduction of new pharmaceuticals to treat obesity, and a greater focus on supporting lifestyle changes in the prevention of chronic diseases, there could finally be a shifting trend towards healthier populations, with lower prevalence of obesity and incidence of chronic diseases. However, these new interventions and treatments are costly, and with most cases of chronic diseases (including type 2 diabetes) already occurring in low- and middle-income countries, it is likely that the vast majority of potential beneficiaries will not have access to these new scientific advances any time soon.

Currently, a lot of focus within nutritional research is centred around precision nutrition. The expectation is to be able to personalize diets and recommendations by taking into account individual differences in genetics, metabolism, lifestyle, and health status [122]. This would ultimately lead to personalized diets that are adapted to each individual's unique needs, rather than a conventional one-size-fits-all approach. However, although some individually tailored diets have shown promising results that may aid in type 2 diabetes prevention, results so far have been mixed [122, 178-182]. While this might be expected in a field that is still emerging, only the future knows if the high expectations will be met.

Another field that has gathered a lot of recent attentions is the role of the gut microbiome in the development of type 2 diabetes [183]. Differences and changes in gut microbiota has been associated with both beneficial and harmful effects that might potentially affect type 2 diabetes risk. Diets tailored by precision nutrition for type 2 diabetes prevention have been shown to beneficially modify the gut microbiota with the potential to reduce cardiometabolic risks [184]. However, it has been contested whether the association between the gut microbiome and type 2 diabetes risk is truly causal [185].

Another area related to precision nutrition is the prospects of AI, which may help tailoring precision nutrition and personalizing diets [186]. However, as the

algorithm needs to be trained on existing data, the AI will only be as good as the data it has at its disposal. Since the generalizability of dietary patterns associated with the incidence of type 2 diabetes in different populations might be limited, it could lead to the AI performing poorly when faced with new, previously unseen data [187].

Several advancements have also been made in the area of dietary assessment. This has been achieved through the introduction of objective methods, including new technologies and dietary biomarkers. New wearable technologies, cameras, and image-based and AI-assisted assessments all have the potential to facilitate the collection of more reliable dietary data [188-190]. However, some of these techniques have also caused privacy concerns that might need to be addressed [191].

Meanwhile, new discoveries within the field of metabolomics can help us objectively assess dietary intake through new dietary biomarkers [192]. Through the combined assessment of a large number of metabolites, dietary intake can already be assessed with fairly good accuracy, demonstrating the compelling future potential of metabolomics. Furthermore, metabolomics is likely to play an important future role in diabetes risk prediction, as well as in precision nutrition, assisting in tailoring personalized diets and ultimately becoming an integral part of type 2 diabetes prevention [112, 193, 194].

There has also been recent scientific progress in our understanding of the molecular basis of our food preferences, which may play a role in future precision nutrition [195, 196]. The food reward sensation in our brains is likely due to both the sensation of the food in our mouth and nose, connected to our sensory cortex, as well as through a second, independent gut-to-brain pathway [195]. Habitual intake of unhealthy foods, high in fat and sugar, has been shown to alter our food preferences and reward system, reducing our preference for and perception of foods low in fat and sugar [196].

A topic that has received a lot of attention recently, and sparked scholarly debate, is that of ultra-processed foods [197-200]. An overwhelming amount of evidence has shown associations between intake of ultra-processed foods and type 2 diabetes risk. These foods are often classified by using the NOVA classification system, and include foods such as sugar-sweetened beverages, snacks, sweets, chocolate, fast foods, and other processed foods high in sugar, salt, refined starch, and saturated fat [201]. However, criticism has arisen regarding the imprecise and inconsistent definition of ultra-processed foods, as well as the failure to recognize the importance of overall nutrient intake for our health rather than the level of food processing [202, 203].

Lastly, it is important to highlight the recent research into sustainable and plant-based diets [85, 157, 204, 205]. As we get a deeper understanding of diet's role in climate change, it is encouraging to learn that studies find a lower risk for multiple chronic diseases, including type 2 diabetes, with greater adherence to a plant-based

diet [204]. Hopefully, the new Nordic Nutrition Recommendations 2023 will be part of a larger paradigm shift, where our food choices no longer are concerned with solely our own health, but also the health of our planet [158].

In the end, despite all these new scientific advances and discoveries, what will matter most for future health and type 2 diabetes prevention is the ability and willingness of individuals and populations to adhere to current dietary guidelines and recommendations. Often overlooked in nutritional research and the scientific discussion, it could be argued that new discoveries into precision nutrition and other areas matter very little if compliance is not supported and facilitated. Thus, beyond focusing on associations between diet and health, we should also be concerned with the individual's environment, preferences, life circumstances, and conditions in order to achieve successful health promotion and disease prevention that will ensure a healthier future for all.

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About the author

KJELL OLSSON is a healthcare strategist at Region Skåne, Malmö, with a focus on health promotion and disease prevention. He is a registered dietitian with a Bachelor's in Dietetics from Umeå University, Sweden, and a Master's in Public Health from Lund University, Sweden. Enrolled as a doctoral student at Lund University since October 2017, the aim of his thesis has been to study the association between carbohydrate quality and the risk of developing type 2 diabetes.

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