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Abteilung Molekulare Epidemiologie

Identifying risk of microvascular and macrovascular complications of type 2 diabetes

Findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study

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Affidavit

I hereby declare in lieu of oath that the work presented in this dissertation is my own and have not used sources or means without declaration in the text. The present thesis, in whole or in parts, has not been submitted to any other university.

Potsdam, 31st of May 2022 Elli Polemiti

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Abbreviations

24-HDR	24-hours Dietary Recall
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADDITION-Cambridge	Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen- Detected Diabetes in Primary Care
ADVANCE	Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation
AGE	Advanced glycation end products
AHEI	Alternative Healthy Eating Index
ARIC	Atherosclerosis Risk in Communities
AU-ROC	Area Under the Receiver Operating characteristic Curve
BMI	Body Mass Index
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
CVDRS	Cardiovascular Disease Risk Score
DASH	Dietary Approaches to Stop Hypertension
DCCT	Diabetes Control and Complication Trial
DCGP	Diabetes Care in General Practice
DDG	German Diabetes Association
DEGS1	German Health Interview and Examination Survey for Adults
DiRECT	Diabetes Remission Clinical Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food Frequency Questionnaire
GDRS	German Diabetes Risk Score
GFR	Glomerular Filtration Rate
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoprotein
HEI	Healthy Eating Index
HPFS	Health Professionals' Follow-up Study
HR	Hazard Ratio

ICD	International Statistical Classification of Disease
IDF	International Diabetes Federation
LDL	Low-Density Lipoprotein
Look AHEAD	Action for Health in Diabetes
LRT	Likelihood Ratio Test
MAR	Missing at Random
MCAR	Missing Completely at Random
MLE	Maximum Likelihood Estimates
MNAR	Missing Not at Random
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NHS	Nurses' Health Study
OGTT	Oral Glucose Tolerance Test
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PKC	Protein Kinase C
PMM	Predictive Mean Matching
PREDIMED	Prevencion con Dieta Mediterranea
RAGE	Receptor for Advanced Glycation Endproducts
RECODe	Risk Equations for Complications Of type 2 Diabetes
ROS	Reactive Oxygen Species
SDCC	Steno Diabetes Center Copenhagen
TNF	Tumour Necrosis Factor
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VEGF	Vascular Endothelial Growth Factor
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization

Summary

Diabetes is hallmarked by high blood glucose levels, which cause progressive generalised vascular damage, leading to microvascular and macrovascular complications. Diabetes-related complications cause severe and prolonged morbidity and are a major cause of mortality among people with diabetes. Despite increasing attention to risk factors of type 2 diabetes, existing evidence is scarce or inconclusive regarding vascular complications and research investigating both micro- and macrovascular complications is lacking. This thesis aims to contribute to current knowledge by identifying risk factors – mainly related to lifestyle – of vascular complications, addressing methodological limitations of previous literature and providing comparative data between micro- and macrovascular complications.

To address this overall aim, three specific objectives were set. The first was to investigate the effects of diabetes complication burden and lifestyle-related risk factors on the incidence of (further) complications. Studies suggest that diabetes complications are interrelated. However, they have been studied mainly independently of individuals' complication burden. A five-state time-to-event model was constructed to examine the longitudinal patterns of micro- (kidney disease, neuropathy and retinopathy) and macrovascular complications (myocardial infarction and stroke) and their association with the occurrence of subsequent complications. Applying the same model, the effect of modifiable lifestyle factors, assessed alone and in combination with complication load, on the incidence of diabetes complications was studied. The selected lifestyle factors were body mass index (BMI), waist circumference,

smoking status, physical activity, and intake of coffee, red meat, whole grains, and alcohol. Analyses were conducted in a cohort of 1199 participants with incident type 2 diabetes from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam, who were free of vascular complications at diabetes diagnosis. During a median follow-up time of 11.6 years, 96 cases of macrovascular complications (myocardial infarction and stroke) and 383 microvascular complications (kidney disease, neuropathy and retinopathy) were identified. In multivariable-adjusted models, the occurrence of a microvascular complication was associated with a higher incidence of further micro- (Hazard ratio [HR] 1.90; 95% Confidence interval [CI] 0.90, 3.98) and macrovascular complications (HR 4.72; 95% CI 1.25, 17.68), compared with persons without a complication burden. In addition, participants who developed a macrovascular event had a twofold higher risk of future microvascular complications (HR 2.26; 95% CI 1.05, 4.86). The models were adjusted for age, sex, state duration, education, lifestyle, glucose-lowering medication, and pre-existing conditions of hypertension and dyslipidaemia. Smoking was positively associated with macrovascular disease, while an inverse association was observed with higher coffee intake. Whole grain and alcohol intake were inversely associated with microvascular complications, and a U-shaped association was observed for red meat intake. BMI and waist circumference were positively associated with microvascular events. The associations between lifestyle factors and incidence of complications were not modified by concurrent complication burden, except for red meat intake and smoking status, where the associations were attenuated among individuals with a previous complication.

The second objective was to perform an in-depth investigation of the association between BMI and BMI change and risk of micro- and macrovascular complications. There is an ongoing debate on the association between obesity and risk of macrovascular and microvascular outcomes in type 2 diabetes, with studies suggesting a protective effect among people with overweight or obesity. These findings, however, might be limited due to suboptimal control for smoking, pre-existing chronic disease, or short-follow-up. After additional exclusion of persons with cancer history at diabetes onset, the associations between pre-diagnosis BMI and relative annual change between pre- and post-diagnosis BMI and incidence of complications were evaluated in multivariable-adjusted Cox models. The analyses were adjusted for age, sex, education, smoking status and duration, physical

activity, alcohol consumption, adherence to the Mediterranean diet, and family history of diabetes and cardiovascular disease (CVD). Among 1083 EPIC-Potsdam participants, 85 macrovascular and 347 microvascular complications were identified during a median follow-up period of 10.8 years. Higher pre-diagnosis BMI was associated with an increased risk of total microvascular complications (HR per 5 kg/m^2 1.21; 95% CI 1.07, 1.36), kidney disease (HR 1.39; 95% CI 1.21, 1.60) and neuropathy (HR 1.12; 95% CI 0.96, 1.31); but no association was observed for macrovascular complications (HR 1.05; 95% CI 0.81, 1.36). Effect modification was not evident by sex, smoking status, or age groups. In analyses according to BMI change categories, BMI loss of more than 1% indicated a decreased risk of total microvascular complications (HR 0.62; 95% CI 0.47, 0.80), kidney disease (HR 0.57; 95% CI 0.40, 0.81) and neuropathy (HR 0.73; 95% CI 0.52, 1.03), compared with participants with a stable BMI. No clear association was observed for macrovascular complications (HR 1.04; 95% CI 0.62, 1.74). The impact of BMI gain on diabetes-related vascular disease was less evident. Associations were consistent across strata of age, sex, pre-diagnosis BMI, or medication but appeared stronger among never-smokers than current or former smokers.

The last objective was to evaluate whether individuals with a high-risk profile for diabetes and cardiovascular disease (CVD) also have a greater risk of complications. Within the EPIC-Potsdam study, two accurate prognostic tools were developed, the German Diabetes Risk Score (GDRS) and the CVD Risk Score (CVDRS), which predict the 5-year type 2 diabetes risk and 10-year CVD risk, respectively. Both scores provide a non-clinical and clinical version. Components of the risk scores include age, sex, waist circumference, prevalence of hypertension, family history of diabetes or CVD, lifestyle factors, and clinical factors (only in clinical versions). The association of the risk scores with diabetes complications and their discriminatory performance for complications were assessed. In crude Cox models, both versions of GDRS and CVDRS were positively associated with macrovascular complications and total microvascular complications, kidney disease and neuropathy. Higher GDRS was also associated with an elevated risk of retinopathy. The discrimination of the scores (clinical and non-clinical) was poor for all complications, with the C-index ranging from 0.58 to 0.66 for macrovascular complications and from 0.60 to 0.62 for microvascular complications.

In conclusion, this work illustrates that the risk of complication development among individuals with type 2 diabetes is related to the existing complication load, and attention should be given to regular monitoring for future complications. It underlines the importance of weight management and adherence to healthy lifestyle behaviours, including high intake of whole grains, moderation in red meat and alcohol consumption and avoidance of smoking to prevent major diabetes-associated complications, regardless of complication burden. Risk scores predictive for type 2 diabetes and CVD were related to elevated risks of complications. By optimising several lifestyle and clinical factors, the risk score can be improved and may assist in lowering complication risk.

Zusammenfassung

Diabetes ist durch einen hohen Blutzuckerspiegel gekennzeichnet, der eine fortschreitende allgemeine Gefäßschädigung verursacht, die zu mikro- und makrovaskulären Komplikationen führt. Diabetesbedingte Komplikationen verursachen eine schwere und langanhaltende Morbidität und sind eine der Hauptursachen für die Mortalität von Menschen mit Diabetes. Trotz der zunehmenden Aufmerksamkeit der Erforschung der Risikofaktoren des Typ-2-Diabetes, ist die vorhandene Studienlage in Bezug auf vaskuläre Komplikationen nicht eindeutig und nicht ausreichend. Diese Arbeit soll zum aktuellen Wissensstand beitragen, indem sie Risikofaktoren – hauptsächlich lebensstilbedingte Faktoren – für vaskuläre Komplikationen identifiziert, methodische Schwächen bisheriger Studien adressiert und vergleichende Daten zwischen mikro- und makrovaskulären Komplikationen liefert.

Um dieses übergeordnete Ziel zu erreichen, wurden drei spezifische Ziele gesetzt. Das erste war die Untersuchung des Einflusses der Diabetes-Komplikationslast und lebensstilbezogener Risikofaktoren auf das Auftreten weiterer Komplikationen. Studien legen nahe, dass Diabeteskomplikationen in Wechselbeziehung zueinanderstehen. Allerdings wurden sie bisher hauptsächlich unabhängig von der individuellen Komplikationslast untersucht. Es wurde daher ein fünfstufiges Time-to-Event-Modell konstruiert, um die longitudinalen Muster von mikro- und makrovaskulären Komplikationen und deren Zusammenhang mit dem Auftreten von Folgekomplikationen zu

untersuchen. Unter Anwendung desselben Modells wurde die Auswirkung modifizierbarer Lebensstilfaktoren, die allein und in Kombination mit der Komplikationslast untersucht wurden, auf das Auftreten von Diabeteskomplikationen untersucht. Die ausgewählten Risikofaktoren waren der Body-Mass-Index (BMI), der Taillenumfang, der Raucherstatus, die körperliche Aktivität und der Konsum von Kaffee, rotem Fleisch, Vollkornprodukten und Alkohol. Die Analysen wurden in einer Kohorte von 1199 Teilnehmern mit neu diagnostiziertem Typ-2-Diabetes aus der European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam durchgeführt, die zum Zeitpunkt der Diabetesdiagnose frei von vaskulären Komplikationen waren. Während einer Nachbeobachtungszeit von 11,6 Jahren wurden 96 Fälle mit makrovaskulären Komplikationen (Myokardinfarkt und Schlaganfall) und 383 Fälle mit mikrovaskulären Komplikationen (Nierenerkrankungen, Neuropathie und Retinopathie) identifiziert.

Das Auftreten einer mikrovaskulären Komplikation war mit einer höheren Inzidenz weiterer mikrovaskulärer Ereignisse (Hazard Ratio [HR] 1,90; 95% Konfidenzintervall [CI] 0,90, 3,98) und makrovaskulärer Komplikationen (HR 4,72; 95% CI 1,25, 17,68) assoziiert, verglichen mit Personen ohne Komplikationen. Darüber hinaus hatten Teilnehmende, die ein makrovaskuläres Ereignis entwickelten, ein doppelt so hohes Risiko für mikrovaskuläre Komplikationen (HR 2,26; 95% CI 1,05, 4,86). Die Modelle wurden für Alter, Geschlecht, Komplikationsdauer, Bildung, Lebensstil, glukosesenkende Medikamente und Vorerkrankungen wie Bluthochdruck und Dyslipidämie adjustiert. Rauchen war positiv mit makrovaskulären Erkrankungen assoziiert, während eine inverse Assoziation für einen höheren Kaffeekonsum beobachtet wurde. Vollkorn- und Alkoholkonsum waren invers mit mikrovaskulären Komplikationen assoziiert, und eine U-förmige Assoziation wurde für den Konsum von rotem Fleisch beobachtet. BMI und Taillenumfang waren positiv mit mikrovaskulären Ereignissen assoziiert. Die Zusammenhänge zwischen Lebensstilfaktoren und Komplikationen wurden durch gleichzeitige Komplikationsbelastung nicht verändert, mit Ausnahme für den Verzehr von rotem Fleisch und dem Raucherstatus, dort waren die Assoziationen bei Personen mit Komplikationen abgeschwächt.

Das zweite Ziel war die Untersuchung des Zusammenhangs zwischen BMI und BMI-Änderung und dem Risiko für mikro- und makrovaskuläre Komplikationen. Es gibt eine anhaltende Debatte über den Zusammenhang zwischen Adipositas und dem Risiko für

makrovaskuläre und mikrovaskuläre Folgeerkrankungen bei Typ-2-Diabetes, bei der einige Studien einen protektiven Zusammenhang bei Menschen mit Übergewicht oder Adipositas nahelegen. Diese Ergebnisse könnten auf methodische Schwächen zurückzuführen sein, einschließlich einer suboptimalen Adjustierung für Rauchen, bestehende chronische Erkrankungen und eine kurze Nachbeobachtungszeit. Nach zusätzlichem Ausschluss von Personen mit einer bestehenden Krebserkrankung zu Diabetesbeginn, wurden die Zusammenhänge zwischen BMI vor der Diagnose und die relative jährliche Veränderung zwischen BMI vor und nach der Diagnose hinsichtlich der Inzidenz von Komplikationen in Cox-Modellen ausgewertet. Die Analysen wurden für Alter, Geschlecht, Bildung, Raucherstatus und -dauer, körperliche Aktivität, Alkoholkonsum, Einhaltung der mediterranen Ernährung und Familienanamnese von Diabetes und kardiovaskulären Erkrankungen (CVD) adjustiert. Unter den 1083 Teilnehmern wurden 85 makrovaskuläre und 347 mikrovaskuläre Komplikationen während einer Nachbeobachtungszeit von 10,8 Jahren identifiziert. Ein höherer BMI vor der Diagnose war mit einem erhöhten Risiko für mikrovaskuläre Komplikationen insgesamt (HR pro 5 kg/m2 1,21; 95% CI 1,07, 1,36), Nierenerkrankungen (HR 1,39; 95% CI 1,21, 1,60) und Neuropathie (HR 1,12; 95% CI 0,96, 1,31) assoziiert; für makrovaskuläre Komplikationen wurde jedoch kein Zusammenhang beobachtet (HR 1,05; 95% CI 0,81, 1,36). Analysen nach BMI-Kategorien bestätigten diese Ergebnisse. Es gab keine Hinweise für Effektmodifikation mit Geschlecht, Raucherstatus oder Alter. In den Analysen für BMI-Änderung zeigte sich, dass eine BMI-Abnahme von mehr als 1 % mit einem verringerten Risiko für mikrovaskuläre Komplikationen (HR 0,62; 95% CI 0,47, 0,80), Nierenerkrankungen (HR 0,57; 95% CI 0,40, 0,81) und Neuropathie (HR 0,73; 95% CI 0,52, 1,03) verbunden war, verglichen mit Teilnehmern mit einem stabilen BMI. Für makrovaskuläre Komplikationen wurde kein eindeutiger Zusammenhang beobachtet (HR 1,04; 95% CI 0,62, 1,74). Die Assoziationen waren in den Strata nach Alter, Geschlecht, BMI vor der Diagnose oder Medikation hinweg konsistent, schienen aber bei lebenslangen Nichtrauchern stärker zu sein als bei Rauchern oder ehemaligen Rauchern.

Das letzte Ziel war es zu untersuchen, ob Personen mit einem Hochrisikoprofil für Diabetes und CVD auch ein höheres Risiko für Komplikationen haben. Im Rahmen der EPIC-Potsdam-Studie wurden zwei präzise Prognoseinstrumente entwickelt, der German Diabetes Risk Score (GDRS) und der CVD Risk Score (CVDRS), die das 5-Jahres-Risiko für

Typ-2-Diabetes bzw. das 10-Jahres-Risiko für CVD vorhersagen. Beide Scores sind als nicht-klinische und klinische Version verfügbar. Zu den Komponenten der Risikoscores gehören Alter, Geschlecht, Taillenumfang, Prävalenz von Bluthochdruck, familiäre Krankheitsvorgeschichte (Diabetes oder CVD), modifizierbare Lebensstilfaktoren und klinische Parameter (nur in den klinischen Versionen). Die Assoziation der Risikoscores mit Diabeteskomplikationen und ihre Diskriminierungsfähigkeit für Komplikationen wurden bewertet. In unadjustierten Cox-Modellen waren beide Versionen (GDRS und CVDRS) positiv mit makrovaskulären Komplikationen und insgesamt mit mikrovaskulären Komplikationen, Nierenerkrankungen und Neuropathie in Personen mit Typ-2-Diabetes assoziiert. Ein höherer GDRS war auch mit einem erhöhten Risiko für eine Retinopathie assoziiert. Die Diskriminierung der Scores (klinisch und nicht-klinisch) war für alle Komplikationen gering, wobei der C-Index für makrovaskuläre Komplikationen von 0,58 bis 0,66 und für mikrovaskuläre Komplikationen von 0,60 bis 0,62 reichte.

Zusammenfassend zeigt diese Arbeit, dass das Risiko für die Entwicklung von Komplikationen bei Personen mit Typ-2-Diabetes mit der bestehenden Komplikationslast zusammenhängt und dass eine regelmäßige Überwachung von zukünftigen Komplikationen wichtig ist. Sie unterstreicht die Bedeutung des Gewichtsmanagements und der Einhaltung gesunder Lebensgewohnheiten, einschließlich eines hohen Verzehrs von Vollkornprodukten, eines moderaten Konsums von rotem Fleisch und Alkohol, sowie des Verzichts auf das Rauchen, um schwere diabetesassoziierte Komplikationen, unabhängig von der Komplikationslast, zu verhindern. Die Risiko-Scores für Typ-2-Diabetes und Herz-Kreislauf-Erkrankungen waren mit einem erhöhten Komplikations-Risiko assoziiert. Durch die Optimierung des Lebensstils und der klinischen Faktoren kann der Risikoscore verbessert werden, was das Auftreten von diabetesassoziierten Komplikationen verringern könnte.

1.
Introduction and literature review

1.1 Overview of the chapter

This chapter highlights the state of the available scientific knowledge related to type 2 diabetes and its chronic vascular complications. Firstly, the pathophysiology and epidemiology of type 2 diabetes (section 1.2) and vascular complications (section 1.3) are provided. Next, section 1.4 addresses the interrelationships between micro- and macrovascular complications. The next section (1.5) outlines the current literature on the role of diet and lifestyle, with an emphasis on diabetes-related vascular complications. Finally, an overview of prediction risk scores for vascular complications of type 2 diabetes is provided in section 1.6.

1.2 Type 2 diabetes mellitus

1.2.1 Definition and diagnosis

Diabetes mellitus is a group of chronic endocrine disorders portrayed by raised blood glucose levels (hyperglycaemia). Diabetes is clinically classified into three main types: i) type 1 diabetes, caused by an absolute lack of pancreatic insulin secretion, ii) type 2 diabetes,

characterised by cell inability to use the secreted insulin (insulin resistance), or a relative lack of insulin secretion (insulin deficiency), or both, and iii) gestational diabetes, where the physiological increase in insulin resistance that occurs to ensure the increased foetal glucose demands, may increase excessively, leading to persistent hyperglycaemia (American Diabetes Association, 2019a, Plows et al., 2018). Hyperglycaemia causes progressive injury to vasculature and organs, leading to chronic vascular complications that eventually may become disabling and life-threatening.

Clinical presentation of marked hyperglycaemia involves fatigue, polyuria, polydipsia, unintentional weight loss and sometimes polyphagia and blurred vision (International Diabetes Federation (IDF), 2019). In contrast to the sudden onset seen in type 1 diabetes, type 2 diabetes develops insidiously and may be asymptomatic, rendering the determination of the exact time of type 2 diabetes onset impossible. Consequently, there is often a long period before diagnosis, and if hyperglycaemia or glycosuria is not detected incidentally through screening, it may be too late to prevent chronic diabetes-related complications (Vanbergen and Wintle, 2019).

During the asymptomatic phase of type 2 diabetes, diagnosis is achieved by measuring plasma glucose during fasting or two hours after oral glucose tolerance test (OGTT) or glycated haemoglobin (HbA1c) (American Diabetes Association, 2019a). A positive test should be repeated on a different day unless symptoms of hyperglycaemia coexist. The diagnostic criteria of diabetes according to the guidelines of the German Diabetes Association (DDG) are presented in **Table 1.1** (Kerner and Brückel, 2014), which are in line with the recommendations from the World Health Organization (WHO) and American Diabetes Association (ADA) (American Diabetes Association, 2019a, World Health Organization (WHO), 2016). Furthermore, a group of individuals at an increased risk of diabetes onset, who present higher than normal glucose levels but without meeting the criteria for diabetes diagnosis, is recognised. This intermediate hyperglycaemia is referred to as prediabetes and it is defined as impaired glucose tolerance or impaired fasting glucose (diagnostic cut-off points are shown in **Table 1.1**). It is estimated that if left untreated, 5–10% of people with prediabetes will progress to diabetes every year (Tabák et al., 2012). Albeit the utilisation of threshold values for the diagnosis of prediabetes and diabetes, abnormalities in the glucose levels is a continuum progression from normoglycaemia to overt diabetes.

Table 1.1 Diagnostic criteria of diabetes and intermediate hyperglycaemia according to the German Diabetes Association guidelines

	Diabetes	Impaired glucose tolerance[a]	Impaired fasting glucose[b]
Fasting plasma glucose	≥7.0 mmol/L (≥126 mg/dL)	<7.0 mmol/L (<126 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)
	or	and	
Two-hour plasma glucose[c]	≥11.1 mmol/L (≥200 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	
	or		
HbA1c[d]	≥48 mmol/mol (≥6.5%)		
	or		
Random plasma glucose[e]	≥11.1 mmol/mol (≥200 mg/dL)		

[a] Two-hour plasma glucose of 7.8–11.0 mmol/L (140–199 mg/dL) alone signifies impaired glucose tolerance, according to the American Diabetes Association guidelines

[b] Fasting plasma glucose of 6.1–6.9 mmol/L (110–125 mg/dL) and (if available) two-hour plasma glucose of <7.8 mmol/L (<140 mg/dL) identifies persons with impaired fasting glucose, according to the World Health Organisation guidelines

[c] Plasma glucose two hours after oral ingestion of 75 g glucose load

[d] HbA1c range of 39–47 mmol/mol (5.7–6.4%) denotes individuals with prediabetes, according to the American Diabetes Association guidelines

[e] In the presence of symptoms of hyperglycaemia. Also incorporated in the guidelines of the American Diabetes Association

1.2.2 Pathophysiology

Glucose homeostasis is primarily maintained by the balanced interplay between insulin action and insulin secretion. Insulin is a peptide hormone secreted from pancreatic β-cells, located in the islets of Langerhans, in response to the elevated postprandial glucose levels. Circulating insulin binds to cell surface insulin receptors, initiating the increase of glucose uptake in muscle and adipose tissue via insulin-dependent GLUT-4 transporter upregulation (Vanbergen and Wintle, 2019).

Impairment in the function of the feedback loop between insulin-sensitive tissues (liver, muscle and adipose tissue) and β-cells leads to abnormal glucose levels. Deficiencies in insulin action and inadequate insulin secretion frequently coexist, and often, it is unclear

which occurred first (American Diabetes Association, 2019a). Individuals at increased risk of diabetes, such as persons with a family history of diabetes, elderly, or women with gestational diabetes or polycystic ovary syndrome, exhibit a decreased β-cell function, which is a critical determinant of glucose tolerance decline (Kahn et al., 2014, Cnop et al., 2007). Furthermore, insulin resistance is commonly present in persons with obesity and a sedentary lifestyle (Stumvoll et al., 2005).

The development of insulin resistance is progressive and contributes to increased hepatic glucose production and decreased glucose uptake in insulin-sensitive tissues at a certain insulin level (Zheng et al., 2018). An increased insulin output by pancreatic islets is induced to compensate for the decreased insulin sensitivity and maintain glucose homeostasis. This stage is defined as impaired glucose tolerance (Vanbergen and Wintle, 2019). As insulin resistance advances, insulin requirements increase, paralleled with depletion and progressive deterioration of β-cells. The detrimental effect of chronic hyperglycaemia is referred to as glucotoxicity (Fonseca, 2009). Eventually, the β-cell dysfunction results in a decreased insulin secretion and impaired glucose homeostasis. At this stage, the individual will meet the diagnostic criteria for diabetes.

In addition to glucotoxicity, other potential mechanisms have been proposed to explain insulin resistance and β-cell dysfunction in type 2 diabetes, such as lipotoxicity, oxidative stress, endoplasmic reticulum stress and tissue inflammation (Donath and Shoelson, 2011). These mechanisms can be triggered by overnutrition and are closely linked to each other. In lipotoxicity, prolonged increases in long-chain saturated free fatty acids, often observed in persons with insulin resistance, induce β-cell dysfunction and apoptosis. Furthermore, hyperglycaemia and free fatty acids cause oxidative stress due to increased reactive oxygen species generation, which in turn result in β-cell dysfunction and insulin resistance (Evans et al., 2002). An increased influx of proteins in the endoplasmic reticulum of β-cells (a cell organelle responsible for protein folding, maturation and trafficking), in response to increased insulin production, provokes an accumulation of unfolded proteins, causing stress. Under extensive endoplasmic reticulum stress, cells undergo apoptosis (Donath and Shoelson, 2011, Kitamura, 2008). Lastly, obesity and increased glucose and free fatty acid levels stress the pancreatic islets and insulin-sensitive tissues, releasing pro-inflammatory cytokines and chemokines. In turn, immune cells are recruited, further contributing to

inflammation and promoting it to other tissues, including the islets, that may trigger insulin resistance, impaired β-cell secretory function and apoptosis (Donath and Shoelson, 2011).

1.2.3 Prevalence and economic burden

In 2021, the global estimate of diabetes age-adjusted prevalence in adults (20–79 years) was 10.5%, equivalent to 537 million, tripling from the past 20 years. If current trends are not tackled, age-adjusted prevalence is expected to reach 12.2%, corresponding to 783.2 million people by 2045 (International Diabetes Federation (IDF), 2021). Type 2 diabetes accounts for around 90% of diabetes cases, and it is estimated that more than one-third of the individuals with diabetes type 2 are undiagnosed (International Diabetes Federation (IDF), 2019). There is a considerable variation of type 2 diabetes prevalence according to geographical region, with more than 80% of adults with diabetes living in low- and middle-income countries (Chatterjee et al., 2017). Nevertheless, between 1980 and 2014, the age-standardised prevalence of diabetes rose in every country or at best remained stable, as in the case of women in continental western Europe (NCD Risk Factor Collaboration (NCD-RisC), 2016).

Results from the first wave (2008–2011) of the population-based German Health Interview and Examination Survey for Adults (DEGS1), the prevalence of diabetes in adults (18–79 years) was 7.2% (Heidemann et al., 2013). Diabetes prevalence was double in people with low socioeconomic status compared to individuals with high socioeconomic status. Nationwide land-line telephone interviews of the German-speaking population aged 18 years and over (German Health Update study [GEDA] 2009, 2010 and 2012) yielded higher estimates of diabetes prevalence at 8.8%, 8.6% and 8.9%, respectively (Robert Koch-Institut (RKI) (Hrsg), 2011, Robert Koch-Institut (RKI) (Hrsg), 2012, Robert Koch-Institut (RKI) (Hrsg), 2014). Germany ranked eighth among countries with the highest number of people with diabetes aged 20–79 globally, corresponding to 9.5 million in 2019. Furthermore, it is estimated that 6.3 million adults with diabetes in Germany aged older than 65 years, ranking fourth in this age group worldwide. The age-standardised comparative prevalence in Germany was estimated at 10.4 (95% CI 8.5, 11.6), standing second among countries in continental Europe in 2019 (International Diabetes Federation (IDF), 2019). Estimates of

the IDF Diabetes Atlas for 2021 reported a decrease in the number of adults (20–79 years) with diabetes, which reached 6.2 million, ranking third in continental Europe. This estimate corresponds to a diabetes prevalence of 10.0% (95% CI 8.1, 11.0) and an age-standardised comparative prevalence of 6.9% (95% CI 5.5, 7.7), positioning 17th in continental Europe (International Diabetes Federation (IDF), 2021). More than 1.3 million adults 20–79 years are expected to have undiagnosed diabetes in Germany, ranking fifth in continental Europe in 2021.

Diabetes has a detrimental economic burden on health-care systems, national economies but also on patients and their families. Health insurance coverage is frequently lacking in low-income households, where a large percentage of annual income is spent on diabetes care (Seuring et al., 2015). In 2021, the direct cost[1] of diabetes was estimated at USD 966 billion, with an expected rise of USD 1.03 and 1.05 trillion by 2030 and 2045, respectively, assuming that diabetes prevalence and mean expenditure per person remain constant. Germany had the fourth-highest diabetes-related health expenditure globally, analogous to USD 41.3 billion (International Diabetes Federation (IDF), 2021). Based on DEGS1 data, total cost[2] was 28% higher in individual with type 2 diabetes compared to those without diabetes. The direct diabetes care cost covered almost 78% of total cost (König et al., 2021).

1.3 Microvascular and macrovascular complications of diabetes

In parallel to the rise of global diabetes prevalence, a growing number of people develop chronic vascular complications, which are a major cause of premature mortality and decreased quality of life in diabetes patients. Diabetes vascular complications are classified into microvascular, due to damage to the endothelium of small blood vessels, and macrovascular complications, due to damage to the arteries. Microvascular complications

[1] **Direct cost** – the cost of health services for prevention, detection and management of diabetes, family planning activities, nutrition activities and emergency aid.
[2] **Total cost** – the direct and indirect cost. Indirect cost is defined as the cost due to loss of productivity, i.e., sick leave, early retirement, premature mortality.

include kidney disease, neuropathy and retinopathy. The major macrovascular complications include myocardial infarction and stroke. The underlying cause of most pathological manifestations is chronic hyperglycaemia (Vanbergen and Wintle, 2019). The risk of complication development is proportional to the degree and duration of hyperglycaemia, particularly for microvascular events (Fowler, 2008). Concurrently, genetic susceptibility as well as presence of hypertension and dyslipidaemia, which is frequently elevated in type 2 diabetes, accelerate the risk of vascular injury (Giacco and Brownlee, 2010, Avogaro and Fadini, 2019).

1.3.1 Kidney disease

Chronic kidney disease describes the irreversible gradual decline of kidney function and is characterised by increased albumin excretion in the urine (albuminuria) and decreased glomerular filtration rate (GFR) (Eckardt et al., 2013). The glomerular filtration barrier, responsible for plasma filtration and urine formation, is a complex biological sieve consisting of the fenestrated vascular endothelium, the glomerular basement membrane and the outermost podocyte layer. In a healthy state, the glomerular filtration barrier is permeable to water, small and midsized plasma solutes but retains large macromolecules, such as plasma proteins, within the circulation (Fakhruddin et al., 2017).

Diabetes-induced kidney damage leads to structural and functional alterations of the glomerulus initially marked as albuminuria reflecting endothelial surface layer destruction, reduced fenestrated vascular endothelium and increased basement membrane thickness. Subsequently, further decline in kidney function is characterised by podocyte injury, glomerulosclerosis, overt proteinuria, decreased glomerular function and GFR, concluding to end-stage renal damage. (Pavkov et al., 2018, Fakhruddin et al., 2017). Although abnormalities in blood pressure and lipoproteins are a consequence of renal impairment, hypertension and dyslipidaemia usually precede glomerular injury in type 2 diabetes, contributing further to the progression of kidney disease by inducing glomerulosclerosis (Webster et al., 2017, Pavkov et al., 2018).

According to guidelines of the DDG the clinical diagnosis of diabetic kidney disease is based on the presence of persistent albuminuria, measured as albumin/creatinine ratio that

exceeds 20 mg/g for men or 30 mg/g for women in (at least) two samples collected within two to four weeks (Hasslacher et al., 2014). Annual screening of albumin concentrations in urine samples is recommended. In addition, annual GFR determination is recommended because, in diabetes, renal function may be compromised even without albuminuria. GFR can be accurately measured by the clearance of exogenous filtration markers (e.g., inulin, iothalamate, iohexol, or ^{51}Cr-EDTA). However, this method is impractical and expensive (Pavkov et al., 2018). Alternatively, the estimation of GFR is achieved by using equations including serum creatinine, age, sex, ethnicity and weight, such as the Modification of Diet in Renal Disease formula and the Chronic Kidney Disease Epidemiology Collaboration formula (Hasslacher et al., 2014, Pavkov et al., 2018). The classification of chronic kidney disease according to DDG is presented in **Table 1.2**.

The prevalence of chronic kidney disease is approximately 10.5–13.1% in the general population (James et al., 2010) and exceeds 20% in individuals older than 60 (Eckardt et al., 2013). Kidney disease is one of the most common complications of diabetes, affecting approximately 30–50% of diabetes patients and accounts for about 50% of the cases of end-stage renal disease in western societies (Tuttle et al., 2014, Webster et al., 2017). Diabetes and hypertension account for 80% of all cases of end-stage renal disease globally (International Diabetes Federation (IDF), 2019).

Table 1.2 Classification of kidney disease stages according to the German Diabetes Association guidelines [adapted from (Hasslacher et al., 2014)]

Stage/description	Glomerular filtration rate (ml/min/1.73 m^2)	Albumin/creatinine ratio in urine (mg/g)
Kidney damage with normal kidney function		
1a. microalbuminuria	≥90	W/M 20–200/ 30–300
1b. macroalbuminuria	≥90	W/M >200/ >300
Kidney damage with kidney insufficiency (KI)		
2. low KI	60–89	All ranges possible
3. moderate KI	30–59	Usually decreasing
4. high KI	15–29	Usually decreasing
5. terminal KI	<15	

W, women; M, men

1.3.2 Neuropathy

Diabetic neuropathies can be classified into two distinct entities, elicited from their natural history: (1) those that progress with increasing duration of diabetes and (2) those that reach almost complete remission. Sensory, motor and autonomic neuropathies, which belong to the composite group 'peripheral neuropathy', progress gradually over time, while mononeuropathies, radiculopathies and acute painful neuropathies are short-termed (Barrett et al., 2017). The most common type of neuropathy in diabetes is distal symmetrical polyneuropathy, describing the injury of the peripheral nerves located in the distal parts of the limbs, particularly those of the feet. Individuals with diabetic neuropathy[3] typically exhibit distal sensory loss, numbness, pain, tingling and muscle weakness that may develop alone or as a constellation of symptoms (Callaghan et al., 2012, International Diabetes Federation (IDF), 2019).

The prevalence of peripheral neuropathy ranges from 1–3% in the general population and reaches 7% amongst elderly individuals, although the evidence is somewhat outdated (Hanewinckel et al., 2016). In persons with newly diagnosed diabetes type 2, the prevalence is estimated at 10–15%, which may rise to 50% throughout the disease (Pop-Busui et al., 2017). Furthermore, peripheral neuropathy facilitates the development of foot ulcers, which may lead to gangrene and amputation. Diabetes patients with severe neuropathy are at a 1.7-fold higher risk of amputations (Barrett et al., 2017). Another disabling morbidity of neuropathy is neuropathic pain which occurs in 10–15% of diabetes patients, although these estimates are likely underestimated (Callaghan et al., 2012).

The peripheral nervous system comprises two broad categories of cells: the neurons and the neuroglial, or glial, cells. The role of neurons is to generate and transmit information in the form of electrical signals. Neurons have a cell body (soma) containing the nucleus and organelles, a long extension from the soma called an axon, and dendritic branches, or dendrites. The axon conveys electrical signals to other cells, and dendrites receive the signals from the axonal extremities, transmitting them into the soma. The glial cells of the peripheral

[3] Henceforth, distal symmetrical polyneuropathy, diabetic neuropathy and peripheral neuropathy will be used interchangeably.

nervous system, known as Schwann cells, wrap the axons, forming a membranous coating, the myelin. Myelin plays a crucial role in the speed at which the electrical signals travel (Purves et al., 2008).

A reduced nerve conduction velocity is often present at type 2 diabetes diagnosis and steadily progresses at a rate of approximately one metre per second per year (Barrett et al., 2017). Longer nerves show decreased nerve conduction velocity earlier and a loss of sensation and reflexes is usually first seen in the feet. Thereafter, symptoms usually ascent towards other areas, particularly the hands (Forbes and Cooper, 2013). Cell damage due to hyperglycaemia may result in progressive axon degeneration and demyelination. Furthermore, damage to the cells of the microvasculature within the peripheral nerves may occur by impairing vasodilation, thickening of the basement membrane, pericyte degeneration and endothelial cell hyperplasia with subsequent oxygen tension diminishment and hypoxia (Barrett et al., 2017, Forbes and Cooper, 2013).

The DDG guidelines for diabetic neuropathy screening recommend the assessment of i) subjective symptoms, applying the Neuropathy Symptom Score and ii) the severity of sensory deficit, using the Neuropathy Disability Score (Ziegler et al., 2021). Simple neurological examinations should be performed bilaterally, including the testing of Achilles tendon and knee reflexes, pain sensation, touch sensation (e.g., with cotton-wool swab), pressure and touch sensation (with the 10 g monofilament), temperature sensation (e.g., with a tuning fork, ice water-cooled test tube or TipTherm), and vibration sensation measured with C64 Hz Rydel-Seiffer tuning fork. Complications of neuropathy, specifically foot complications, should be examined bilaterally by inspecting skin colour and temperature, trophic changes in the skin, foot deformities and ulcers and signs of bacterial or fungal infection. Examination for peripheral arterial occlusive disease should also be performed (Ziegler et al., 2021).

1.3.3 Retinopathy

Diabetic retinopathy is a progressive disorder that manifests through the appearance of a spectrum of lesions in the retina. The retina is the innermost layer of the eye, consisting of a pigmented layer and a neural layer. The pigmented layer is a sheet of epithelial cells located

between the choroid and the neural layer of the retina. The choroid is a vasculature structure that supplies blood to the retina. In the centre of the pigmented retina is found the macula, a flat spot responsible for high-resolution vision. The neural retina contains light-sensitive cells and converts visual data into electrical impulses to be sent to the axons of the optic nerve (Rehman et al., 2021).

Clinical grading of diabetic retinopathy consists of two major disease stages: non-proliferative retinopathy and proliferative retinopathy. In the early stages of diabetic non-proliferative retinopathy, retinal microaneurysms and occasional blot haemorrhages can be detected and is largely asymptomatic (Barrett et al., 2017). These abnormalities are due to the weakening of the retinal blood vessels because of hyperglycaemia-mediated pericyte death and thickening of the basement membrane; thus, altering the blood-retinal barrier and vascular permeability (Forbes and Cooper, 2013). Non-proliferative retinopathy may progress to the appearance of hard exudates (lipid deposits resulting from lipoprotein leakage in the vasculature), cotton wool spots (small, localised infarction of the neural layer) and capillary occlusion (Barrett et al., 2017). Visual impairment occurs with the development of macular oedema (caused by a built-up fluid due to the breakdown of the inner blood-retinal barrier) and proliferative retinopathy (neovascularisation leading to preretinal and vitreous [transparent fluid between the lens and retina] haemorrhage), which occur as a result of increasing retinal ischaemia and hypoxia (Forbes and Cooper, 2013, Barrett et al., 2017, Curtis et al., 2009).

According to the DDG guidelines, the diagnostics of diabetic retinopathy encompass the examination of visual acuity, the anterior segment of the eye and the ocular fundus in dilated pupil using binocular-biomicroscopic fundoscopy (Hammes et al., 2021). Changes in the eye pressure should be examined in case of severe non-proliferative, proliferative retinopathy or neovascularisation of the iris. Optical coherence tomography should be performed in the presence of maculopathy or optionally for differential diagnosis of maculopathy. In certain features of advanced diabetic retinopathy or maculopathy, fluorescein angiography should be conducted (Hammes et al., 2021).

The prevalence of retinal microaneurysms and haemorrhages was estimated at 2–11% in persons older than 40 without diabetes and was more frequently linked to hypertension (Klein et al., 1993a). Diabetic retinopathy is considered a leading cause of blindness in

working-age adults and occurs in about one-third of individuals with diabetes. In a pooled analysis of 35 studies that took place between 1980 and 2008, the global prevalence of any diabetic retinopathy was estimated at 34.6% in persons aged 20–70. Among them, 7.0% had proliferative retinopathy and 6.8% diabetic macular oedema (Yau et al., 2012), with a considerable variation between regions (Lee et al., 2015).

1.3.4 Macrovascular complications

Macrovascular complications are the principal cause of mortality and morbidity in people with type 2 diabetes (International Diabetes Federation (IDF), 2019). The term macrovascular complications refers to a group of disorders that encompasses coronary heart disease, ischaemic stroke, peripheral artery disease and congestive heart failure. Only myocardial infarction and ischaemic stroke will be examined in this work; hence, macrovascular complications will refer to these two conditions. Global crude prevalence estimates of myocardial infarction and stroke in 2007–2017 among persons with type 2 diabetes living in the middle- and high-income countries were 10.0% and 7.6%, respectively (Einarson et al., 2018). The prevalence of myocardial infarction and stroke in diabetes was twice or more as high as in persons without diabetes (Barrett-Connor et al., 2018, Pikula et al., 2018).

The aetiology of macrovascular complications in type 2 diabetes is comparable to the aetiology in the general population. Classic cardiovascular disease (CVD) risk factors, such as dyslipidaemia, hypertension, obesity and smoking, are important determinants of macrovascular complications. However, the increased prevalence of CVD in diabetes has been demonstrated independently of those risk factors (Barrett-Connor et al., 2018, Pikula et al., 2018). Multiple underlying processes associated with insulin deficiency exacerbate diabetic endothelial dysfunction, resulting in an increased occurrence of atherosclerosis and accelerated formation of atherosclerotic plaques (Forbes and Cooper, 2013, Low Wang et al., 2016).

Atherosclerotic plaques are arterial wall deposits characterised by the accumulation of lipid-rich necrotic debris, a ‘necrotic core’, and a ‘fibrous cap’ composed of smooth muscle cells and extracellular matrix. The advancement of the plaques is accompanied by

calcification and neovascularisation associated with haemorrhage and may lead to lesion instability, ensuing rupturing (Lusis, 2000). Advanced plaques may cause occlusion of blood vessels at the site of lesion formation or promote atherothrombosis (due to plaque rupture), resulting in a rapid occlusion at distant sites (Forbes and Cooper, 2013). Complete occlusion in the coronary arteries leads to ischaemia and loss of myocytes, resulting in cardiac contractility and function impairment and ultimately to chronic cardiac failure or death – a myocardial infarction; while occlusion in the cerebral arteries leads to ischaemic necrosis of brain tissue – a stroke (Vanbergen and Wintle, 2019).

1.3.5 Underlying mechanisms of hyperglycaemia-induced vascular injury

Mechanisms involved in the pathogenesis of micro- and macrovascular complications are so interrelated that often one is not considered separately from the other. The following paragraphs provide an overview of the contributing factors postulated to mediate the tissue-damaging effects of hyperglycaemia. This includes the activation of protein kinase C (PKC) isoforms, increased polyol pathway flux, elevated formation of advanced glycation end products (AGE-s) and enhanced reactive oxygen species (ROS) production (oxidative stress). Nevertheless, the list is not exhaustive and comprehensive reviews can be found elsewhere (Barrett et al., 2017, Forbes and Cooper, 2013, Giacco and Brownlee, 2010, Rask-Madsen and King, 2013, Vincent et al., 2011).

PKC activation. PKC is a family of protein kinase enzymes that catalyses the phosphorylation[4] of serine and threonine residues in proteins and affects several cellular functions. Hyperglycaemia increases PKC isoforms activity (primarily α, β, and δ) via the diacylglycerol pathway, resulting in, among others, endothelial dysfunction, alteration of vascular permeability, angiogenesis, vascular cell apoptosis, basement membrane thickening and extracellular matrix expansion, ROS generation and inflammation (Barrett et al., 2017, Paneni et al., 2013). PKC activity is upregulated in retinal pericytes, renal mesangial[5],

[4] **Phosphorylation** – a reaction where a phosphoryl group is added to a molecule.
[5] **Mesangial cells** – compose the glomerular basement membrane together with the mesangial matrix, and their primary function is to perform filtration.

proximal tubular cells[6] and aortic endothelial cells, but its role on the peripheral nerves is unclear (Barrett et al., 2017).

Hyperactive polyol pathway. The polyol pathway is a two-step process (glucose→sorbitol, sorbitol→fructose) that converts glucose to fructose (Vanbergen and Wintle, 2019). Excess plasma glucose upregulates aldose reductase, an enzyme involved in the sorbitol synthesis pathway, resulting in enhanced production of sorbitol by utilising nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is a necessary cofactor for glutathione production, which is the primary intracellular antioxidant. Hyperactivity of the polyol pathway leads, thus, to reduced availability of NADPH, rendering cells vulnerable to oxidative assaults (Barrett et al., 2017, Vanbergen and Wintle, 2019). Furthermore, certain tissues lack sorbitol dehydrogenase, an enzyme involved in the sorbitol→fructose pathway, leading to sorbitol accumulation and osmotic stress, which in turn cause structural and functional protein impairment. This is particularly apparent in retinal and Schwann cells (Forbes and Cooper, 2013, Vanbergen and Wintle, 2019).

Increased AGEs formation. Glycation is the nonenzymatic reaction in which a sugar molecule binds to a protein, forming AGEs, and is accelerated by persistent hyperglycaemia and oxidative stress (Forbes and Cooper, 2013). Furthermore, diabetes patients with renal impairment have a reduced capacity of plasma AGEs clearance (Vincent et al., 2011). AGE-modification of intracellular and extracellular proteins alters their structure and function; thus, inhibiting the function of the retina, glomeruli, nerves and aorta (Vincent et al., 2011, Forbes and Cooper, 2013, Rask-Madsen and King, 2013). In addition, AGE-modified extracellular proteins may interact with cell surface receptors (RAGE), expressed in endothelial cells, pericytes, smooth muscle cells, mesangial cells, podocytes and neurons (Barrett et al., 2017). Binding to RAGE promotes inflammatory responses and increases ROS production (Vincent et al., 2011, Rask-Madsen and King, 2013).

ROS accumulation. ROS are molecules or atoms with an unpaired electron (superoxide anion, peroxide and hydroxyl), are highly reactive and may be endogenous or exogenous. They cause oxidative damage by oxidising other molecules (proteins, lipids, DNA) when

[6] **Proximal tubules** – reabsorb water, ions and small molecules and secrete undesirable substances.

entering redox reactions[7] indiscriminately, leading to functional impairment (Vanbergen and Wintle, 2019). In the diabetic state, mitochondria generate excessive superoxide anions during oxidative phosphorylation[8] (Forbes and Cooper, 2013). Overproduction of ROS activates other pathogenic pathways, such as PKC activation, polyol pathway flux, increase formation of AGEs and increased expression of RAGE. Additionally, it inactivates the endothelial nitric oxide synthase and prostacyclin synthase, two enzymes involved in vasodilation and inhibition of platelet aggregation (Giacco and Brownlee, 2010). The inactivation of the two antiatherosclerosis enzymes is also mediated by increased release of free fatty acids due to insulin resistance in the adipocytes, resulting in their oxidation and subsequently to mitochondrial superoxide overproduction. Through these pathways, increased ROS cause ischaemia leading to defective angiogenesis, atherosclerosis and inflammation (Giacco and Brownlee, 2010).

Indeed, chronic inflammation is a characteristic feature at sites of diabetes complications and increasing levels of circulating inflammatory markers have been shown to be related to the onset and progression of diabetes complications in clinical studies (Forbes and Cooper, 2013, Donate-Correa et al., 2015, Zhang et al., 2011). Animal and in vitro studies postulated that the proinflammatory cytokines interleukin-1β and tumour necrosis factor (TNF)-α accelerate atherosclerosis (Low Wang et al., 2016), induce endothelial cell apoptosis, contributing to retinal vessel occlusion and degeneration and glomerular injury (Zhang et al., 2011, Ostendorf et al., 1996, Donate-Correa et al., 2015), and are involved in nerve damage and miscommunication between Schwann cells and axons (Forbes and Cooper, 2013). Furthermore, the pathological activation of the interleukin-1 system has been linked to CVD and microvascular complications in prospective and cross-sectional studies (Herder et al., 2015). Among other inflammatory markers, increases in interleukin-1 dependent factors, such as interleukin-6, C-reactive protein (CRP) and chemokine (C-C motif) ligand 2 (CCL2) have also shown to play a role in diabetic vascular complications (Herder et al., 2009, Schamarek et al., 2016, Donate-Correa et al., 2015, Zhang et al., 2011,

[7] **Redox (reduction-oxidation) reaction** – the process where a molecule may be oxidised by losing electron(s) or reduced by gaining electron(s).
[8] **Oxidative phosphorylation** – the process in which adenosine triphosphate (ATP) is formed as electrons are transferred to molecular oxygen.

Agrawal and Kant, 2014). Furthermore, in diabetes, serum concentrations of vascular endothelial growth factor (VEGF), a potent pro-angiogenic factor, are increased. The expression of VEGF differs at the several sites of diabetes complications (Shi and Vanhoutte, 2017). Increased expression of VEGF is considered a major mediator of retinal neovascularisation, leading to proliferative diabetic retinopathy, and has shown to play a role in kidney disease and atherosclerotic plague (Costa and Soares, 2013, Forbes and Cooper, 2013). Whereas inhibited angiogenesis, as a result of decreased VEGF expression, contributes to impaired wound healing and myocardial perfusion (Costa and Soares, 2013).

1.3.6 Treatment of major risk factors of diabetes-related vascular complications

Findings from several randomised controlled trials provided evidence that intensive glycaemic control improves microvascular outcomes and may be beneficial in preventing macrovascular events. In individuals with type 1 diabetes, intensive treatment delayed the onset and progression of retinopathy and reduced the risk for albuminuria and neuropathy compared with conventional therapy during a 6.5-year follow-up in the Diabetes Control and Complications Trial (DCCT) (Diabetes Control and Complications Trial Research Group, 1993). Evaluation of the effect of treatment on macrovascular complications was likely not possible due to the young age of participants (≈27 years). However, the risk of CVD was reduced by 57% in the group previously treated with intensive therapy during post-trial follow-up of 17 years in the DCCT/ Epidemiology of Diabetes Interventions and Complications (EDIC) observational study (Nathan et al., 2005). The UK Prospective Diabetes Study (UKPDS), involving newly diagnosed type 2 diabetes patients, reported a 25% and 16% reduction of microvascular events (composite endpoint of retinopathy and renal disease) and myocardial infarction, respectively, in the intensive treatment arm compared with the conventional treatment group over a follow-up of ten years (UK Prospective Diabetes Study (UKPDS) Group, 1998). A continued benefit of the intensive therapy was observed in the post-trial 10-years follow-up, despite the loss of the glycaemic difference between the groups within a year after the trial (Holman et al., 2008).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which included 10,251 participants with type 2 diabetes and a high risk of CVD, was discontinued after 3.5 years due to increased total mortality in the intensive treatment group. An increased total cardiovascular mortality was also apparent (Gerstein et al., 2008). The ADVANCE trial (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation), involving 11,140 patients with type 2 diabetes, reported a 21% reduction in kidney disease and a non-significant reduction in retinopathy and macrovascular events among individuals treated with intensive therapy (Patel et al., 2008). Over a median follow-up of 5.6 years in the Veterans Affairs Diabetes Trial (VADT), comprising predominantly men with long-standing type 2 diabetes, a significant reduction in albuminuria and a non-significant reduction in macrovascular events was found in the intensive care arm compared to the standard therapy group (Duckworth et al., 2009). Hypertension and dyslipidaemia were identically controlled in both arms. Nevertheless, a meta-analysis of five randomised controlled trials in type 2 diabetes (including the UKPDS, ADVANCE, VADT, ACCORD and PROactive [PROspective pioglitAzone Clinical Trial In macroVascular Events] studies) concluded that intensive glucose-lowering treatment reduced substantially non-fatal myocardial infarction and coronary heart disease events; whereas a non-significant effect was observed for stroke (Ray et al., 2009).

There were clear benefits from controlling blood pressure and cholesterol in people with type 2 diabetes by reducing the risk of major cardiovascular events and microvascular endpoints (UK Prospective Diabetes Study Group, 1998, Heart Outcomes Prevention Evaluation Study Investigators, 2000, Pyörälä et al., 1997). Furthermore, an intervention implementing behaviour modification and pharmacological therapy, targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria, more than halved the risk of CVD, kidney disease, neuropathy and retinopathy in people with type 2 diabetes compared with standard therapy (Gaede et al., 2003).

1.3.7 Secular trends of diabetes-related vascular complications

While the adverse effects of diabetes and its vascular complications on global health have long been recognised, and despite the ongoing worldwide estimations of an increasing

diabetes prevalence, data on complication burden are widely lacking. Comparisons of global trends on incidence and mortality of complications are challenging, as the vast majority of the studies originate from high-income countries and due to discrepancies in the diagnostic criteria, methodologies, population characteristics and time periods assessed.

Since the 1990s, consistent decreases were observed in diabetes-related CVD incidence. The age-adjusted relative decline ranged from 13% (in Spain, 2004–2010) to 37% (Republic of Korea, 2006–2013 and Sweden [women], 1996–2003) for acute myocardial infarction; and from 3% (UK, 2004–2009) to 56% (Sweden, 1996–2003) for stroke (Harding et al., 2019). The longest-term data available are from US surveillance records (1990–2010), showing a 68% and 53% absolute reduction in myocardial infarction and stroke, respectively (Gregg et al., 2016b); and a 52% relative decline (1992–2012) for stroke (Harding et al., 2019). A reduction in cardiovascular mortality among persons with diabetes has also been observed, ranging from 46% (Iceland, 1993–2004) to 53% (US, 1988–1994 and 2010–2015). Nevertheless, CVD remains the leading cause of mortality in diabetes, accounting for more than one-third of deaths (International Diabetes Federation (IDF), 2019).

Information on kidney disease, neuropathy and retinopathy is broadly lacking. The incidence of end-stage renal disease declined by 6% per year in the People's Republic of China (2000–2012) among adults with type 2 diabetes and by 28% in the US (type 1 and type 2 diabetes, 1990–2010) (Harding et al., 2019). US surveillance data indicated an increase in hospitalisation rates due to neuropathy (by 42%, 2000–2014), although these data are likely biased due to changes in coding and awareness of neuropathy (Harding et al., 2019). A decline in age-adjusted incidence rates of lower-extremity amputations was observed for most countries, ranging from 3% (Western Australia, 2000–2010) to 84% (Sweden [women], 1996–2003). However, an increase of 5% was observed for Germany (1990–2005) (Harding et al., 2019). Global data for the period 2016–2021 showed increasing rates in minor lower-extremity amputations over this period, while major and higher limp amputations declined (Ali et al., 2022). Incidence trends of diabetic retinopathy were mixed, where increases were observed for Ireland (83%, 2004–2013) and the UK (165%, 2004–2014), while a decrease of 16% was observed in the Republic of Korea (Harding et al., 2019). Data on blindness due to diabetic retinopathy showed a reduced age-adjusted incidence rate in Ireland (53%, 2004–2013) and Scotland (UK, 60%, 2000–2009) in type 2 diabetes. Lastly, a consistent decline in

age-adjusted all-cause mortality has been observed among people with diabetes, ranging from 4% among Taiwanese women (2000–2009) to 37% in Canada (1996–2009). However, a recent study utilising data from the WHO mortality database for the period between 2000 and 2016 reported an increase in age-standardised mortality rates due to microvascular complications in individuals with type 2 diabetes, driven primarily by growth in renal complications (Ling et al., 2020). Mortality rates due to microvascular complications in type 1 diabetes decreased over the same period.

The observed declines in the incidence and mortality of diabetes-related complications are likely attributable to earlier identification of diabetes, improved management and control of risk factors, such as hypertension, dyslipidaemia and hyperglycaemia (see section 1.3.6). Nevertheless, people with diabetes remain at higher risk of developing micro- and macrovascular complications and death than individuals without diabetes (Harding et al., 2019, Rawshani et al., 2017). Importantly, the future character of diabetes complications is unclear as current data do not provide a complete picture. Lack of information from low- and middle-income countries, worldwide rise in obesity, increased incidence of young-onset type 2 diabetes, as well as reduced mortality accompanied with increased total years lived with diabetes render the status of complication burden and progress uncertain (Gregg et al., 2016b, Harding et al., 2019).

1.3.8 Economic impact of diabetes-related vascular complications

Estimates from high-income countries underline the large economic impact of vascular complications on the overall costs of diabetes care. Results from a pan-European study involving individuals with type 2 diabetes showed that costs increased by 70% and 109% with the presence of micro- and macrovascular complications, respectively, compared with persons without complications. The cost of management was 3.5 times higher when both micro- and macrovascular complications occurred (Williams et al., 2002). Data from Germany in 2001 and the US in 2010 estimated that 53% of the medical expenses per patient were due to diabetes-related complications. Of the total complication cost, microvascular events accounted for 27.7% in Germany, while macrovascular complications accounted for 38.8%, and 57% in the US (von Ferber et al., 2007, Zhuo et al., 2013). Furthermore, post-

trial monitoring data from the UKPDS showed that per decade of age, the inpatient complication cost in type 2 diabetes increased by 30–50% and by approximately 5% for non-inpatient care (Alva et al., 2015).

A large German study based on nationwide health insurance data in 2012–2015 among individuals with type 2 diabetes showed that the costliest complications were lower extremity amputations, end-stage renal disease and acute cardiovascular events (myocardial infarction, stroke and ischaemic heart disease). The cost ranged approximately from EUR 9.3 to 28.0 thousand for ischaemic heart disease and end-stage renal disease, respectively, at the first three months of complication onset, which declined in the following months up to two years. However, the reduction in cost did not return to pre-event levels. The cost for retinopathy, coronary heart disease and kidney disease was EUR 5.0 thousand or higher in the first three months of diagnosis. Again, subsequent expenses were higher than pre-diagnosis costs (Kähm et al., 2019).

1.4 Clustering of diabetes-related vascular complications

Hitherto we have seen that micro- and macrovascular complications share common risk factors and pathophysiological mechanisms, which are interconnected via the overproduction of ROS. Indeed, co-occurrence of vascular complications is frequently observed (Arnold et al., 2018, Bjerg et al., 2018b), and there is a growing body of studies supporting that the occurrence of one is associated with the incidence of another one. It is yet to be clarified whether there is a causal link between them or the presence of one is merely an indication of a widespread continuum of vascular injury (Avogaro and Fadini, 2019). An overview of epidemiological studies is provided in the next paragraphs, focusing on type 2 diabetes unless otherwise stated.

1.4.1 Microvascular complications and risk of macrovascular events

In a meta-analysis of eight prospective studies, the presence of diabetic retinopathy was associated with a 1.8 times higher incidence of CVD (Guo et al., 2016), although these

findings were crude. In another meta-analysis of eight population-based studies, with a total of 7604 individuals, which investigated the relationship between severe stages of diabetic retinopathy (proliferative, macular oedema) and CVD, both conditions were positively associated with CVD incidence. However, after adjustment for cardiometabolic risk factors and diabetes duration, the associations were not statistically significant (Xie et al., 2017). Similarly, in a post hoc analysis of the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial involving individuals with a recent acute coronary syndrome, there was no association between baseline retinopathy and myocardial infarction or stroke in fully adjusted models (Seferovic et al., 2018). Among 49,047 participants from the UK Clinical Practice Research Datalink (CPRD) with no history of cardiovascular disease, the occurrence of retinopathy elevated the risk of a subsequent cardiovascular event by 39% (95% CI 1.09, 1.79), after adjusting for established risk factors (Brownrigg et al., 2016).

The CPRD study also reported an increased risk of incident CVD for individuals with baseline kidney disease (HR 1.35; 95% CI 1.15, 1.58) and neuropathy (HR 1.40; 95% CI 1.19, 1.66), with a cumulative burden of microvascular events further increasing the risk (Brownrigg et al., 2016). Moreover, an increased risk of macrovascular events was observed among persons with a microvascular complication in the ADVANCE trial and ADVANCE-ON post-trial study when compared with those with no previous complication in fully adjusted models (Mohammedi et al., 2017). The coexistence of micro- and macrovascular complications at baseline showed the highest risk of macrovascular events.

In a large English primary care cohort, free of CVD at study entry, isolated peripheral neuropathy was associated with an increased risk of CVD, independently of cardiovascular risk factors (Brownrigg et al., 2014b). Furthermore, an excess risk of CVD death was observed among participants with diabetic foot ulcers in a meta-analysis of longitudinal studies and two retrospective studies involving type 1 and type 2 diabetes patients (Brownrigg et al., 2012, Brownrigg et al., 2014a, Chammas et al., 2016). The elevated risk of CVD morbidity and mortality has also been documented with albuminuria and lower GFR in several longitudinal studies, among individuals with and without diabetes (Sarnak et al., 2003, van der Velde et al., 2011, Lee et al., 2010b). Findings from a systematic review of 14 prospective studies suggest that the presence of albuminuria and reduced GFR were associated with approximately twice the risk of developing cardiovascular outcomes in type

2 diabetes, compared with individuals without microvascular disease (Rosenson et al., 2011). Lastly, among 9795 individuals with type 2 diabetes and low CVD risk, albuminuria and reduced estimated GFR progressively increased the risk for macrovascular complications, independently of cardiovascular risk factors (Drury et al., 2011).

1.4.2 Microvascular complications and risk of further microvascular events

In addition to the elevated risk of macrovascular disease with the onset of microvascular complications, epidemiological studies have demonstrated a higher incidence of subsequent microvascular events. Findings from the ADVANCE and ADVANCE-ON study suggest that compared with individuals without complications, the incidence of secondary microvascular events (kidney disease or retinopathy) was approximately five times higher among those with a baseline microvascular complication (Mohammedi et al., 2017). The presence of both micro- and macrovascular complications at baseline elevated the risk of microvascular complications by six-fold.

Kidney disease and retinopathy have been shown to be associated; although, most studies are cross-sectional (Klein and Klein, 2018). Prospective data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) did not show a clear association between proteinuria and proliferative retinopathy in individuals with type 2 diabetes, possibly due to restrictions with the sample size (Klein et al., 1993b). More recent prospective cohort studies reported a positive association of kidney disease with the development of retinopathy after adjusting for cardiometabolic risk factors (Hsieh et al., 2018, Romero-Aroca et al., 2018, Chen et al., 2012, Jeng et al., 2016). The occurrence of retinopathy has been suggested to increase the risk of renal function decline in longitudinal studies, with higher severity of retinopathy being associated with a greater kidney disease progression (Edwards et al., 2005, Yamanouchi et al., 2019, Park et al., 2019b, Pearce et al., 2019). Nevertheless, most of the studies are hospital-based.

Longitudinal studies investigating the associations between retinopathy and neuropathy, as well as kidney disease and neuropathy, in type 2 diabetes are lacking. A recent meta-analysis of cross-sectional studies showed a significant positive correlation between retinopathy and neuropathy (Li et al., 2019). Furthermore, a positive association between

retinopathy and risk of neuropathy was observed in a retrospective analysis of primary care data from German practices. However, there was suboptimal control for confounders. The same study did not find an association in data from UK practices (Kostev et al., 2014). A prospective population-based cohort from Taiwan reported an increased risk of non-proliferative and proliferative retinopathy in individuals with newly diagnosed diabetic neuropathy (unspecified type of diabetes) compared with those without neuropathy (Lin et al., 2015). Similarly, an increased risk of retinopathy was observed with the presence of kidney disease at baseline in type 2 diabetes in a prospective hospital-based study, although there was inadequate adjustment of confounders (Abougalambou and Abougalambou, 2015).

Studies on type 1 diabetes point towards a similar direction. Prospective data from the DCCT showed that progression of retinopathy and development of albuminuria each increased the risk of incidence of the other (Kramer and Retnakaran, 2013). Among 3586 individuals enrolled at the Steno Diabetes Center Copenhagen (SDCC), the presence of each microvascular complication (kidney disease, neuropathy, or retinopathy) increased the risk of developing a subsequent microvascular complication. Moreover, a higher complication burden further elevated the risk (Bjerg et al., 2018a). The DCCT/EDIC study reported that macroalbuminuria was associated with an increased risk of peripheral neuropathy in minimally adjusted models during a follow-up period of more than 23 years (Braffett et al., 2020).

1.4.3 Macrovascular complications and risk of microvascular events

The impact of macrovascular disease on microvascular complications has been investigated to a smaller extent. The ADVANCE and ADVANCE-ON study showed an increased risk of a composite microvascular event (retinopathy, blindness, end-stage renal disease and renal death) and isolated retinopathy in participants with baseline cardiovascular disease compared with persons without complications (Mohammedi et al., 2017). A Taiwanese retrospective population-based study reported an increased risk of kidney disease with a prior cardiovascular disease (Cheng et al., 2015). Furthermore, prospective studies reported a positive association between carotid atherosclerosis and renal function decline (Cardoso et

al., 2019, Takenouchi et al., 2016, Yu et al., 2011, Shimizu et al., 2015), although findings were not consistent (Jenks et al., 2017). Finally, a prospective cohort study of high-risk individuals for CVD showed a positive association between peripheral arterial disease, measured with ankle-brachial index, and incidence of peripheral neuropathy (Cardoso et al., 2018).

1.5 The role of diet and lifestyle on diabetes and vascular disease

The steep rise in type 2 diabetes prevalence and consequently, its vascular complications was fuelled by an increase in obesity, nutritional transition towards processed and high-calorie foods, sedentary lifestyle and smoking. Notably, many of these risk factors are modifiable, and their management could prevent over three-quarters of new type 2 diabetes cases (Steinbrecher et al., 2011, Laaksonen et al., 2010, Rajaobelina et al., 2019, Ibsen et al., 2020). Yet, the effect of modifiable risk factors on diabetes vascular complications remains to a large degree unclear.

1.5.1 Dietary patterns and food groups

As foods are not consumed in isolation, investigation of dietary patterns is an important aspect of nutritional epidemiology, since they may account for inter-relations and synergies of food choices (Schulze et al., 2018). Still, examining individual food groups may provide evidence to identify beneficial or harmful components of diets and contribute to health-care guidelines.

1.5.1.1 Healthy dietary patterns

Meta-analyses of prospective cohort studies showed that higher adherence to the Mediterranean diet, a diet rich in olive oil, fruits, vegetables, nuts, legumes, fish, seafood and moderate alcohol consumption, decreased the risk of type 2 diabetes and CVD (Jannasch et al., 2017, Sofi et al., 2014). Mediterranean diet was also associated with a reduced risk of renal function decline in longitudinal studies in the general population (Bach et al., 2019).

The findings were confirmed in the Prevencion con Dieta Mediterranea (PREDIMED) intervention trial, where a decreased risk of 25% and 31% for diabetes and CVD, respectively, was observed in the Mediterranean diet group compared to the control group (low-fat diet advice) (Salas-Salvadó et al., 2014, Salas-Salvadó et al., 2018). A beneficial effect on kidney function was observed in PREDIMED, but it was not superior to the low-fat diet arm (Díaz-López et al., 2012).

The PREDIMED trial further showed that individuals with type 2 diabetes in the intervention arm had a 29% decreased risk of incident cardiovascular events (Estruch et al., 2018). A post hoc analysis of the PREDIMED data reported a reduction of 41% in incident retinopathy among diabetics in the intervention group compared to the control diet; while no clear association was observed for kidney disease (Díaz-López et al., 2018, Díaz-López et al., 2015). A beneficial effect on renal function with higher adherence to the Mediterranean diet was observed in a case-control study among women with type 2 diabetes. Though, there was an inadequate adjustment of confounders (Jayedi et al., 2019).

Other established dietary patterns are the Dietary Approaches to Stop Hypertension (DASH) diet, the Healthy Eating Index (HEI) and the alternative HEI (AHEI). The DASH diet emphasises the consumption of vegetables, fruits and low-fat dairy and includes whole grains, poultry, fish and nuts, and small amounts of red meat, sweets and sugar-containing drinks (Sacks et al., 2001). The HEI is composed of ten components, such as grains, vegetables, fruit, milk, meat, total and saturated fat, cholesterol, sodium and variety (Kennedy et al., 1995); while the AHEI, which was derived from food choices and sources associated with reduced chronic disease risk, consists of nine (cereal fibre, vegetables, fruit, nut and soy protein, white to red meat ratio, *trans* fat, polyunsaturated to saturated fatty acids ratio, alcohol consumption and multivitamin use) (McCullough et al., 2002). DASH, HEI and AHEI have been shown to have a beneficial effect in preventing type 2 diabetes, CVD and chronic kidney disease in prospective cohort studies in the general population (Jannasch et al., 2017, Schwingshackl and Hoffmann, 2015, van Westing et al., 2020). Among individuals with diabetes, DASH was associated with a decreased risk of macrovascular complications in prospective cohorts (Kahleova et al., 2019); but a positive non-significant association was observed for kidney disease in the Atherosclerosis Risk in Communities (ARIC) prospective study (Rebholz et al., 2016).

1.5.1.2 Individual food groups

Accumulated knowledge on the role of individual dietary components in type 2 diabetes, CVD, and chronic kidney disease in the general population is provided by several prospective cohort studies. Higher whole grain and coffee intake were consistently associated with lower risk of all endpoints, while an increased risk was observed with increased consumption of processed and unprocessed red meat (Mozaffarian, 2016, Schwingshackl et al., 2017a, van Westing et al., 2020, Kennedy et al., 2020, Bechthold et al., 2019). Meta-analyses showed an inverse association between fruit and vegetable intake and type 2 diabetes and CVD (Mozaffarian, 2016, Schwingshackl et al., 2017a, Bechthold et al., 2019). For diabetes risk, increasing intakes up to 300 g/day for fruit and vegetables reduced risk by 10% and 9%, respectively, whereas higher intake did not appear to be beneficial (Schwingshackl et al., 2017a). The few prospective studies on kidney disease indicated a negative association with higher consumption of non-fermented and allium vegetables (van Westing et al., 2020).

An inverse association was found between dairy products, specifically fermented, and cardiometabolic disease in meta-analyses in the general population (Mozaffarian, 2016, Schwingshackl et al., 2017a), with a U-shaped relationship being observed for coronary heart disease (Bechthold et al., 2019). Furthermore, a higher intake of low-fat dairy was inversely associated with chronic kidney disease in the ARIC study (Haring et al., 2017). Higher fish consumption was related with a decreased risk for CVD (Bechthold et al., 2019), whereas no clear association was observed for diabetes and kidney disease (Schwingshackl et al., 2017a, van Westing et al., 2020). An inverse association between nut consumption and kidney disease and CVD was observed in the ARIC study and meta-analyses, respectively (Haring et al., 2017, Bechthold et al., 2019, Mozaffarian, 2016). The role of nuts in diabetes risk is unclear (Mozaffarian, 2016, Schwingshackl et al., 2017a). Sugar sweetened beverages were associated with an increased risk for diabetes and CVD (Bechthold et al., 2019, Schwingshackl et al., 2017a), but studies were conflicting for kidney disease (van Westing et al., 2020).

In terms of diabetes-related complications, prospective data are limited. A linear inverse association between nut consumption and incidence and mortality of macrovascular complications was observed in the Nurses' Health Study and Health Professionals Follow-Up Study (Liu et al., 2019a). Participants who ate 5 or more servings of nuts per week had a

17% reduced incidence of CVD compared with those consuming less than 1 serving per month. A 52% and 48% decreased risk of incident retinopathy was observed with higher consumption of fruits and fatty fish, respectively (Sala-Vila et al., 2016, Tanaka et al., 2013b). Among individuals in the diabetes stratum in the ARIC study, there was an inverse non-significant association between coffee consumption (3 cups/day) and incidence of kidney disease compare with never-drinkers (Hu et al., 2018). In individuals with type 2 diabetes and normo- or microalbuminuria participating in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), there was a decreased risk for incident kidney disease with higher consumption of whole grains, fruits, nuts and seeds, dairy products, and fish in fully adjusted models including baseline albuminuria (Dunkler et al., 2013).

1.5.2 Obesity and weight change

1.5.2.1 Obesity, obesity paradox and vascular disease

Obesity, a condition described as an excess accumulation of adipose tissue, has reached epidemic proportions, and together with overweight, affects more than a third of the global population (Hruby and Hu, 2015). In 2015, the global prevalence of obesity in adults was 12.0%. Since 1980, obesity prevalence has doubled in more than 70 countries out of 195, while a continuous increase was observed for most others (GBD 2015 Obesity Collaborators, 2017). In Europe, during a mean follow-up of six years (1992–1998 to 1998–2005), obesity prevalence increased from 13% to 17%. The overall trends were higher in areas with lower socioeconomic status (Hruby and Hu, 2015). In Germany, obesity prevalence was approximately 23.6% among adults during a survey period from 2008–2011 (Mensink et al., 2013).

Obesity is an established risk factor for a plethora of chronic diseases, including type 2 diabetes, CVD and kidney disease (Dale et al., 2017, Garofalo et al., 2017). Interestingly, two recent meta-analyses, investigating the role of obesity on all-cause and cardiovascular mortality in type 2 diabetes, demonstrated a better survival prognosis among overweight or obese individuals than normal weight persons (Gao et al., 2018, Zaccardi et al., 2017). A

phenomenon commonly known as the 'obesity paradox'. These findings, however, might be artefacts due to methodological limitations, such as reverse causality attributable to pre-existing disease, short follow-up, weight effects of pharmacological treatment, or suboptimal control for important confounders, like smoking (Tobias and Manson, 2018).

Still, the impact of obesity on complications remains controversial, as results from longitudinal studies in type 2 diabetes are inconsistent. Similar to the findings for cardiovascular mortality, several studies on macrovascular events reported an inverse or a U-shaped association. A hospital-based prospective study involving more than 29,000 newly diagnosed diabetes patients reported a significant inverse association between body mass index (BMI) and risk of stroke, that persisted among never-smokers (Li et al., 2015). Furthermore, high BMI was associated with a lower risk of a composite CVD endpoint in two retrospective cohort studies, among which one included over 37,000 participants with newly diagnosed diabetes (Park et al., 2019a, Thomas et al., 2014). A U-shaped association was evident for non-fatal myocardial infarction in the ACCORD study, with the lowest risk being observed at a BMI of 34 kg/m^2 (Xing et al., 2018). Furthermore, reduced risk for macrovascular events was observed in individuals with overweight and obesity compared with normal-weight persons in a large nationwide Korean study (Lee et al., 2018a), and among obese White Europeans participating in a multi-ethnic primary-care study in the UK (Owusu Adjah et al., 2019). However, large prospective studies (>10,000 participants) from the US, Sweden and England reported a positive association between BMI and macrovascular disease (Costanzo et al., 2015, Eeg-Olofsson et al., 2009, Gray et al., 2015).

Heterogeneous results were also observed for microvascular complications, with the outcome definition varying between studies and most of them examining kidney disease. Higher BMI was associated with an increased risk of renal dysfunction in several studies from Europe, Japan and the US (Gray et al., 2015, Rossi et al., 2010, Svensson et al., 2015, Tanaka et al., 2016, Nakanishi et al., 2019). Contrastingly, the WESDR study and two other prospective studies observed no association (Chung et al., 2017, Klein et al., 1997, Mohsen et al., 2012); while a U-shaped association was reported in the ADVANCE study, favouring overweight individuals (Mohammedi et al., 2018). Two small prospective studies among individuals with pre-existing disease showed an inverse association between BMI and renal function (Bentata and Abouqal, 2014, Huang et al., 2014). The few studies that exist on

retinopathy and neuropathy have reported a positive (Gray et al., 2015, Schlesinger et al., 2019a, Tanaka et al., 2016) or no association (Ahmed et al., 2011, Klein et al., 1997, Yoshida et al., 2001). Among studies that have also examined other anthropometric measures, such as waist circumference, have found analogous associations as those reported for BMI. Altogether, most of existing literature was subject to the aforementioned methodological limitations, namely overt diabetes and/or vascular disease, suboptimal adjustment for lifestyle (including diet, physical activity and smoking), short follow-up, or small sample size.

1.5.2.2 Weight change in vascular complications

Evidence from a Cochrane Review of randomised controlled trials with a duration of two or more years indicated that intensive lifestyle modifications aiming at weight loss, through diet and physical activity, may prevent type 2 diabetes in individuals with impaired glucose tolerance, impaired fasting glucose, or both (Hemmingsen et al., 2017). Notably, the Diabetes Remission Clinical Trial (DiRECT) showed that intensive weight management after the onset of diabetes allowed diabetes remission and withdrawal of glucose-lowering drugs in approximately half of the participants (Lean et al., 2018). Furthermore, meta-analyses of randomised clinical trials reported that lifestyle weight loss might improve cardiometabolic risk factors, suggesting a potential beneficial effect on vascular disease prevention (Balk et al., 2015, Franz et al., 2015).

Despite these promising findings, evidence on whether weight loss may benefit diabetes-related complications is limited. To begin with, long-term follow-up of clinical trials that investigated weight loss and diabetes prevention is generally lacking; and those that exist have generated inconclusive results. During ten years of follow-up after the Finnish Diabetes Prevention Study (DPS) ended, lifestyle intervention did not reduce CVD morbidity in persons with impaired glucose tolerance (Uusitupa et al., 2009). Similarly, there was no difference in CVD events between the intervention and control groups over a 20-year follow-up in the China Da Qing Diabetes Prevention study among individuals with impaired glucose tolerance (Li et al., 2008). But after 30 years of follow-up, participants assigned to the intervention group had a 26% and 35% reduced risk of CVD and microvascular events, respectively (Gong et al., 2019). Follow-up data over 15 years in the Diabetes Prevention Program (DPP) study showed no substantial differences in microvascular disease between

the intervention arms. However, among women in the lifestyle intervention group, a lower prevalence of microvascular events was observed (Diabetes Prevention Program Research Group, 2015).

Conflicting data exist on the impact of weight loss on macrovascular complications in type 2 diabetes. Weight loss through an intensive lifestyle intervention did not reduce the 10-year CVD risk in the Action for Health in Diabetes (Look AHEAD) trial (Look AHEAD Research Group, 2013); only post hoc analyses indicated that a weight loss of at least 10% of body weight reduced CVD incidence by 21% (Gregg et al., 2016a). Secondary analysis of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Cambridge) trial showed that ≥5% weight loss within a year after diabetes diagnosis decreased the 10-year CVD incidence by 48% (Strelitz et al., 2019b). This difference may be explained by the fact that the Look AHEAD initiated weight loss on average seven years after diabetes onset. However, secondary analyses in newly diagnosed individuals participating in the Diabetes Care in General Practice (DCGP) study reported that intentional weight loss of 1 kg annually over six years was related to an increased non-significant CVD risk (Køster-Rasmussen et al., 2016). Post hoc analysis of the ACCORD study data with a mean follow-up of eight years showed a U-shaped non-significant association for non-fatal myocardial infarction, where participants with stable weight had the lowest risk (Xing et al., 2019). A large prospective cohort study among newly diagnosed individuals observed a positive association between weight gain and stroke during a 2-year follow-up. No association was observed for myocardial infarction as well as between weight loss and any cardiovascular outcome (Kim et al., 2019).

Regarding the relationship between weight change and microvascular complications, data are scarce and rather preliminary. Intentional weight loss through lifestyle or medical therapy might improve renal outcomes in obese individuals with type 2 diabetes but studies are frequently short-term and include individuals with overt kidney disease (Holland et al., 2019). Post hoc analysis of the Look AHEAD trial showed that individuals in the intensive lifestyle intervention group had a reduced incidence of very-high-risk kidney disease than the comparator group (Look AHEAD Research Group, 2014). Furthermore, lifestyle interventions may improve neuropathy symptoms in people with impaired glucose tolerance (Smith et al., 2006).

1.5.3 Other lifestyle factors

Other lifestyle factors, such as physical activity, smoking and alcohol consumption, may also contribute to the course of vascular health secondary to diabetes.

1.5.3.1 Physical activity

Several health benefits of physical activity have been demonstrated in persons with diabetes. That is, improvements in insulin sensitivity and cardiovascular risk factors, as well as in reducing inflammation and oxidative stress (Amaral et al., 2020). Small-scale clinical trials ranging from six weeks to four years examining the effects of physical activity in diabetes patients showed a reduction in microalbuminuria (Lazarevic et al., 2007), delay in peripheral neuropathy progression (Balducci et al., 2006, Dixit et al., 2014, Gholami et al., 2018, Kiani et al., 2018) and reduction of neuropathic symptoms and pain (Kluding et al., 2012). Furthermore, a meta-analysis of randomised controlled trials ranging from eight to 52 weeks and involving a total of 266 individuals with type 2 diabetes reported that regular exercise significantly improved cardiorespiratory fitness (Boulé et al., 2003).

In a meta-analysis of 11 longitudinal cohort studies (one retrospective and 10 prospective studies) with a follow-up period from five to 21 years, there was a consistent decreased risk of macrovascular complications with higher physical activity levels in persons with diabetes (Kodama et al., 2013). There was no clear association between physical activity and retinopathy in a meta-analysis of longitudinal cohort studies, with high heterogeneity between the studies that could not be explained by the type of diabetes, adjustments, or geographic location (Ren et al., 2019). Assessment methods of physical activity varied considerably across studies.

There are relatively limited data for diabetes-related kidney disease and peripheral neuropathy. Compared with sedentary persons, regular physical activity decreased the risk of kidney disease development and progression in diabetes type 2 (Dunkler et al., 2015b, Chen et al., 2015) and type 1 (Wadén et al., 2015) in prospective studies. A retrospective study in type 2 diabetes showed a negative association between physical activity and kidney disease (Lin et al., 2014). No association was observed between physical activity and peripheral neuropathy in the DCCT/EDIC study over a follow-up of 23 years of individuals

with type 1 diabetes (Braffett et al., 2020); while an inverse association was reported in a retrospective study among ethnic Chinese individuals with type 2 diabetes (Chiang et al., 2016). Overall, except for two (Lin et al., 2014, Wadén et al., 2015), studies did not control for smoking status.

1.5.3.2 Smoking

Smoking was associated with a more than 40% increased risk of coronary heart disease, stroke and myocardial infarction secondary to diabetes in a meta-analysis of prospective studies. The excess risk was not influenced by the type of diabetes, years of follow-up and participants' sex or age. A greater risk was evident among current smokers than former smokers (Qin et al., 2013). Prospective data from the Framingham Offspring Study over a mean follow-up of 25 years showed that smoking cessation was associated with a decreased risk of CVD events after controlling for established CVD risk factors and weight change (Clair et al., 2013).

Meta-analyses of observational studies showed a positive association between smoking and albuminuria in participants with diabetes (Kar et al., 2019, Xu et al., 2018a). Four prospective studies in type 2 diabetes indicate a 16% increased risk for smokers compared with non-smokers; with limited evidence pointing towards a dose-dependent relationship (Xu et al., 2018a). Furthermore, smoking was associated with kidney disease progression in prospective studies in type 2 diabetes (Rossing et al., 2004, Yokoyama et al., 1997), although findings were not consistent (Dunkler et al., 2015b). Quitting smoking ameliorated the progression of renal dysfunction in individuals with type 2 diabetes and microalbuminuria after initiation of a smoking cessation intervention, compared with participants who continued smoking (Phisitkul et al., 2008, Voulgari et al., 2011).

The relationship between smoking and retinopathy in type 2 diabetes is not clear. Meta-analysis of 21 longitudinal cohort studies in type 2 diabetes with follow-up ranging from two to 14 years indicated that ever/current smokers had a 4% (95% CI 0.91, 1.01) reduced risk of retinopathy compared to non-smokers (Cai et al., 2018), with studies reaching no consensus. The same study reported a significant positive association between smoking and incident retinopathy in type 1 diabetes. Similarly, the impact of smoking on peripheral neuropathy in type 2 diabetes is uncertain. Pooled estimates of ten prospective studies with

a follow-up period of two to ten years combining type 1 and type 2 diabetes showed an increased risk among smokers compared to non-smokers (Clair et al., 2015). However, no clear association was apparent in a separate analysis for type 2 diabetes that combined estimates from three studies with a follow-up period of three to five years.

1.5.3.3 Alcohol intake

Meta-analyses have described the relationship of habitual alcohol intake with incident type 2 diabetes (26 studies) and coronary heart disease (31 cohorts) in the general population by a U-shaped curve, favouring moderate alcohol consumption (Ronksley et al., 2011, Li et al., 2016). Furthermore, an inverse association was observed for incident kidney disease combining data from 25 prospective cohort studies (Yuan et al., 2021).

The relation of alcohol intake and diabetes-related vascular complications is less investigated. The Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS) demonstrated that light to moderate alcohol intake was inversely associated with incident coronary heart disease compared with non-drinkers (Solomon et al., 2000, Ajani et al., 2000). The HPFS further reported that the type of alcoholic beverage (wine, beer, or liquor) did not alter this association (Tanasescu et al., 2001). Post hoc analysis of the ADVANCE study data also showed that compared with abstinent individuals, a moderate alcohol intake decreased the risk for cardiovascular and microvascular events secondary to type 2 diabetes. Similarly to the HPFS, the type of alcohol did not substantially influence the observed associations (Blomster et al., 2014).

Moderate alcohol consumption was associated with a decreased risk of kidney disease in the ONTARGET study during 5.5 years of follow-up (Dunkler et al., 2015b). No association was observed between alcohol consumption (continuously assessed) and incidence or progression of retinopathy in the WESDR study over four years of follow-up in type 2 diabetes (Moss et al., 1994). But heavy drinking (>10 pints of beer or equivalent per week vs ≤10) was associated with retinopathy development in unadjusted models among 466 men with diabetes (unspecified) and free of retinopathy at baseline during five years follow-up (Young et al., 1984). Regarding peripheral neuropathy, the DCCT/EDIC study reported an increased non-significant association with occasional or regular drinking than non-drinkers (Braffett et al., 2020).

1.6 Prognostic risk scores of diabetes-related vascular complications

Prognosis or prediction refers to estimating the probability of the occurrence of a future event. This event might be illness, complications, or death. To estimate such probabilities, prognostic risk scores are developed, which use a number of predictors (individual's characteristics) of the event of interest and provide event probabilities (absolute risk) over a defined time frame for different combinations of these predictors (Moons et al., 2009). Risk scores are particularly useful tools to identify eligible participants for clinical research, make clinical decisions in primary care, or for individuals to inform themselves about their disease risk or disease progression.

The value of a risk score lies in its ability to accurately quantify the predicted risk (calibration) and discriminate between individuals with and without the studied outcome (discrimination). Discrimination can be quantified using the area under the receiver operating characteristic curve (AU-ROC) or C-statistic. Values of more than 0.7 indicate good/acceptable discrimination, more than 0.8 is considered excellent and more than 0.9 is considered outstanding. An additional requirement for risk scores is to be externally validated, as its performance is generally poorer in a new cohort different from the derivation population (Altman et al., 2009).

1.6.1 Risk equations for CVD in type 2 diabetes

Several risk prediction models have been generated for cardiovascular complications of type 2 diabetes. A recent systematic review identified 15 risk scores developed for individuals with diabetes and 11 scores developed in the general population but validated in diabetes cohorts (Chowdhury et al., 2019). The review considered only studies that were conducted in population-based cohorts. The endpoint definition varied considerably between them. Additionally, a risk equation for cardiovascular events was developed using data from the ACCORD study (RECODe, Risk Equations for Complications Of type 2 Diabetes) (Basu et al., 2017).

Among the 16 diabetes-specific risk scores (i.e., 15 from the systematic review and the RECODe equation), the median number of predictors was nine with a range of 4–18. The most common predictors were age, sex, diabetes duration, smoking status, prior CVD event, systolic blood pressure, and biomarker measurements for glycaemia (mainly HbA1c), blood lipids and albuminuria. Internal discrimination ranged from 0.60 to 0.80. A few studies provided risk equations that additionally included biomarkers such as interleukin-6, interleukin-15, high-sensitivity troponin T, activin A, apolipoprotein C-III, soluble receptor for AGE and N-terminal pro-brain natriuretic peptide (NT-proBNP). Inclusion of those biomarkers improved the discriminatory ability of the risk scores, with the internal discrimination ranging from 0.72 to 0.91 (Price et al., 2014, Looker et al., 2015, Ofstad et al., 2013). Nevertheless, the applicability of risk equations with novel biomarkers is limited, as they are not commonly available in physician-independent settings or clinical practice. External validation was performed in eight of the diabetes-specific risk scores. Five of them were validated multiple times by four or five cohorts. Pooled C-statistic ranged from 0.66 (95% CI 0.60, 0.72) for the UKPDS risk engine to 0.70 (95% CI 0.59, 0.81) for the Fremantle diabetes study risk equation (Chowdhury et al., 2019). The C-statistic for studies that were externally validated by one cohort ranged from 0.72 (95% CI 0.65, 0.78) to 0.73 (95% CI 0.71, 0.75). The highest C-statistic was reported by the RECODe, which also showed high external and internal calibration (Basu et al., 2017).

The risk scores that were developed in the general population (n=11) showed lower overall external discriminatory ability. Three of them had multiple validations and were generated in the Framingham Heart Study for a 12-year follow-up period. All three prediction equations included blood pressure, total cholesterol, high-density lipoprotein (HDL) or low-density lipoprotein (LDL) and smoking (Anderson et al., 1991, Wilson et al., 1998, D'Agostino et al., 2008). The C-statistic ranged from 0.64 (95% CI 0.61, 0.66) to 0.67 (95% CI 0.62, 0.71). The other eight risk scores had a single external validation with the C-statistic ranging from 0.59 (95% CI 0.52, 0.67) to 0.80 (95% CI 0.75,0.85). The Joint British Societies Risk Chart had the highest external discrimination, but there was poor calibration (Chowdhury et al., 2019).

1.6.2 Risk equations for microvascular complications in type 2 diabetes

Increasing prognostic models for several renal outcomes have been proposed. The most common predictors were age, sex, ethnicity, smoking status, HDL cholesterol, HbA1c, albumin:creatinine ratio and prior CVD event. Among risk equations that predicted early kidney disease (n=5), external validation was performed for three of them with a C-statistic of 0.66 and 0.68 (Dunkler et al., 2015a) and an AU-ROC of 0.77 (Jiang et al., 2020). Poor internal discrimination was found for the other two (C-statistic ≤0.65) (Basu et al., 2017, Jardine et al., 2012). Three prediction models for overt renal disease showed good to excellent internal discrimination with the AU-ROC/C-statistic ranging from 0.77 to 0.84, but external validation was not performed (Aminian et al., 2020, Tanaka et al., 2013a, Basu et al., 2017).

Several prediction models for end-stage renal disease from ten studies have been suggested. Derivation cohort size ranged from 641 to more than 149,000 participants. Six studies (13 models) reported excellent internal discrimination with an AU-ROC/C-statistic higher than 0.84 (Elley et al., 2013, Jardine et al., 2012, Wan et al., 2017, Desai et al., 2011, Lin et al., 2017, Sun et al., 2020). The C-statistic for ten models, derived from the Chronic Kidney Disease Japan Cohort Study, showed poor (0.56, two predictors) to excellent internal discrimination (0.88, seven predictors) (Hasegawa et al., 2019). One study did not report any discrimination measure (Keane et al., 2006). Four models derived from a cohort of individuals with diabetic kidney disease were externally validated. The C-statistic for the derivation cohort (n=641) ranged from 0.61 to 0.98, while for the validation cohort (n=280) from 0.51 to 0.88. (Cheng et al., 2020). The UKPDS Outcomes Model 2 was externally validated by three cohorts with a pooled C-statistic of 0.55 (Buchan et al., 2021). The RECODe developed separate equations for end-stage renal disease (internal C-statistic=0.60; pooled external C-statistic [3 cohorts] 0.73), a composite of macroalbuminuria, renal disease progression (doubling of serum creatinine, or >20 mL/min per 1.73 m^2 in estimated GFR) and end-stage renal disease (internal C-statistic=0.73), and a composite of microalbuminuria, macroalbuminuria and end-stage renal disease (internal C-statistic=0.61; external C-statistic 0.65) (Basu et al., 2017, Buchan et al., 2021).

RECODe also developed separate risk equations for several endpoints of neuropathy, using as predictors age, sex, ethnicity, systolic blood pressure, prior CVD event, HbA1c, total and HDL cholesterol, serum creatinine and urine albumin:creatinine ratio. The neuropathy outcomes were Michigan Neuropathy Screening Instrument score higher than 2 (C-statistic=0.60), vibratory sensation loss (C-statistic=0.64), ankle jerk loss (C-statistic=0.57) and pressure sensation loss (C-statistic=0.62). External validation was feasible only for the pressure sensation loss endpoint, with a C-statistic of 0.69 (95% CI 0.63, 0.74) (Basu et al., 2017).

A systematic review identified 16 prognostic models predicting retinopathy in type 2 diabetes, which were developed in studies with more than a year follow-up period (van der Heijden et al., 2020). Most studies used moderate to severe retinopathy as endpoint; two of them predicted blindness and two unspecified retinopathy. The most common predictors were age, sex, diabetes duration, HbA1c, systolic blood pressure, total cholesterol and presence of retinopathy. The internal discrimination was reported for 11 risk scores ranging from 0.55 to 0.90. Among risk scores with C-statistic (internal) higher than 0.70, only one presented external discrimination (C-statistic was between 0.78 and 0.82, in three different populations) (Scanlon et al., 2015). External validation was reported for four more risk equations, ranging from 0.57 (95% CI 0.51, 0.63) for RECODe (Basu et al., 2017) to 0.76 (95% CI 0.74, 0.78) for a risk equation tested in the Danish diabetes database (Aspelund et al., 2011). Van der Heijden and colleagues validated eight of the identified risk scores using data from the Hoorn Diabetes Care System cohort with more than 10,000 participants (van der Heijden et al., 2020). The risk score tested in the Danish diabetes database showed the highest discrimination for sight-threatening retinopathy and photocoagulated or proliferative retinopathy, with a C-statistic equal to 0.83 (95% CI 0.81, 0.84) and 0.89 (95% CI 0.8, 0.91), respectively. The risk equation developed in the Japan Diabetes Complications Study/ Japanese Elderly Diabetes Intervention Trial (JDCS/J-EDIT) had the highest discriminatory ability for moderate retinopathy (C-statistic 0.76; 95% CI 0.75, 0.78).

2.
Study aims and rational

Diabetes-related vascular disease poses a major threat to human well-being and health-care systems worldwide. Despite the advances in understanding the pathophysiology of diabetes complications, treatment is based primarily on managing major cardiometabolic risk factors. While it is certainly possible to stabilise the disease, therapies that reverse vascular complications once established remain elusive (Forbes and Fotheringham, 2017). Importantly, optimisation of lifestyle may delay the onset and progression of vascular injury.

The relationship between lifestyle and diabetes has been investigated to a great extent. However, given the evidence described in this literature review, it is clear that there are several gaps in our knowledge regarding the link between lifestyle and chronic vascular complications of type 2 diabetes. This is largely due to the lack of well-designed longitudinal studies. Motivated by a cohort of individuals with incident type 2 diabetes embedded in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, this thesis aims to i) identify risk factors of vascular complications, with a focus on lifestyle, ii) address methodological limitations of previous literature, and iii) provide comparative data between micro- and macrovascular complications. Alongside these core aims, the present work centres on three main objectives described in the following.

Objective 1. Development of microvascular and macrovascular complications and the concurrent effect of lifestyle factors

Life expectancy is increasing, and so does for individuals with diabetes, meaning that more years are lived with diabetes and its complications, thus, altering the disease profile of this population by increasing the risk of further complications. In clinical practice, the co-existence of multiple diabetes-related complications is common, and past literature suggests that the occurrence of one is related to the development of another one (see section 1.4). However, they have been studied mainly in isolation of individuals' complication burden, and our knowledge of the longitudinal patterns of their clustering is limited. Undoubtfully, intermediate events may exacerbate or hinder the risk of developing the outcome of interest. Quantifying risk of complication incidence by incorporating intermediate states that the individual encounters over time and including state-specific covariates may allow the analysis of life history data that frequently occur in a clinical setting (Andersen, 1988).

Therefore, one objective (**Objective 1a**) was to investigate the sequence of events associating diabetes complications with the incidence of further complications using multistate modelling. Furthermore, multistate models provide a helpful framework to investigate the association between lifestyle factors, alone and combined with current complication load, and incidence of complications (**Objective 1b**). In this work, eight lifestyle factors were considered for investigation: BMI, waist circumference, smoking status, and habitual intake of coffee, whole grains, red meat, and alcohol. The selection was based on the fact that there is an accumulated and consistent evidence on their relationship with type 2 diabetes and other chronic diseases (see section 1.5).

Objective 2. BMI and BMI change following diabetes diagnosis and risk of microvascular and macrovascular complications

Given the controversy in the literature concerning the association between obesity and vascular complications (see section 1.5.2.1), an in-depth investigation was performed in order to address the methodological limitations that may have resulted in the paradoxical observations (**Objective 2a**). BMI was selected to assess obesity for three main reasons. Firstly, BMI is the most commonly used obesity measure in epidemiological studies and clinical practice, as it offers an easy and simple tool. Secondly, weight was collected in all

follow-up rounds of the EPIC-Potsdam study, as opposed to waist circumference. Thirdly, BMI and waist circumference showed similar associations with diabetes complications in the current data as well as previous studies.

Weight loss of more than or equal to 5% of body weight is routinely recommended in individuals who are overweight or obese at diagnosis of diabetes type 2 (American Diabetes Association, 2020). Yet, epidemiological studies have not reached a consensus on the effect of weight loss on diabetes complications, and studies on microvascular complications are limited (see section 1.5.2.2). Thus, the association between BMI change following diabetes diagnosis and risk of vascular complications was evaluated (**Objective 2b**).

Objective 3. Application of the German diabetes risk score and cardiovascular disease risk score for prediction of microvascular and macrovascular complications

As with type 2 diabetes, the development and progression of vascular injury is a clinically silent process. Diabetes complications may take years to be diagnosed, deteriorating the patient's prognosis. Thus, alternative earlier screening approaches are of utmost importance. Several risk assessment tools have been proposed to identify individuals at high risk of diabetes complications (see section 1.6). Five CVD risk scores were externally validated in the EPIC-Potsdam among participants with type 2 diabetes, showing low discriminatory ability (C-statistic from 0.61 [0.52–0.70] to 0.68 [0.60–0.76]) (van der Leeuw et al., 2015). Simple recalibration of the risk models resulted in acceptable estimates of absolute risk. To the best of my knowledge, there is no risk score for microvascular complications of type 2 diabetes developed or adapted for German populations.

Within the EPIC-Potsdam study, the German Diabetes Risk Score (GDRS) and a recent CVD Risk Score (CVDRS) were developed, which can be used to estimate an individual's risk for type 2 diabetes and CVD, respectively (Mühlenbruch et al., 2014a, Mühlenbruch et al., 2014b, Schiborn, 2020, Schulze et al., 2007). Both have demonstrated good internal and external predictive performance and provide a clinical and a non-clinical version, making them valuable tools in a medical and at-home setting. In fact, the GDRS is available as an online tool (https://drs.dife.de), which in addition to diabetes risk assessment, provides personalised behavioural recommendations and allows to explore how changes in modifiable

risk factors affect future risk. Likewise, CVDRS will be available as an online tool in the near future. Major predictors of the DGRS and CVDRS include obesity, prevalent hypertension, smoking status, family history of disease, and intake of coffee, whole grains and red meat (see **Table 3.4** in section 3.3.3). These components are not only risk factors of type 2 diabetes and CVD but may also affect the course of vascular complications (see section 1.5). Therefore, the association of the GDRS and CVDRS with diabetes complications was investigated (**Objective 3a**) to assess whether individuals with a high-risk profile for diabetes and CVD also have a greater risk of complications. Moreover, the discriminatory performance of the scores for complications was evaluated (**Objective 3b**).

3.
Materials and methods

3.1 Overview of the chapter

This chapter presents the EPIC-Potsdam study design and analytical study population (section 3.2), followed by a description of the data assessment (section 3.3), and finally, detail the statistical methods applied (section 3.4). In particular, section 3.4 starts with an introduction of the theoretical background of the statistical methods used in this work (section 3.4.1 and beginning of 3.4.2). The statistical approaches utilised for handling missing data and achieving each objective are depicted in the remainder of section 3.4.2 and section 3.4.3, respectively. The reader not interested in the formal details of the statistical theory may skip section 3.4.1 and the beginning of section 3.4.2 and proceed section 3.4.2.1, 'Missing data overview'.

3.2 Study design and population

The EPIC project is a network of prospective cohort studies established to investigate the complex relationship of diet and lifestyle with the occurrence of cancer and other chronic diseases. The rationale behind the EPIC study was to provide a cohort with adequate overall power to identify diet-disease relationships by increasing between-participant variations

(combining study populations with heterogeneous lifestyles and dietary habits and varying disease incidence rates), as well as by decreasing the random measurement error (utilising a combination of different dietary assessment methods, repeated measurements and biomarkers) (Riboli and Kaaks, 1997).

The recruitment of apparently healthy individuals was initiated in 1992 from 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the UK). The EPIC cohort consists of 521,468 participants (366,521 women and 154,947 men), mostly aged 34 to 69 years (Gonzalez, 2006). The choice of study populations was not required to be a random sample of defined populations, but it was based on geographical and logistical criteria to achieve high participation and long-term follow-up (Riboli et al., 2002). At recruitment, the core protocol included the collection of data on lifestyle, education, occupational history, previous illness, anthropometry, blood samples for long-term storage, and food frequency questionnaires (FFQ-s) for collection of dietary information (Riboli et al., 2002). Each participating country was requested to develop and validate the FFQs according to national dietary habits (Kaaks et al., 1997). Participants were contacted at regular intervals to obtain information on lifestyle and other variables that may have changed over time and followed up to detect the incidence of chronic diseases.

The German EPIC group, the first large-scale prospective epidemiological study in Germany, entails two centres located in Potsdam and Heidelberg (Boeing et al., 1999b). For the purposes of the present work, data from the EPIC-Potsdam study were used. The information provided henceforth concerns the Potsdam cohort.

3.2.1 Recruitment procedures

The study population was selected from the city of Potsdam (approximately 140,000 inhabitants) and the surrounding small to middle-sized towns and rural communities, with the aim of recruiting 30,000 participants (Boeing et al., 1999b). According to the core protocol of the EPIC project, the target population was women aged 35–64 years and men aged 40–60 years at the time of recruitment. The resident registries of the selected municipalities periodically provided a random sample from the general population that met the age criteria (Boeing et al., 1999a). Due to public relations activities, interested individuals

were able to contact the study centre independently. The age criteria were not strictly applied; individuals who exceeded the age limit before examination or did not meet the age criteria precisely but showed interest in participating were accepted as study participants (Boeing et al., 1999a).

The recruitment period was from August 1994 to September 1998. Individuals received a personal invitation by mail five weeks before a predefined examination date. If individuals did not respond to the first letter within two weeks, a reminder invitation was sent. Participants who did not attend the agreed appointment at the examination centre were reminded by trained staff via a phone call. The participation rate was 22.7%, with a considerable variation by municipality and gender. By the end of the recruitment period, almost 100% of eligible individuals in the study region were contacted (Boeing et al., 1999a). In total, 27,548 individuals (16,644 women and 10,904 men) were enrolled, aged mainly 35 to 64 years (age range: women 19–70 years; men 22–69 years) (Schulz et al., 2005). The final study population had a more favourable socioeconomic status and health-related indicators than the source population.

3.2.2 Follow-up procedures

Follow-up started in 1998 and was implemented every two to three years, where participants received the follow-up questionnaires via mail. A staff member offered personal support, either at home or the study centre, to individuals who encountered difficulties completing the questionnaires. In addition, missing information deemed essential for the study, such as contact details of the treating physicians, was filled in with telephone interviews (Bergmann et al., 1999).

Participants who did not respond within two weeks of the initial letter were reminded via a phone call, or where not possible, by mail. In Germany, the mail forwarding system operates for up to one year; thus, some of the participants who changed address received the questionnaire along with a reminder to submit the new address and phone number. In case the initial mail was returned to the study centre undelivered, an inquiry at the resident registry was made. A similar procedure was applied for those who could not be reached via the

phone. The resident registry provided the new address or notified that the old address was valid or that the person was deceased (Bergmann et al., 1999).

Due to the repeated reminder activities and comprehensive tracing system, vital status was ascertained for nearly 100% of the study population and the response rate was higher than 90% for all follow-up rounds up to December 2009 (end of fifth follow-up).

3.2.3 Incident type 2 diabetes cohort

For the purposes of the present study, only individuals with incident type 2 diabetes were included. Overall, 1601 participants with incident type 2 diabetes were identified between recruitment and December 2009. In May 2014, participants' treating physicians were asked to provide information on diabetes-related micro- and macrovascular complications extracted from medical records. Individuals for whom information on vascular complications could not be retrieved were excluded from the analysis (n=234). Participants diagnosed with myocardial infarction, stroke, kidney disease, or neuropathy before diabetes diagnosis (n=138) were further excluded. Additional exclusions were applied for the three study objectives (**Figure 3.1)**. For the first objective, prevalent heart failure cases (n=30) at diabetes diagnosis were excluded, leaving 1199 participants for analysis. For the second objective, the analytical study population included 1083 persons after excluding prevalent heart failure and cancer cases at diabetes diagnosis (n=146). The exclusions were made to prevent bias due to pre-existing disease. For the third objective, three participants with missing information on units of smoke per day were excluded, resulting in 1226 participants in the analytical sample.

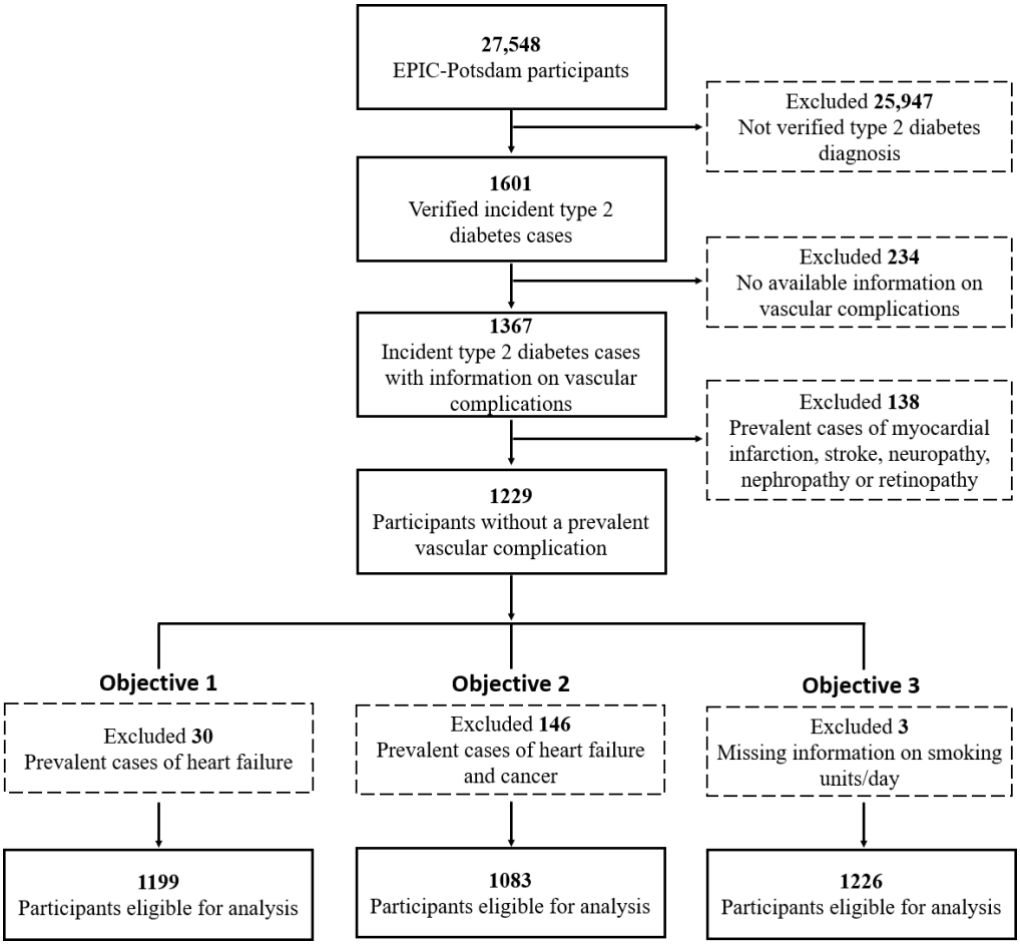

Figure 3.1 Flowchart of sample size derivation for each study aim

3.2.4 Ethics

The study protocol of the EPIC-Potsdam study was approved by the ethics committee of the Medical Society of the State of Brandenburg, Germany (reference number: "AS 29/93" 07/11/1993). A leaflet with brief general information about the study and examinations was enclosed with the invitation letter. In addition, all examinations were described in detail before enrolment during the first visit at the study centre. All participants provided written informed consent prior to enrolment in the study. It was clarified that they have the right to withdraw from the study at any time without explanation.

Experienced medical staff performed blood sampling, and well-trained personnel was involved in the data collection. The training sessions were regularly updated based on protocols for blood collection and processing, measurements and surveys. The quality of the

collected data was continuously monitored throughout the study. The data was stored in accordance with the provisions of the Brandenburg Data Protection Act and the agreements with the Data Protection Officer of the State of Brandenburg, Germany. All data collected was stored or evaluated in a database under a pseudonymized form, without any direct reference to participants' data to be identified.

3.3 Data assessment

During the recruitment phase, invited individuals who agreed to a personal appointment at the study centre received an FFQ and a lifestyle questionnaire by mail. Individuals were requested to have the completed questionnaires with them for their scheduled appointment. The data collection included face-to-face interviews with quality control and immediate inspection of implausible values, optical reading of the questionnaires with a computerised completeness check and physical examinations. Double entry of anthropometric data and blood pressure measurements was applied. All interviews and examinations were conducted by trained personnel who were regularly supervised and followed standard protocols (Kroke et al., 1999a).

During follow-up, data collection was conducted every two to three years or periodically via self-administered questionnaires sent via mail (**Table 3.1**). The assessment tools and procedures followed for data collection are described in the following sections.

Table 3.1 Information collected at recruitment and follow-up in the EPIC-Potsdam study [adapted from (Polemiti et al., 2021)]

	Recruitment	Follow-up				
		1st	2nd	3rd	4th	5th
	(1994–1998)	(1997–2001)	(1999–2003)	(2001–2005)	(2004–2008)	(2007–2009)
Sociodemo-graphic	Age, sex, education					
Diet and lifestyle	Dietary habits, Physical activity, alcohol intake, smoking status, units/day & duration	Smoking status[a]	Physical activity, alcohol intake, smoking status, units/day & duration	Dietary habits, alcohol intake, smoking status & duration	Physical activity, smoking status, units/day & duration	Physical activity, alcohol intake, smoking status, units/day & duration
Anthropometry and medical information	Weight, height, waist circumference, medical history, blood pressure, blood sampling	Weight, medical history, medication	Weight, medical history, medication	Weight, medical history, medication	Weight, waist circumference, medical history, medication	Weight, medical history, medication, family history (mother, father, siblings) of MI, stroke or type 2 diabetes

[a] It was based on subsequent follow-up information on smoking status and year of giving up smoking

EPIC, European Prospective Investigation into Cancer and Nutrition; MI, Myocardial Infarction

3.3.1 Dietary intake and lifestyle assessment

3.3.1.1 The habitual diet

At recruitment, a 148-item self-administered FFQ (FFQ_{REC}) was developed to assess the habitual dietary and nutrient intake over the past 12 months. Additional questions were included regarding the fat content of dairy and meat products, types of fat used for food preparation, and added sugar in beverages. Food intake frequency was ranked in ten categories ranging from 'never', 'one time per month or less' to 'five times per day or more' (Brandstetter et al., 1999). Coloured photographs and, if available, standard portion sizes were displayed for each food item to estimate portion sizes (Example page, **Appendix 1**).

The single food item list and portion sizes were defined by the German National Nutrition Survey, in which 7-day records of dietary intake were collected from approximately 22,000 individuals; while foods and dishes consumed by a subgroup of 1000 participants were grouped into 340 single food items and 25 food groups. Food items contributing substantially to the consumption of the respective food group were selected for inclusion in the FFQ_{REC} (Bohlscheid-Thomas et al., 1997b). The single food items included in the dietary questionnaire were classified into 49 food groups based on their nutrient content, culinary usage, as well as experiences from other studies (Schulze et al., 2001).

A major challenge in nutritional epidemiology is to develop instruments for evaluating the habitual, long-term food and nutrient intake accurately and inexpensively while minimising the respondent's burden. As per the core protocol of the EPIC study, the validity and reproducibility of the FFQ_{REC} were evaluated (Kaaks and Riboli, 1997). The relative validity was assessed using a 24-hour dietary recall (24-HDR) once a month for a year and the reproducibility by completing the FFQ_{REC} twice over a six-month interval. The 24-HDRs were carried out through face-to-face interviews, spread across the week (Monday to Friday). Spearman rank correlation on the food group level in 104 potential EPIC cohort members indicated a moderate to good relative validity, ranging from 0.42 for cereals to 0.90 for alcoholic beverages (**Table 3.2**) (Bohlscheid-Thomas et al., 1997b). Reproducibility correlation was lower for bread (0.49) and moderate to good for the remaining selected food groups, ranging from 0.57 for fats to 0.89 for alcoholic beverages (**Table 3.2**). Further studies

on the validity and reproducibility of the FFQ_{REC} have been conducted at the micro- and macronutrient level (Boeing et al., 1997, Bohlscheid-Thomas et al., 1997a, Kroke et al., 1999b).

The FFQ_{REC} at recruitment was self-administered, but often interviewer assistance was necessary to ensure complete responses. Therefore, the FFQ_{REC} was deemed unsuitable for the follow-up collection of dietary intake data that would be exclusively self-administered. A shorter and simpler FFQ (FFQ_{FUP}) was developed for the follow-up of the EPIC-Potsdam study to ensure a high response but still reflect variation in dietary behaviour. The FFQ_{FUP} included 102 items, which showed to be the most informative to discriminate between participants according to nutrient and food intake from FFQ_{REC} (Nöthlings, 2004). As portion sizes showed to be of minor importance in measuring intake variance, food intake frequency was inquired in a semiquantitative format of specified portion sizes, provided as household measures (Example page, **Appendix 2**). The FFQ_{FUP} was applied in the third follow-up round.

Table 3.2 Validity and reproducibility of intake levels of selected food groups estimated by the food frequency questionnaire [adapted from (Bohlscheid-Thomas et al., 1997b)]

Food group	Validity[a] (24-HDR vs FFQ_{REC})	Reproducibility[a] (FFQ_{REC-1} vs FFQ_{REC-2})
Meat	0.53	0.77
Bread	0.51	0.49
Cereals	0.42	0.73
Fats	0.43	0.57
Coffee, tea	0.70	0.71
Soft drinks	0.67	0.65
Alcoholic beverages	0.90	0.89

[a] Assessed with Spearman rank correlation coefficient

24-HDR, 24-hour Dietary Recall; FFQ_{REC}, Food Frequency Questionnaire used at recruitment

The performance of the FFQ_{FUP} was compared to the FFQ_{REC} in 512 individuals (55% women) eligible to participate in the third follow-up. The average time between the application of the two questionnaires was 28 days; thus, assuring that respondents did not simply recall what they filled in before (in FFQ_{FUP}) and that real dietary changes were unlikely to occur during this period. Although the two FFQs differed considerably in length

and format, they were reasonably correlated. Spearman correlation coefficient between FFQ_{REC} and FFQ_{FUP} was on average 0.57 at both food group and nutrient intake level (Nöthlings, 2004). Spearman rank correlation coefficients between the two FFQs were moderate to good for most selected food groups, ranging from 0.45 for red meat (men), olive oil (women) and other vegetable oils (women) to 0.79 for cereals (men) and ≥0.78 for beer and wine. The Spearman rank correlation coefficient was relatively lower for whole grain bread in men (ρ=0.39) (Jannasch et al., unpublished data). Furthermore, FFQ_{FUP} performed better in terms of data completeness, as 34% of participants completed it without missing values, and about 94% had ten or fewer missing items; whereas for FFQ_{REC}, 19% of participants had no missing values and 74% had ten or fewer missing items (Nöthlings, 2004).

In the present analysis, four food groups (red meat, whole grain products, coffee and alcoholic beverages) were investigated as potential risk factors for diabetes-related vascular complications and as components of CVRS and GDRS. Two food groups, namely plant oil and high energy soft drinks, were assessed as components of CVDRS. The food groups and their constituents as collected from the two FFQs are described in **Table 3.3**. Furthermore, diet quality was assessed with the MedPyramid score, reflecting adherence to the Mediterranean diet in non-Mediterranean countries (Galbete et al., 2018). The score ranges from 0 to 15 points, and a higher score indicates greater adherence. Information on the score calculation and its components are summarised in **Appendix 3a** and **3b**.

3.3.1.2 Lifestyle

In addition to the dietary intake data, recreational physical activity and smoking habits were collected (**Table 3.1**). Physical activity was assessed separately for summer and winter and calculated as the average time per week for the preceding year. At recruitment and second follow-up, separate questions on sports, biking and gardening were included. For the fourth and fifth follow-up rounds, participants were inquired to report all sports activities they engaged in. Various aspects of smoking habits were obtained, such as smoking status (never, former, current smoker), type of tobacco (cigarettes, cigars/cigarillos, pipes), the number of smoking units per day and smoking duration. Information on smoking habits was not assessed in the first follow-up; however, smoking status and duration were based on subsequent follow-up information on smoking status and year of giving up smoking.

Table 3.3 Selected food groups and corresponding single food items derived from the food frequency questionnaire at recruitment and follow-up assessment [adapted from (Schiborn, 2020)]

Food group	Single food items	
	FFQ_{REC}	FFQ_{FUP}
Red meat	Pork schnitzel, pork cutlet, steak, filet, roast pork, pork goulash, diced pork, Kassler, spare rib, boiled pork meat, knuckle of pork, pork belly, hamburger, meat balls, meat loaf, minced meat sauce, hash, liver, calf and lamb meat, rabbit, steak, filet and loin from beef, roast beef, boiled beef, beef roulade, beef goulash, diced beef	Pork meat, beef, hamburger, meat balls, meat loaf
Whole grain products	Whole grain bread, dark and whole grain rolls, grain flakes, grains muesli	Whole grain bread, whole grain rolls, grains muesli, flaxseed
Plant oil	Olive oil (with meat/fish, vegetables, as salad dressing), plant oil (excluding coconut fat) for cooking (with meat/fish, vegetables), sunflower and seed oil, other oil (with meat/fish, vegetables), sunflower and safflower oil, other oil (as salad dressing)	
Coffee	Coffee with caffeine (black, with milk, with condensed milk, with sweeteners)	
High energy soft drinks	Cola, lemonade, alcohol-free beer, malt beer	Cola, lemonade, alcohol-free beer
Alcoholic beverages	Beer, wine, sparkling wine, champagne, spirits, cider, aperitif	Beer, white wine, red wine, sparkling wine, champagne, spirits, cider, aperitif, liqueur, dessert wine

FFQ_{REC}, Food Frequency Questionnaire used at recruitment; FFQ_{FUP}, Food Frequency Questionnaire used at follow-up

3.3.2 Medical information and physical examinations

3.3.2.1 Medical information

The occurrence of 24 chronic diseases was collected through the personal interview at recruitment and follow-up questionnaires. For each self-reported condition, the age and place of diagnosis, as well as the contact details of the treating physician, were obtained. Furthermore, changes in dietary and lifestyle habits and medication use in the last four weeks were recorded. In addition to active follow-up procedures, passive follow-up was implemented. Different information sources such as cancer registries, death certificates, clinics and treating physicians were jointly employed to verify all newly reported diseases in the follow-up questionnaires. Mortality data were obtained from local health offices and the state office of statistics of Brandenburg. The date of death was retrieved from resident registries (Bergmann et al., 1999).

In the fifth follow-up of the EPIC-Potsdam study, familial history of myocardial infarction, stroke and type 2 diabetes was evaluated. The family history was defined as positive if the participant reported having a first-degree relative (father, mother, or sibling) ever been diagnosed with these conditions. Dyslipidaemia was defined as lipid-lowering medication use or prior diagnosis of hypertriacylglycerolaemia or hypercholesterolaemia from self-reports. The glucose-lowering medication was collected from standardised questionnaires completed by the treating physicians during diabetes verification (see section 3.3.4).

3.3.2.2 Anthropometry

Anthropometric measurements included body weight, height and waist circumference. At recruitment, the measurements were performed at the study centre in light clothing, without shoes after emptying the bladder. Body weight was measured with an electronic digital scale (Soehnle, type 7720/23, Murrhardt, Germany), accurate to 0.1 kg and height using flexible anthropometer to the nearest 0.1 cm. Waist circumference was obtained with a non-stretching tape at the minimum abdominal girth (midpoint between the inferior border of the lowest rib and upper border of the iliac crest) to the nearest 0.5 cm. A high degree of reliability

between and within interviewers was observed (reliability coefficient>0.99, coefficient of variation≤1.67%) for all included anthropometric measures (Klipstein-Grobusch et al., 1997). Self-reported weight and waist circumference were obtained through follow-up questionnaires. Weight was recorded in all follow-up rounds, and waist circumference in the fourth follow-up (**Table 3.1**).

3.3.2.3 Blood pressure measurement

An automated oscillometer (BOSO Oscillomat, Bosch & Sohn, Jungingen, Germany) over an aneroid manometer was chosen for blood pressure measurements to avoid observer bias and device inaccuracy during recruitment examination (Kroke et al., 1999a, Kroke et al., 1998). The measurement was performed on the right upper arm in a seated position after a resting period of 15 to 30 minutes. As blood pressure demonstrates a high intra-individual variation, three consecutive measurements were performed with a 2-minute interval between measurements. An average of the second and third readings was used because it was shown that the first reading tends to overestimate blood pressure, while small differences between the second and the third readings were observed (Schulze et al., 2000).

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or prior diagnosis of hypertension or use of antihypertensive medication self-reported during the interview. Follow-up assessment of hypertension was based on self-reported questionnaires, and potential cases were verified by treating physicians.

3.3.2.4 Biological material and biomarker measurement

At recruitment, 20ml of blood samples were drawn into monovettes containing citrate as an anticoagulant and 10ml into monovettes without anticoagulant. The blood samples were fractioned into serum, plasma, buffy coat and erythrocytes and were aliquoted into straws of 0.5ml each. The straws were stored in tanks of liquid nitrogen (–196˚C) and deep freezers (–80˚C) (Boeing et al., 1999b). Among incident type 2 diabetes cases (n=1601), 95.4% provided blood samples, 15.8% of whom were fasting. Red blood cells concentrations of HbA1c and plasma concentrations of total cholesterol and HDL cholesterol were measured at the University Clinic Tübingen, using the automatic ADVIA analyzer (Siemens Medical

Solutions, Erlangen, Germany). Values of biomarker measured in plasma were multiplied by 1.16 in women and 1.17 in men to account for plasma dilution due to citrate infusion.

3.3.3 Calculation of risk scores

The nonclinical GDRS and CVDRS were based on anthropometric, dietary and lifestyle risk factors that are consistent with established evidence and generally available in a home setting (Mühlenbruch et al., 2014a, Mühlenbruch et al., 2014b, Schiborn, 2020, Schulze et al., 2007). Based on the nonclinical version of the scores, the clinical extensions were developed, using clinical parameters routinely available in a primary care setting (Mühlenbruch et al., 2018, Schiborn, 2020). β-coefficients for the defined outcomes were derived from Cox proportional hazards regression models (see section 3.4.1). Subsequently, β-coefficients were multiplied by 100 and used to assign points to each component. The scores for each individual were calculated by taking the sum of all points, and a higher score value indicated a higher risk for type 2 diabetes or CVD, accordingly. Based on the following equations, the total points derived from the nonclinical and clinical scores can be used to calculate absolute 5-year risk for developing diabetes [equations (1) and (2), respectively], and 10-year risk for CVD [equations (3) and (4)]:

(1) $$P(Diabetes, 5\text{–}years) = 1 - 0.99061^{exp\,(\frac{GDRS\ points\ -\ 474.17096591}{100})}$$

(2) $$P(Diabetes, 5\text{–}years) = 1 - 0.99035^{exp\,(\frac{clinical\ GDRS\ points\ -\ 784.13834152}{100})}$$

(3) $$P(CVD, 10\text{–}years) = 1 - 0.98630^{exp\,(\frac{CVDRS\ points\ -\ 547.695}{100})}$$

(4) $$P(CVD, 10\text{–}years) = 1 - 0.98698^{exp\,(\frac{clinical\ CVDRS\ points\ -\ 718.691}{100})}$$

The risk scores' components and allocated points are reported in **Table 3.4**.

Table 3.4 Parameters of the risk scores and allocated points

Components	GDRS	CVDRS
Nonclinical score		
Age (years)	+5.1	+8
Sex (male)	—	+62
Height (cm)	–2.7	—
Waist circumference (cm)	+7.6	+1
Prevalent hypertension	+47	+49
Prevalent diabetes	—	+50
Physical activity (h/week)	–2	—
Former smoker (<20 units/day)	+15	–4
Former smoker (≥20 units/day)	+45	+11
Current smoker (<20 units/day)	+23	+75
Current smoker (≥20 units/day)	+77	+118
Red meat intake (150 g/day)	+55	+34
Whole grain intake (50 g/ day)	–7	–11
Plant oil intake (10 g/day)	—	–13
Coffee intake (150 g/day)	–5	–4
High energy soft drinks (200 ml/day)	—	+8
One parent with diabetes	+56	—
Both parents with diabetes	+106	—
A sibling with diabetes	+48	—
One parent with CVD	—	+45
Both parents with CVD	—	+66
A sibling with CVD	—	+80
Clinical score		
Nonclinical GDRS points	+0.9	—
Nonclinical CVDRS points	—	0.9
HbA1c (%)	+63.8	—
Total cholesterol	—	+0.4
HDL cholesterol	—	–0.5
Systolic blood pressure	—	+0.6
Diastolic blood pressure	—	+1.2

GDRS, German diabetes risk score; CVDRS, Cardiovascular disease risk score; CVD, Cardiovascular disease; HDL, High-density lipoprotein; HbA1c, glycated haemoglobin

3.3.4 Ascertainment of type 2 diabetes and its vascular complications

Incident cases of type 2 diabetes were identified through self-reported follow-up questionnaires, which demonstrated good reliability in the EPIC-Potsdam study (Bergmann et al., 2004). Participants who reported type 2 diabetes diagnosis, disease-relevant medication intake or dietary treatment were considered potential cases. Death certificates and health record linkage were used to obtain additional information (Bergmann et al., 1999). Participants' treating physicians verified all potential incident diabetes cases by completing standardised forms. Only physician-verified type 2 diabetes cases (International Statistical Classification of Diseases, 10th Revision (ICD-10)[9] code: E11) with diagnosis date after recruitment were included.

Independently of participants' vital status, the incidence of micro- and macrovascular complications of type 2 diabetes was collected through standardised forms sent to the treating physicians in 2014. The forms collected medical information related to the latest clinic visit, occurrence and date of diagnosis of complications. Incident macrovascular events were also ascertained from the regular follow-up of EPIC-Potsdam participants, following the same procedure as described for diabetes ascertainment. Overall, 37 additional cases of macrovascular complications were identified.

Microvascular complications comprised diabetic kidney disease (ICD-10 E11.2; including unspecified diabetes-related nephropathy, renal replacement therapy, micro- or macroalbuminuria), retinopathy (ICD-10 E11.3; proliferative, non-proliferative or blindness) and neuropathy (ICD-10 E11.4; unspecified diabetes-related peripheral neuropathy, amputation, loss of sensation of lower limbs or diabetic foot syndrome). Macrovascular complications were defined as myocardial infarction (ICD-10 I21) or stroke (ICD-10 I60, I61, I63, I64).

[9] http://apps.who.int/classifications/icd10/browse/2016/en

3.4 Statistical methods

3.4.1 Event history analysis[10]

Event history analysis, or survival analysis, deals with longitudinal data involving times (i.e., time-to-event), starting from a well-defined time origin until the occurrence of the event of interest. Event history data, in its simplest form, may be modelled as a process with two states and one possible transition, e.g., from an initial, transient state '0: alive' to an absorbing, final state '1: dead' (**Figure 3.2**).

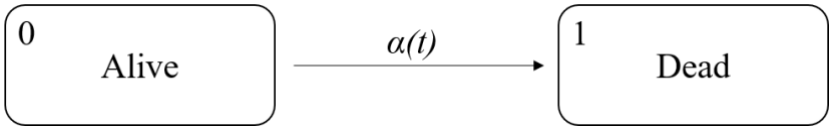

Figure 3.2 Two-state model for event history data

Let T denote the survival time of an individual, which is a continuous non-negative random variable. In a homogeneous population, the different values of T follow a probability distribution, which may be characterised by the cumulative distribution function $F(t)$ and the hazard function $\alpha(t)$, where t represents a point in the range of T. The distribution function of T corresponds to the probability that the survival time is less than a value t, given by

$$F(t) = P(T < t) = \int_0^t f(u)du\,.$$

The survival function $S(t)$ represents the individual's survival probability from the time origin to a time beyond t,

$$S(t) = 1 - F(t) = P(T \geq t), \qquad 0 < t < \infty\,.$$

[10] Unless otherwise specified, the definitions provided in this section are based on COLLETT, D. 2003. *Modelling Survival Data in Medical Research,* Boca Raton, USA, CRC Press LLC, KALBFLEISCH, J. D. & PRENTICE, R. L. 2002. *The Statistical Analysis of Failure Time Data,* Hoboken, John Wiley & Sons, Incorporated.

The survival function is a nonincreasing right-continuous function of t with $S(0) = 1$ and $\lim_{t->\infty} S(t) = 0$. Integrating the two-state model, $S(t)$ corresponds to the probability of being in state 0 at time t, and $F(t)$ to be in state 1. If all individuals are in state 0 at $t = 0$, then $F(t)$ also represents the transition probability from state 0 to 1 for the time interval $[0, t]$ (Andersen and Keiding, 2002).

The hazard function expresses the survival probability per time unit, conditional on the event of interest has not occurred prior to time t,

$$\alpha(t) = \lim_{\delta t \to 0} \left\{ \frac{P(T \in [t, t + \delta t) \,|T \geq t)}{\delta t} \right\}$$

where, $P(T \in [t, t + \delta t) \,|T \geq t)$ is the probability that the survival time lies between t and $t + \delta t$, conditional on T being greater or equal to t. Therefore, $\alpha(\cdot)$ expresses the instantaneous transition probability per time unit from state 0 to 1. Combining the definition of probability density function $f(t)$, it can be shown mathematically that

$$\alpha(t) = \frac{f(t)}{S(t)} = -\frac{d}{dt} log\, S(t)\,.$$

In the sequel,

$$S(t) = exp\left(-\int_0^t a(u)du \right) = \exp\left(-H(t)\right)$$

where, $H(t)$ is the cumulative hazard, i.e., the total hazard experience up to time t. The cumulative hazard is linked to the survival function and can be also expressed as $H(t) = -\log(S(t))$, or equivalently $S(t) = e^{-H(t)}$.

One feature of survival models is the censoring of survival time. Survival time is censored when the event of interest has not been observed, either due to drop-out, loss of follow-up or termination of the study. Illustratively, a participant who entered the study at time t_0 experiences the event of interest at $t_0 + t$. However, due to censoring, t is unknown. What is known in this case is $t_0 + c$, where c represents the censored survival time. This type of incomplete observation is known as right-censoring. For completeness, it should be mentioned that there are two other types of censoring: left-censoring, encountered when an individual's actual survival time is less than that observed, and interval-censoring, where the

event is known to have occurred within an interval of time. More than one type of censoring may occur, but this work deals only with right-censoring.

A crucial assumption in the analysis of time-to-event data is that the censoring is independent or non-informative. Right-censoring is independent if the hazard rates of individuals who are censored at time t are representative of those who remained at risk at time t. It is required that at each time t

$$\lim_{\delta t \to 0} \left\{ \frac{P(T \in [t, t+\delta t) \mid T \geq t, x)}{\delta t} \right\} = \lim_{\delta t \to 0} \left\{ \frac{P(T \in [t, t+\delta t) \mid T \geq t, x,\ Y(t) = 1)}{\delta t} \right\}$$

where, $Y(t) = 1$ indicates that the individual is at risk of developing the event of interest at time t, and x represents a vector of relevant covariates that are measured at or before t_0. All we know, therefore, is that the survival time is greater than the censoring time.

3.4.1.1 Kaplan-Meier estimate of the survivor function

The Kaplan-Meier estimate is an estimate of the probability that an individual will not develop the event at time t and uses failure and censoring times. Let n_t and d_t denote the number of individuals and number of events, respectively, that occurred at time t. The estimated survival probability at time t is $s_t = \frac{n_t - d_t}{n_t}$. Assuming that the event occurrence of the individuals in the sample is independent of one another, then the Kaplan-Meier estimate of the survivor function for any time t is given by

$$\hat{S}(t) = \prod_{j=1}^{k} \frac{n_j - d_j}{n_j}$$

where, $t_1 < t_2 < t_r$ are sorted event times.

3.4.1.2 Cox proportional hazards model

Cox proportional hazards model, abbreviated Cox model, is the most commonly used approach for the analysis of time-to-event data. As before, suppose that there are n_t individuals at time t, and d_t events occur at t, then the estimated risk of an event occurring at t is $r_t = \frac{d_t}{n_t}$ and correspondingly, $H_t = \sum \frac{d_i}{n_i}$. If the survival times are continuously distributed, the Cox model is based on risk sets, $R(t)$, of individuals still at risk of developing

the event at each time that an event occurred. In other words, it is based on time intervals, time-clicks, that contain at most one event (Kirkwood and Sterne, 2003, Cox, 1972); however, the handling of ties is also possible as described thereinafter. At each time-click, the individual who experienced the event is compared with individuals still being followed in terms of exposure values. The model does not require that the survival times follow a particular distribution. However, it assumes that the ratio of the hazards of different exposure groups remain constant over time (the proportional hazard assumption).

Suppose that x is a vector of p explanatory variables $x = (x_1 + x_2 + \cdots + x_p)$, which are assumed to be recorded at or before the time origin. The mathematical form of the Cox model is

$$a(t) = a_0(t)e^{\beta x} \tag{5}$$

where, β is a vector of unknown regression coefficients of the explanatory variables $x_1 + x_2 + \cdots + x_p$ and $a_0(t)$ an unspecified baseline hazard function when $x = 0$. Equation (5) can be expressed in the linear form as[11]

$$log\left(\frac{a(t)}{a_0(t)}\right) = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p \ .$$

Thus, the covariates in the proportional hazards model are the linear predictors for the logarithm of the hazard ratio (log-linearity assumption for continuous variables).

The β-coefficients are estimated by maximising the log partial likelihood function. Suppose that among n individuals d events occurred and $t_1 < \cdots < t_r$ are the observed ordered times of those events. The partial likelihood may be written as

$$L(\beta) = \prod_{j=1}^{r} \frac{\exp(\beta x_j)}{\sum_{l \in R_j} \exp(\beta x_l)}$$

where, x_j is the vector of covariates for the individual who developed the event at the jth ordered event time t_j, and R_j is the risk set of individuals still being followed at t_j. Individuals who have been censored do not contribute to the numerator, but they contribute to the risk sets. The log partial likelihood is

[11] Note: 'log' denotes the natural logarithm throughout this chapter.

$$\log L(\beta) = \sum_{j=1} \beta x_j - \sum_{j=1} log\left[\sum_{l \in R_j} \exp(\beta x_l)\right].$$

So far, we have considered the survival times to be continuous. However, survival times are usually recorded to the nearest day, often resulting in more than one event and censoring at a given time. To handle tied survival times the Efron approximation of the likelihood function has been proposed (Efron, 1977). Suppose that d_j is the individuals, $k = 1, 2, \ldots, d_j$, who developed the event of interest at the jth ordered event time, t_j, $j = 1, 2, \ldots, r$. Let s_j denote the vector of sums of each of the p covariates for d_j. The likelihood function is then

$$\prod_{j=1}^{r} \frac{\exp(\beta s_j)}{\prod_{k=1}^{d_j}\left[\sum_{l \in R_j} \exp(\beta s_l) - (k-1) d_k^{-1} \sum_{l \in D_j} \exp(\beta x_l)\right]}$$

where, $D_j = (j_1, \ldots, j_{d_j})$ is the set of all individuals who develop the event at time t_j.

3.4.1.3 Model checking

As previously described, the two fundamental assumptions in the Cox model are i) the proportional hazards assumption and ii) the log-linearity assumption. Whether the effect of an exposure is constant over time can be assessed by plotting the weighted Schoenfeld residuals against the observed survival times (Schoenfeld, 1982). For each individual, there is one Schoenfeld residual for each explanatory variable included in the Cox regression model. Let x_j and R_j denote the covariate vector and risk set for the jth ordered survival time, t_j. Schoenfeld residuals are defined as

$$r_j = x_j - \frac{\sum_{l \in R_j} x_l \exp(\hat{\beta} x_l)}{\sum_{l \in R_j} \exp(\hat{\beta} x_l)}$$

where, $\hat{\beta}$ is the estimator of β under maximised log partial likelihood. If there are tied survival times at t_j then, each x_j corresponds to a distinct individual with uncensored survival time, while R_j=$R_{j'}$ if t_j=$t_{j'}$ (Winnett and Sasieni, 2001). The weighted Schoenfeld residuals, r_j^*, are defined as

$$r_j^* = dvar(\hat{\beta}) r_j$$

where, d is the number of events among n individuals, and $var(\hat{\beta})$ the variance-covariance matrix of the parameter estimates in the fitted model (Grambsch and Therneau, 1994). It was shown that the expected value of the weighted residual for the ith explanatory variables $x_i, i = 1, 2, \dots, p$ at jth survival time is

$$E(r_{ij}^*) \approx \beta_i(t_j) - \widehat{\beta}_i$$

where, $\beta_i(t)$ is considered a time-varying coefficient of x_i, $\beta_i(t_j)$ coefficient value at the survival time t_j, and $\widehat{\beta}_i$ is the estimated value of β_i under maximised partial likelihood. Under the proportional hazard assumption, $\widehat{\beta}_i = \beta_i(t_j)$; therefore, $E(r_{ij}^*) = 0$, which occurs if the r_{ij}^* values are randomly distributed across time. A horizontal line suggests that β_i is constant and the proportional hazards assumption is fulfilled.

The linearity assumption between a continuous explanatory variable, x, and the log hazard function can be assessed with restricted cubic splines. A spline is a mathematical function that consists of piecewise polynomials of low degree connected at a number of predefined knots. In particular, suppose that the values of x range from k_{min} to k_{max} and is divided into two intervals by one knot at k_1 point. There are then two boundary knots, k_{min} and k_{max}, and one internal knot k_1. A cubic polynomial is defined for $x \in (k_{min}, k_1)$ and for $x \in (k_1, k_{max})$, which are smoothly joined at k_1. Like this, x is transformed into a cubic spline. A restricted cubic spline is a cubic spline where splines are assumed to be linear beyond boundary knots k_{min} and k_{max}. Such knots are not necessarily placed at the extreme values of x.

The restricted cubic spline function of x with k number of knots, $k_1, \dots, k_k$ with $k_1 > k_{min}$ and $k_k < k_{max}$ is given by

$$s(x) = \gamma_0 + \gamma_1 x + \sum_{i=2}^{k-1} \gamma_i v_i(x)$$

where, γ_0 is the intercept, γ_i are the parameter values for $i = 2, \dots, k-1$ and,

$$v_i(x) = (x - k_i)_+^3 - \left(\frac{k_{max} - k_i}{k_{max} - k_{min}}\right)(x - k_{min})_+^3 - \left(1 - \frac{k_{max} - k_i}{k_{max} - k_{min}}\right)(x - k_{max})_+^3$$

and, $u_+ = u$ if $u > 0$; $u_+ = 0$ if $u \leq 0$.

To assess the nonlinear effect of a continuous covariate x_1, assuming that the linearity assumption holds for the remaining covariates, $x_2, \ldots, x_p$, in the Cox model we may fit the restricted cubic spline function of x_1 (Royston and Parmar, 2002). The Cox model [equation (5)] is then modified to

$$a(t) = a_0(t)e^{[s(x_1)+\beta x]}.$$

3.4.1.4 Multistate models

So far, the experience of an individual has been considered as a process with one transition from a transient state "0: alive" to an absorbing state "1: dead" with $a(t)$ transition rate, which is the hazard of death at time t (**Figure 3.2**). In real-life situations, the initial state "alive" can often be divided into two or more intermediate, transient states before the individual reaches the absorbing state. An example is the illness-death model, where the individual enters at state 0. With the progression of time, they may become ill (state 1) and in the sequel may die (state 2) (**Figure 3.3**).

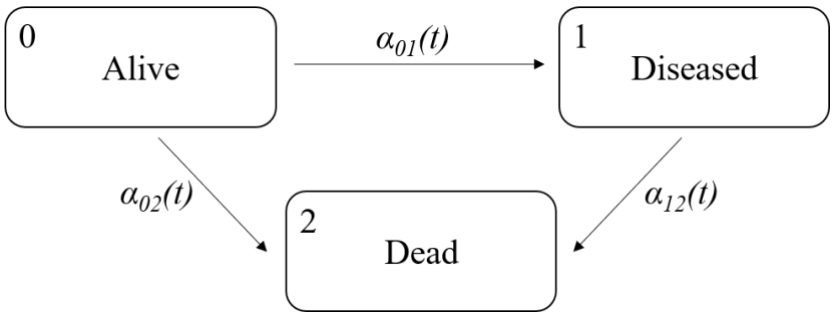

Figure 3.3 Unidirectional illness-death model

The intermediate events may substantially change the risk of developing the outcome of interest. Handling the sequence of intermediate events within a multistate framework, allowing the individuals to move among the several states over time, may enable to analyse models for more detailed life history data. The complexity of a multistate model depends on the number of states and possible transitions.

A multistate process is a stochastic process $[X(t), t \in T]$ with a finite state space $S = (1, \ldots, N)$ and with right-continuous sample paths: $X(t+) = X(t)$. Here, $T = [0, \tau]$ with $\tau \leq +\infty$. The initial distribution of the process is $\pi_h(0) = Prob[X(0) = h]$, where $h \in S$. The

process $X(\cdot)$ generates measurable sets X_t consisting of the observation of the process in the interval $[0, t]$ (Andersen and Keiding, 2002). Transition probabilities from state h to j may be expressed as

$$P_{hj}(s,t) = Prob[X(t) = j|\, X(s) = h, X_{s-}]$$

where, $h, j \in S, s, t \in T, s \leq t$. The transition intensity is given by

$$a_{hj}(t) = lim_{\Delta t \to 0} \frac{P_{hj}(t, t + \Delta t)}{\Delta t}$$

which, provide the hazard for a movement from one state to another. The model is Markovian if $a_{hj}(t)$ only depends on the history of the process through the current state (h) at time $t-$. However, it may also depend on the duration in state h, in which case it is a semi-Markov model (Andersen and Perme, 2008).

In Cox models a semi-Markov process may be modelled by including covariates for the sojourn time spent in a given state. The assumption of proportional hazards can be relaxed by performing stratified Cox models to separate baseline hazards that are not assumed to be proportional. Covariates may be incorporated in the model as time-fixed or transition-specific covariates (allowing for their effect to differ for the different transitions) and they do not need to be the same for the different states. The transition intensity of the ith of n individuals for a transition from state h to j is

$$a_{ihj}(t) = Y_{ihj}(t) a_{hj,0}(t) \mathrm{e}^{[\beta_{hj} x(i)_{hj}]}$$

where, $Y_{ihj}(t)$=1 if individual i is in state h and at risk of entering state j, and $Y_{ihj}(t)$=0, otherwise. The baseline intensity function for this transition is denoted by $a_{hj,0}(t)$, x_i is the vector of covariates at baseline for the ith individual, and $x(i)_{hj}$ is the vector of transition-specific covariates for i (Mikolai and Lyons-Amos, 2017).

3.4.2 Missing data and multiple imputation

In large longitudinal observational studies, like EPIC-Potsdam, missing data is inevitable, despite careful planning and meticulous efforts to collect complete information. Performing statistical analysis including only complete cases, i.e., individuals without missing data, may

lead to biased estimates (Sterne et al., 2009). For statistical models with several parameters, missing data in many of those variables may cause substantial power loss, even in the absence of bias. To understand the process behind missing data and whether there is a dependency with the underlying values in the dataset, three missing-data mechanisms have been proposed (Little and Rubin, 1987), as described below.

Suppose $Y = (y_{ij})$ represents the complete dataset without missing values, where y_{ij} is the value of variable Y_j of the ith individual. Let $M = (m_{ij})$ be the event of missingness, such that $(m_{ij}) = 1$ if y_{ij} is missing and $(m_{ij}) = 0$, otherwise. The missing completely at random (MCAR) mechanism assumes that missingness does not depend on either the observed or missing values; that is

$$P(M|\, Y, \varphi) = P(M|\, \varphi)$$

where, φ denotes unknown parameters. The MCAR assumption is often too strong, and a less restrictive mechanism is the missing at random (MAR), where the probability of data missing depends on the observed data, Y_{obs}:

$$P(M|\, Y, \varphi) = P(M|\, Y_{obs}, \varphi).$$

If data are missing not at random (MNAR), the probability of missingness depends on the missing data, Y_{mis}.

Complete case analysis gives accurate estimates under MCAR, while if appropriately implemented, the multiple imputation method provides unbiased estimates under MCAR or MAR. If data are MNAR, multiple imputation method will provide invalid estimates unless known MNAR mechanisms are accommodated (White et al., 2011, Baraldi and Enders, 2010).

Multiple imputation is a three-step statistical method for handling missing data (Van Buuren, 2018). For an observed, incomplete dataset, multiply imputed datasets are generated by replacing each missing value with m plausible values drawn from the observed data (step 1). One way of generating imputations is the multiple imputation by chained equations (MICE) procedure. After specifying an imputation model, the MICE algorithm starts by imputing all missing values with a random draw from the observed dataset in a variable-by-variable manner. In the sequel, the first incomplete variable, x_1, is regressed on all other

variables $x_2, \dots, x_p$ under the specified model, restricted to individuals with observed x_1. The procedure continues with the second incomplete variable x_2, which is regressed on all other variables $x_1, x_3, \dots, x_p$, and using the imputed values of x_1. The type of regression model depends on the type of the incomplete variable. One cycle is completed when the process is repeated for all variables with missing values. The procedure is repeated for several cycles to produce a single imputation dataset. The whole procedure is then repeated m times in order to generate m imputed datasets (White et al., 2011, Van Buuren, 2018).

The second step involves the application of statistical methods separately for each imputed dataset. Finally, the m parameter estimates and variance are combined into a single set of values (step 3), using Rubin's rules (White et al., 2011).

Let $\widehat{Q}_\iota$ and $\widehat{U}_\iota$ denote the point and variance estimates for the ith imputation ($i = 1, 2, \dots, m$) of parameter Q. The combined point estimate $\hat{Q}$ is the average of the m estimates:

$$\hat{Q} = \frac{1}{m}\sum_{i=1}^{m} \widehat{Q}_\iota.$$

Similarly, the within-imputation variance is given by

$$\widehat{U} = \frac{1}{m}\sum_{i=1}^{m} \widehat{U}_\iota.$$

The between-imputation variance is calculated as

$$B = \frac{1}{m-1}\sum_{i=1}^{m} \left(\hat{Q} - \widehat{Q}_\iota\right)^2.$$

The combined variance of $\hat{Q}$ is formed incorporating the within- and between-complication variance:

$$var\left(\hat{Q}\right) = \widehat{U} + \left(1 + \frac{1}{m}\right)B.$$

For scalar Q, the relative increase in variance due to missing values is defined as

$$r = \frac{(1 + m^{-1})B}{\widehat{U}}$$

which, represents the proportion of the increase in the variance attributable to the missing data. If there is no missing information about Q, both r and B are equal to zero. The fraction of missing information is given by

$$\hat{\lambda} = \frac{r + {}^{2}/_{(v_m + 3)}}{r + 1}$$

where, v_m represents the degrees of freedom. A low $\hat{\lambda}$ indicates that the model contains sufficient information to impute the missing values (Van Buuren, 2018).

The relative efficiency represents the efficiency of an estimate based on m, as follows:

$$RE = \left(1 + \frac{\lambda}{m}\right)^{-1}.$$

A high relative efficiency ($RE \approx 1$) shows optimal statistical efficiency, that is, little advantage is gained by increasing the number of imputations (Graham et al., 2007).

3.4.2.1 Missing data overview

Participants for whom information on diabetes-related complications could not be obtained from the treating physicians were excluded before applying multiple imputation (n=234). The characteristics of individuals included in the multiple imputation "responders" and those excluded "non-responders" are provided in **Appendix 4**. Non-responders were less likely to complete the fifth follow-up round of the EPIC-Potsdam study and were more likely to be deceased before May 2014.

Multiple imputation was performed for the remaining 1367 participants. **Appendix 5** presents the distributions of characteristics between participants with complete and incomplete data. Individuals with missing values in any of the variables required for the present study were likelier to be men, current or former smokers, to receive insulin therapy, to have prevalent conditions at diabetes diagnosis, and to develop a diabetes-related vascular complication compared to those with complete data. Furthermore, they were less likely to complete the fifth follow-up round and report a family history of type 2 diabetes and cardiovascular disease.

3.4.2.2 Application of multiple imputation

Ten imputed datasets were created using the MICE procedure. The variables were sorted by the amount of missingness, starting with those with no missing values. Binary and categorical parameters were imputed with logistic and multinomial logistic regression, respectively. For continuous parameters, linear regression and predictive mean matching was used. Predictive mean matching (PMM) is an *ad hoc* method, that serves to preserve the original distribution of the observed data. For each missing entry z_i, PMM forms a small set of q individuals (donor-pool) from the observed values of z, which have the closest predicted values to the predicted value for z_i. A random draw is made among those q individuals, and the observed value of the selected donor replaces the missing value (Van Buuren, 2018). Herein, PMM is set to $q = 5$. For non-normally distributed, continuous variables Box-Cox transformation was performed before added to the imputation procedure. Box-Cox transformation is a family of power transformation functions, with λ denoting the transformation parameter (Box and Cox, 1964). Specifically, if $z = (z_1, z_2, \dots, z_n)$ is a non-normally distributed variable, the Box-Cox transformation is given by

$$z^{\lambda} = \begin{cases} \dfrac{(z+\psi)^{\lambda} - 1}{\lambda}, & \lambda \neq 0, \\ \log(z+\psi) \quad , & \lambda = 0. \end{cases}$$

If $z > 0$, then ψ is set to zero. If z contains 0 or negative values, ψ is a positive constant, so that $z + \psi > 0$. The optimal value of λ was determined among values -3 to 3, per 0.5 by testing each distribution and choosing the one closest to normal. Complete data were transformed back to their original scales before performing further statistical analysis.

Multiple imputation was performed assuming MAR. Only missing values from recruitment evaluation and completed follow-up rounds were imputed. The imputation model included event indicators, years-to-event, variables needed for the analysis models and other auxiliary variables assumed to explain missingness patterns. **Appendix 6** lists the variables included in the imputation model and the missing frequency. Multiple imputation was performed before the exclusion of prevalent cases. Thus, diabetes-related vascular complications with missing years-to-event would potentially become prevalent cases.

The relative increase in variance was below or close to 8% for all main variables required for the analysis, except for whole grain consumption, where it was around 13% (**Appendix**

7). The fraction of missing information was lower than 8% for all variables but whole grain consumption, where it was around 12%. The relative efficiency of the imputation procedure was higher than 98% for all variables. The imputation procedure hardly affected the distribution of the variables, except for years-to-myocardial infarction and years-to-stroke, where the median years and interquartile range were shifted by an approximately 1-year increase, and the percentage of currents smokers in follow-up one increased by one unit (**Appendix 7**).

Due to data availability, smoking units per day, soft drink and plant oil consumption were not included in the imputation model. Missing values of smoking units during follow-up were imputed by the preceding available value. Similarly, missing values of soft drink and plant oil consumption at the third follow-up (n=51) were imputed by the values at recruitment examination. Biomarker measurement was conducted only in participants from the case-cohort study nested within the prospective study (Schulze et al., 2009). The case-cohort study consisted of a random sub-cohort (n=2500), incident type 2 diabetes cases diagnosed up to August 2005 (n=820), incident myocardial infarction, stroke (n=508) and transient ischaemic attack cases (n=239) identified by November 2006. Multiple imputation was not performed for missing biomarker values for participants who developed type 2 diabetes later, as individuals who developed diabetes earlier might be systematically different in ways that the available data cannot capture.

3.4.3 Objective-specific statistical methods

All statistical analyses were performed using the SAS software, version 9.4, Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

3.4.3.1 Objective 1: Development of vascular complications and concurrent effect of selected lifestyle factors

First, the effect of complication burden on the development of further complications was assessed (**Objective 1a**). The observed complication sequence is illustrated in **Figure 3.4**. A five-state model was used to analyse transition intensities between successive states of complication burden (black coloured boxes and arrows). The states were distinguished by

order of complication occurrence. Application of models with six or seven states (grey colour) was not possible due to data sparsity.

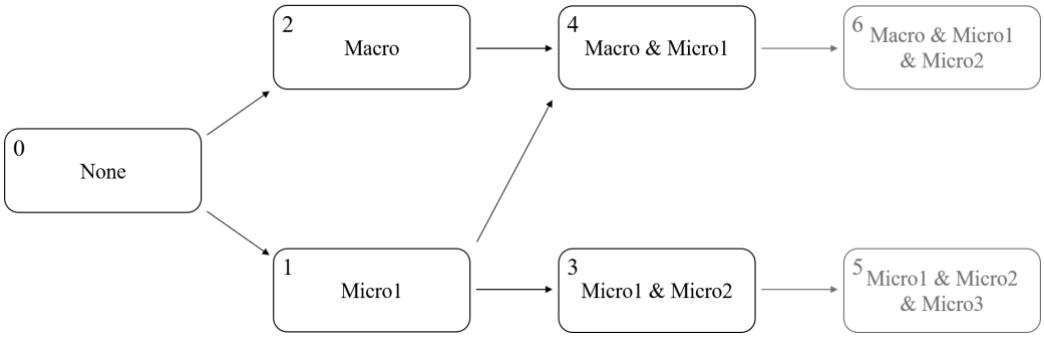

Figure 3.4 Model of complication sequence

The initial state was 'None', where the participants were free of complications, starting at diabetes diagnosis. Thereafter, the transient states 'Macro' and 'Micro1' could be reached, where the first event was either a macrovascular or a microvascular complication, respectively. The states 'Macro & Micro1' (occurrence of a macro- and microvascular event) and 'Micro1 and Micro2' (occurrence of two microvascular events) were considered the absorbing states. Follow-up time was subdivided according to complication state at the respective time-window. The exit time for participants who did not develop a complication or did not reach the absorbing states was the last examination by the treating physician.

Cox models with robust variance estimators (Lin and Wei, 1989) were fitted to the dataset, which contained one record for each individual for each transition (Andersen and Keiding, 2002). **Appendix 8** illustrates an example of the data records for one participant. The models included age as the timescale and were stratified by age at study entry (in years) and a binary variable 'stratum' to separate transitions with the same endpoint (1 for microvascular complications; 2 for macrovascular events), giving rise to non-proportional baseline hazards between them. Two regression models were constructed. The first model was adjusted for sex and state duration (years), thus applying a semi-Markov assumption. The second model additionally included education (3 categories: no vocational training/vocational training, technical college degree, university degree), glucose-lowering medication at diabetes diagnosis (4 categories: no medication, oral medication, insulin, insulin and oral medication), and the time-updated covariates smoking status (3 categories:

never, former, current smoker), smoking duration (years), alcohol intake (4 categories: non-drinker [lifetime non-user and former user], very light user [men/women ≤2/≤1 g/day], below the limit [men/women >2 to ≤24/>1 to ≤12 g/day], above the limit [men/women >24/>12 g/day]), BMI (kg/m^2), physical activity (h/week) and prevalent conditions of hypertension and dyslipidaemia (yes/no). The time-updated variables differed for each transition using the most recent information before the entry at each state. Effect modification by sex was assessed in stratified analysis and by adding the multiplicative interaction term between complication state and sex. A sensitivity analysis was conducted among complete cases. The analysis was performed separately for the ten imputation datasets and results were combined based on Rubin's rules.

The Kaplan-Meier curves were constructed to compare survival patterns between transitions. The curves look nearly parallel for the transitions belonging to the same stratum versus time (**Appendix 9**). Schoenfeld residuals were evaluated by stratum to assess the proportional hazards assumption. Restricted cubic splines with three knots fitted at the 5th, 50th and 95th percentile of the distribution of quantitative covariates were used to examine the shape of the associations. Non-linear trends were tested with the Wald test and a p-value of less then 0.05 was considered to indicate a significant linear trend.

Applying the same data structure, the association of selected food groups and other lifestyle factors with incidence of micro- and macrovascular complications was examined (**Objective 1b**). The linearity of the relationships was tested with cubic splines as described above. Where non-linearity was detected, quantitative lifestyle factors were modelled categorically using tertiles. The overall effect of baseline lifestyle factors (collected at the closest EPIC-Potsdam follow-up round before diabetes diagnosis) and time-updated factors (i.e., the updated lifestyle factor assessed before entry in states 'Micro1' and 'Macro') was investigated. This included BMI (kg/m^2), waist circumference (cm), physical activity (h/week), smoking status (3 categories: never, former, current smoker), alcohol consumption (4 categories: non-drinker [lifetime non-user and former user], very light user [men/women ≤2/≤1 g/day], below the limit [men/women >2 to ≤24/>1 to ≤12 g/day], above the limit [men/women >24/>12 g/day]), intake of coffee (150 g/day), red meat (tertiles: ≤0.23, >0.23 to ≤ 0.43, >0.43 of 150g portion/day) and whole grain (tertiles: ≤0.19, >0.19 to ≤0.67, >0.67 of 50g portion/day). Apart from the exposures of interest, the five-state Cox models

additionally included age (stratified in years), sex, state duration (years), education (3 categories: no vocational training/vocational training, technical college degree, university degree), glucose-lowering medication at diabetes diagnosis (4 categories: no medication, oral medication, insulin, insulin and oral medication), smoking duration (years, time-updated variable) and prevalent conditions of hypertension and dyslipidaemia (yes/no, time-updated variables). The assessment of the time-updated food groups was assessed only among participants who developed diabetes between the two FFQ applications (n=714).

Furthermore, the effect of time-updated exposures according to the current complication burden was investigated. The multiplicative interaction terms between complication state and risk factors were added in the model, one risk factor at a time. The lilelihood ratio test (LRT) (see **Box 1**) was used to compare models with and without the interaction terms and a *p*-value of less than 0.05 was considered to indicate statistically significant differences.

Selection of confounders for objective 1

Adjustment selection was made a priori based on existing literature on determinants of vascular disease occurrence. Age and sex differences are established factors involved in the development and progression of type 2 diabetes and vascular disease (Kautzky-Willer et al., 2016). Socioeconomic status, assessed by education level, adversely affects diabetes care and prognosis of complications (Grintsova et al., 2014). Diabetes duration (here adjusted as the underlying timescale) and poor glycaemic control are among the most recognised risk factors for vascular complications (International Diabetes Federation (IDF), 2019). There is strong evidence supporting that hypertension plays a role in the development of macrovascular complications, retinopathy and kidney disease (International Diabetes Federation (IDF), 2019) and may be associated with neuropathy, although the link is not well-established (Callaghan et al., 2012, Naqvi et al., 2019). Furthermore, dyslipidaemia is an important risk factor for CVD secondary to diabetes and may also play a role in diabetic neuropathy, kidney disease and retinopathy (Barrett et al., 2017, Naqvi et al., 2019, Pavkov et al., 2018). Among lifestyle factors, evidence supports the detrimental effects of smoking on vascular complications (Sliwinska-Mosson and Milnerowicz, 2017), although evidence is uncertain for neuropathy and retinopathy in type 2 diabetes. Moderate alcohol consumption appeared

to be protective for cardiovascular and microvascular events in persons with type 2 diabetes compared to non-drinkers, while an increased risk was observed for heavy drinkers (Blomster et al., 2014). Obesity is a recognised risk factor for the development of type 2 diabetes and has a substantial influence on the cardiovascular system (Bhupathiraju Shilpa and Hu Frank, 2016) and has been suggested as a risk factor for diabetes-related complications. Lastly, physical activity showed a protective effect on type 2 diabetes incidence, CVD and macrovascular complications of diabetes (Ekelund et al., 2012, Lavie et al., 2019, Kodama et al., 2013), but the evidence is not clear for microvascular complications.

Box 1. Likelihood Ratio test

The maximised likelihood can be computed by replacing the β's with their maximum likelihood estimates (MLE) under the specified model. Higher values of the maximised likelihood indicate a better agreement between the model and the observed data. The MLE for each of the β's depends on the values of the other parameters and they are fitted by statistical software using the iteration process until convergence (Kirkwood and Sterne, 2003). The likelihood ratio test (LRT) compares alternative models fitted to the same set of data by utilising the maximised likelihood. LRT is only valid if hierarchically nested models are compared. Let $\lambda = \frac{L_1}{L_2}$ be the likelihood ratio, where $L_1$and L_2 are the maximised likelihood under model 1 and model 2, respectively; while l_1 and l_2 denote the log of $L_1$and L_2. The likelihood ratio test statistic (LRS) is given by

$$LRS = -2\log(\lambda) = -2(l_1 - l_2),$$

which follows a x^2 distribution with degrees of freedom equal to the difference in the number of parameters between the two models.

3.4.3.2 Objective 2: BMI, BMI change and risk of vascular complications[12]

The most recent assessment before diabetes diagnosis was used to estimate the pre-diagnosis weight (mean ± SD time, 15 ± 10.8 months), and the closest assessment after diabetes diagnosis identified post-diagnosis weight (mean ± SD time, 14 ± 9.1 months). BMI was calculated as weight (kg) divided by the square of height (m). BMI was classified into four categories according to WHO cut-off points as normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), obese (30.0 to 34.9 kg/m^2) and (≥35.0 kg/m^2) (World Health Organization (WHO), 2000). Relative annual BMI change was calculated as the difference between post-diagnosis BMI and pre-diagnosis BMI, divided by pre-diagnosis BMI, and further divided by the number of years between the two measurements (mean ± SD time, 2.4 ± 0.55 years). BMI change was divided into three groups: BMI gain (>1%), stable BMI (≤1% gain/loss) and BMI loss (>1%). Separate analyses were conducted for total vascular complications, macrovascular complications, microvascular complications, kidney disease and neuropathy. Analyses for retinopathy, myocardial infarction and stroke as distinct outcomes were not performed due to the limited number of events.

As effect modification by complication load was not observed (see section 4.2.2), standard Cox models were performed to estimate the hazard ratios (HR-s) for the associations between pre-diagnosis BMI (modelled categorically, with reference group 18.5–24.9 kg/m^2, and continuously per 5 kg/m^2) and incidence of complications, and applied robust variance estimators to calculate 95% CIs (Lin and Wei, 1989) (**Objective 2a**). Follow-up was defined as the time between diabetes diagnosis and diagnosis of the respective vascular disease or date of the last examination by the treating physicians. Age was used as the underlying timescale, with entry time defined as the participants' age at diabetes diagnosis and exit time the age at event or censoring. Three Cox models were constructed. The first model was adjusted for age (stratified in years) and sex. The second (main) model was further adjusted for education (3 categories: no vocational training/vocational training, technical college degree, university degree), smoking status (3 categories: never, former,

[12] The methods described were published by POLEMITI, E., BAUDRY, J., KUXHAUS, O., JÄGER, S., BERGMANN, M. M., WEIKERT, C. & SCHULZE, M. B. 2021. BMI and BMI change following incident type 2 diabetes and risk of microvascular and macrovascular complications: the EPIC-Potsdam study. *Diabetologia,* 64**,** 814-25.

current smoker), smoking duration (years), alcohol consumption (g/day), physical activity (h/week), MedPyramid score (units), and family history of myocardial infarction, stroke and type 2 diabetes (yes/no). Additional adjustments were made for prevalent hypertension and dyslipidaemia (yes/no) (model 3). The covariates were derived from the closest follow-up before diabetes diagnosis. The analysis was performed on ten imputation datasets, and results were combined using Rubin's rules. Cubic splines with three knots were fitted at the 5th, 50th and 95th percentile of BMI distribution, where median BMI was used as the reference. The non-linear trend was tested with the Wald test, and a *p*-value less than 0.05 was considered significant.

For analyses of BMI change (**Objective 2b**), participants who developed complications between diabetes diagnosis and post-diagnosis follow-up were excluded (n=11). Follow-up time was defined as described for pre-diagnosis BMI. Secondary analysis with follow-up as the time between post-diagnosis BMI and diagnosis of the corresponding vascular disease or censoring did not alter the results and is not reported. Cox regression and restricted cubic splines were used to estimate HRs for the association between annual BMI change (categorically and per 1%) and incidence of diabetes-related vascular disease, with stable BMI and BMI change equal to 0% serving as references, respectively. The first model included age (stratified in years), sex and pre-diagnosis BMI (kg/m^2). The second (main) model included additionally education (3 categories: no vocational training/vocational training, technical college degree, university degree), smoking status change (5 categories: never, former, former-to-current, current-to-former, current), smoking duration (years), smoking duration change (years), alcohol consumption (g/day), alcohol consumption change (g/day), physical activity (h/week), physical activity change (h/week), MedPyramid score (units), and antihypertensive (yes/no), lipid-lowering (yes/no) and glucose-lowering medication (4 categories: no medication, oral medication, insulin, insulin and oral medication). Changes in lifestyle factors were assessed as the difference between post-diagnosis and pre-diagnosis measurements. Proportional hazards were assessed with Schoenfeld residuals and the linearity of quantitative covariates with cubic splines, as previously described. The assumptions of proportional hazards and linearity were fulfilled.

Sensitivity analyses

Several sensitivity analyses were carried out to evaluate the consistency of findings. Associations were evaluated across strata of sex, age at diabetes diagnosis (<65 vs ≥65 years) and smoking status for pre-diagnosis BMI and BMI change. With regard to BMI change, findings were also assessed according to strata of pre-diagnosis BMI (BMI <30.0 vs ≥30.0 kg/m^2) and oral glucose-lowering medication (yes vs no; excluding insulin users). The LRT was used to compare models with and without the multiplicative interaction term between continuous BMI and BMI change and the several levels of the effect modifiers. A *p*-value of LRT less than 0.05 was considered significant. Furthermore, analyses were performed excluding participants treated with insulin at diagnosis and early outcomes for pre-diagnosis BMI (<2 years after diabetes diagnosis). Early outcomes were not observed for BMI change analysis. Lastly, the analyses were repeated by censoring at first event and among complete cases.

Selection of confounders for objective 2

Confounders were selected based on previous knowledge on their associations with BMI as well as diabetes-related complications (see page 81, 'Selection of confounders for objective 1'). Ageing and sex are well-known factors that have an impact on body weight (Jura and Kozak, 2016, Kautzky-Willer et al., 2016). Furthermore, obesity is more prevalent among individuals with a lower education level (McLaren, 2007). Smoking, may also act as a confounder in the obesity-disease relations, as smokers appear to have lower body weight but higher risk for future illness (Tobias and Manson, 2018). Alcohol consumption has been linked to weight gain among heavy drinkers (Sayon-Orea et al., 2011); whereas higher levels of physical activity and adherence to the Mediterranean diet have been shown to contribute to the maintenance of a healthier body weight (Beunza et al., 2010, Lee et al., 2010a). In addition, higher adherence to the Mediterranean diet has been inversely associated with CVD (Estruch et al., 2018), type 2 diabetes (Esposito et al., 2015), and possibly with microvascular complications (Díaz-López et al., 2018, Díaz-López et al., 2015). Family history of type 2 diabetes and CVD was used as a proxy of shared environmental, behavioural and genetic factors that may result to a predisposition to diabetes-related complications and obesity (Alharithy et al., 2018, Maghbooli et al., 2014, Mühlenbruch et al., 2020a, Sargeant

et al., 2000). Possible mediators for the association between obesity and diabetes complications might be hypertension and dyslipidaemia (Vekic et al., 2019, DeMarco et al., 2014). Therefore, a separate model (model 3) was constructed.

For the association between BMI change and complications, variables denoting the changes in lifestyle factors (between pre- and post-diagnosis follow-up rounds) were additionally included. The change in MedPyramid score was not included as dietary habits were assessed only in two time points (recruitment and third follow-up). Furthermore, the pre-diagnosis BMI was added to control for baseline BMI; and glucose-lowering medication, since it may affect body weight (Apovian et al., 2019).

3.4.3.3 Objective 3: Application of the German diabetes risk score and cardiovascular disease risk score for prediction of vascular complications

The nonclinical GDRS and CVDRS were calculated at two-time points – at EPIC-Potsdam recruitment ($GDRS_{REC}$, $CVDRS_{REC}$) and type 2 diabetes diagnosis ($GDRS_{T2D}$, $CVDRS_{T2D}$). For the latter, information from the most recent data collection round before diabetes diagnosis was used. At recruitment and second follow-up assessments, physical activity was calculated by summing the hours per week spent for sports, biking and gardening and divided by two. Physical activity information for the fourth and fifth follow-up included total hours per week devoted to sports activities divided by two, due to the different assessment methods applied to these assessment rounds (see section 3.3.1.2). The clinical GDRS and CVDRS were calculated only at EPIC-Potsdam recruitment, as the longitudinal assessment of clinical values was not performed. Missing biomarker values were not imputed (see section 3.4.2.2), resulting in an analytical population of 655 and 669 participants out of 1226 individuals for the clinical GDRS and CVDRS, respectively.

Separate models were fitted for total, macrovascular, microvascular complications, kidney disease, neuropathy and retinopathy. Cox regression was used to assess the association of the nonclinical and clinical GDRS and CVDRS with complications, where follow-up time was defined as the underlying timescale (**Objective 3a**). Follow-up time was defined as the interval between the date at recruitment or diabetes diagnosis, accordingly, and the diagnosis date of the respective endpoint or date of the last examination by physicians. HRs were estimated according to score categories reflecting a defined 5-year

probability of developing type 2 diabetes or 10-year risk for CVD (<5%, 5 to 10%, ≥10%), using the lowest probability category as the reference, and continuously (per 50 units). Two models were evaluated. The first model was unadjusted. The second model was adjusted for sex and age at baseline (years) in order to investigate whether the associations could be merely explained by these strongly related to complications non-modifiable risk factors. The analysis was performed separately for the ten imputation datasets and results were combined based on Rubin's rules. Proportional hazards were assessed with Schoenfeld residuals and the linearity assumption with cubic splines and the Wald test. Both assumptions were fulfilled.

The predictive ability of the risk scores in regard to diabetes-related vascular complications was assessed with the C-index (**Objective 3b**). A description of the C-index is provided in **Box 2**. The C-index and 95% CI were calculated using the SAS Macro *%PREDC* (Cook). Confidence intervals were derived with bootstrapping based on 100 different bootstrap samples. The procedure was performed separately for each imputation dataset and the median was taken. All analyses were repeated among complete cases.

Box 2. Discrimination index

Discrimination quantifies the model's ability to correctly classify individuals into the outcome categories (Pencina and D'Agostino, 2004). A popular discrimination measure for dichotomous outcomes is the AU-ROC (of sensitivity and 1–specificity). When dealing with survival data, where the outcome is time-to-event, the C (for concordance) index is commonly applied (Harrell et al., 1996).

Let (i, j) denote a pair of individuals among n individuals, with X_i, X_j representing their actual survival times. The individuals are followed for a given time T_{end} and at a given point in time $T \leq T_{end}$, the participants are divided into two categories, event and non-event. For participants who do not develop the event at time point T, their survival time is equal to T. Let $T_1, T_2, \ldots, T_n$ represent the predicted survival times of participants. It can be shown that the predicted survival times and the predicted probabilities of survival $(Y_1, Y_2, \ldots, Y_n)$ are interchangeable (Pencina and D'Agostino, 2004). A pair is concordant if $X_i < X_j$ and $Y_i < Y_j$, or $X_i > X_j$ and $Y_i > Y_j$. When $X_i < X_j$ and $Y_i > Y_j$, or $X_i > X_j$ and $Y_i < Y_j$, then the pair is considered discordant. Survival times can be compared either when both individuals had the event of interest or when one had the event (e.g. individual i) and j's follow-up time has exceeded the survival time of i (Harrell et al., 1982). Such pairs are called usable. The overall C-index is defined as the proportion of all usable pairs. That is, the pairs where predictions and outcomes are concordant, given by

$$C = \frac{\pi_c}{\pi_c + \pi_d}$$

where, $\pi_c = P\big(X_i < X_j \text{ and } Y_i < Y_j \text{ or } X_i > X_j \text{ and } Y_i > Y_j\big)$

$$= P\big(X_i < X_j \text{ and } Y_i < Y_j\big) + P\big(X_i > X_j \text{ and } Y_i > Y_j\big)$$

$\pi_d = P\big(X_i < X_j \text{ and } Y_i > Y_j \text{ or } X_i > X_j \text{ and } Y_i < Y_j\big)$

$$= P\big(X_i < X_j \text{ and } Y_i > Y_j\big) + P\big(X_i > X_j \text{ and } Y_i < Y_j\big)$$

The estimated C-index may be written as

$$\hat{C} = \frac{1}{Q} \sum_{(i,j) \in U} c_{ij}$$

where, Q is the number of comparisons made, U is the set of all usable pairs, and $c_{ij} = 1$ for concordant pairs and 0 otherwise (Pencina and D'Agostino, 2004). Values of C near 0.5 denote that the risk assignment is not better than coin-flipping. A C higher than 0.7 indicates good discrimination.

4.
Results

4.1 Overview of the chapter

The chapter first presents the risk of complication development in association with the complication load and the impact of lifestyle factors observed in this study (Objective 1, section 4.2). The results from the investigation of the effect of BMI and BMI change on micro- and macrovascular complications follows (Objective 2, section 4.3). Finally, the association of the GDRS and CVDRS with complications are described, as well as the predictive value of the scores for vascular complications of diabetes (Objective 3, section 4.4).

4.2 Development of vascular complications and concurrent effect of selected lifestyle factors

Out of 1199 participants, 438 individuals developed at least one diabetes-related vascular complication over a median (25th–75th percentile) follow-up time of 11.6 (9.1–14.5) years. In total, there were 96 cases of macrovascular disease and 383 individuals with microvascular complications (consisting of 223 kidney disease, 234 neuropathy and 43 retinopathy cases). The participants' flow across the five complication states is shown in **Figure 4.1**. From state 'None', 81 (6.8%) participants moved to state 'Macro' and 26 (32.1%) of them reached the

final state 'Macro & Micro1'. A total of 357 (29.8%) individuals initially moved to state 'Micro1', from which 15 (4.2%) reached state 'Macro & Micro1' and 77 (21.6%) state 'Micro1 & Micro2'.

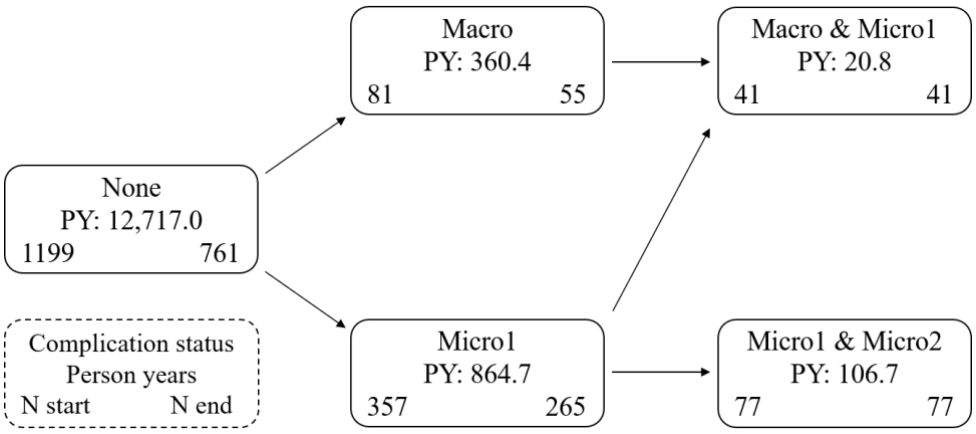

Figure 4.1 Complication flow in the study

Numbers are combined from ten imputation datasets. States were distinguished by order of complication occurrence. The five states were: the first complication was a macrovascular event (Macro); the first complication was a microvascular event (Micro1); occurrence of a macro- and a microvascular event (Macro & Micro1); occurrence of two microvascular events (Micro1 & Micro2). The number in the boxes indicates the number of participants starting in the state (bottom left) and the number of participants ending in the state (bottom right). PY stands for person-years.

The characteristics of participants at study entry by first transition status are reported in **Table 4.1**. Individuals who developed a macrovascular complication as a first event were more likely to be men, be diagnosed with diabetes at an older age, consume more alcohol and be former or current smokers, compared with participants with no complication or a first microvascular complication. Moreover, a higher percentage of them had prevalent hypertension and familial history of myocardial infarction. Participants with a microvascular complication as the first event were more likely to report prevalence of dyslipidaemia at study entry. Compared to individuals who did not develop a complication during the follow-up, participants with complications were more likely to be treated with insulin at diabetes diagnosis.

Table 4.1 Descriptive characteristics at study entry by transition status

Characteristic	None n=761	Microvascular event (state Micro1) n=357	Macrovascular event (state Macro) n=81
Demographics			
Male sex, n (%)	375 (49.3)	206 (57.8)	55 (67.9)
Age at diabetes diagnosis, years, median (25^{th}–75^{th} pct)	59.6 (52.9–65.4)	61.4 (56.0–65.6)	64.4 (58.3–67.3)
Education, n (%)			
No vocational training/vocational training	332 (43.6)	179 (50.1)	35 (42.7)
Technical college degree	198 (26.0)	78.5 (22.0)	18 (22.2)
University degree	231 (30.4)	99 (27.9)	29 (35.2)
Pre-diagnosis lifestyle			
Physical activity, h/week, median (25^{th}–75^{th} pct)	1.0 (0–3.0)	1.0 (0–4.0)	1.0 (0–2.5)
Alcohol intake, g/day, median (25th–75th pct)	8.7 (2.8–21.3)	8.2 (2.6–20.4)	11.1 (3.3–24.7)
Smoking status, n (%)			
Never-smoker	318 (41.8)	137 (38.4)	20 (24.5)
Former smoker	324 (42.6)	158 (44.3)	43 (52.4)
Current smoker	119 (15.6)	62 (17.4)	19 (23.2)
Smoking duration, years, median (25th–75th pct)	23.0 (14.0–32.0)	27.0 (15.0–35.0)	24.1 (15.0–32.0)
BMI, kg/m^2, median (25th–75th pct)	29.8 (27.1–33.1)	30.5 (27.8–33.8)	29.8 (27.4–32.9)

Continued

Table 4.1 continued

Characteristic	None n=761	Microvascular event (state Micro1) n=357	Macrovascular event (state Macro) n=81
Medical information			
Family history of diabetes, n (%)	340 (44.7)	159 (44.6)	35 (43.0)
Family history of myocardial infarction, n (%)	139 (18.3)	57 (16.0)	17 (21.0)
Family history of stroke, n (%)	158 (20.8)	68 (19.1)	12 (14.8)
Hypertension, n (%)	605 (79.5)	284 (79.6)	72 (87.7)
Dyslipidemia, n (%)	529 (69.5)	286 (80.1)	61 (74.3)
Glycose-lowering medication, n (%)			
Oral medication	459 (60.3)	222 (62.3)	52 (63.3)
Insulin	21 (2.8)	17 (4.8)	3 (3.6)
Insulin and oral medication	29 (3.8)	22 (6.2)	5 (6.2)

Pct, percentile

4.2.1 Association of vascular complications with the development of further complications

Overall, the risk of developing a complication was increased among participants with a complication load than participants with no previous complication. **Figure 4.2** shows the HRs and 95% CIs for micro- and macrovascular complications according to complication state compared to individuals without vascular events. In models adjusted for age, sex and state duration, the occurrence of a microvascular complication was associated with 2.34 times higher incidence (95% CI 1.16, 4,74) of a further microvascular event and 4.61 times higher risk (95% CI 1.26, 16.84) for future macrovascular complications (**Figure 4.2**, model 1). Similarly, participants who developed a macrovascular event had a twofold higher risk of a microvascular complication (HR 2.55; 95% CI 1.19, 5.45; **Figure 4.2**, model 1).

The results did not change substantially in models additionally adjusted for education, lifestyle, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia. Compared to participants without a previous complication, the fully adjusted HR (95% CI) for a microvascular complication was 1.90 (0.91, 3.98) for individuals with a prior microvascular event and 2.26 (1.05, 4.86) for those with a past macrovascular event (**Figure 4.2**, model 2). Among individuals with a microvascular event, the fully adjusted HR for a further macrovascular complication was 4.72 (95% CI 1.25, 17.86) (**Figure 4.2**, model 2).

In analyses stratified by sex, the increased risk of developing a complication persisted for both men and women with a preceding vascular event, compared with counterparts without complications (**Table 4.2**); although confidence intervals were considerably wide for some associations. Results from the complete case analysis were comparable to the multiple imputation analyses in terms of the direction of associations, but estimates were more pronounced and less precise (**Table 4.3**).

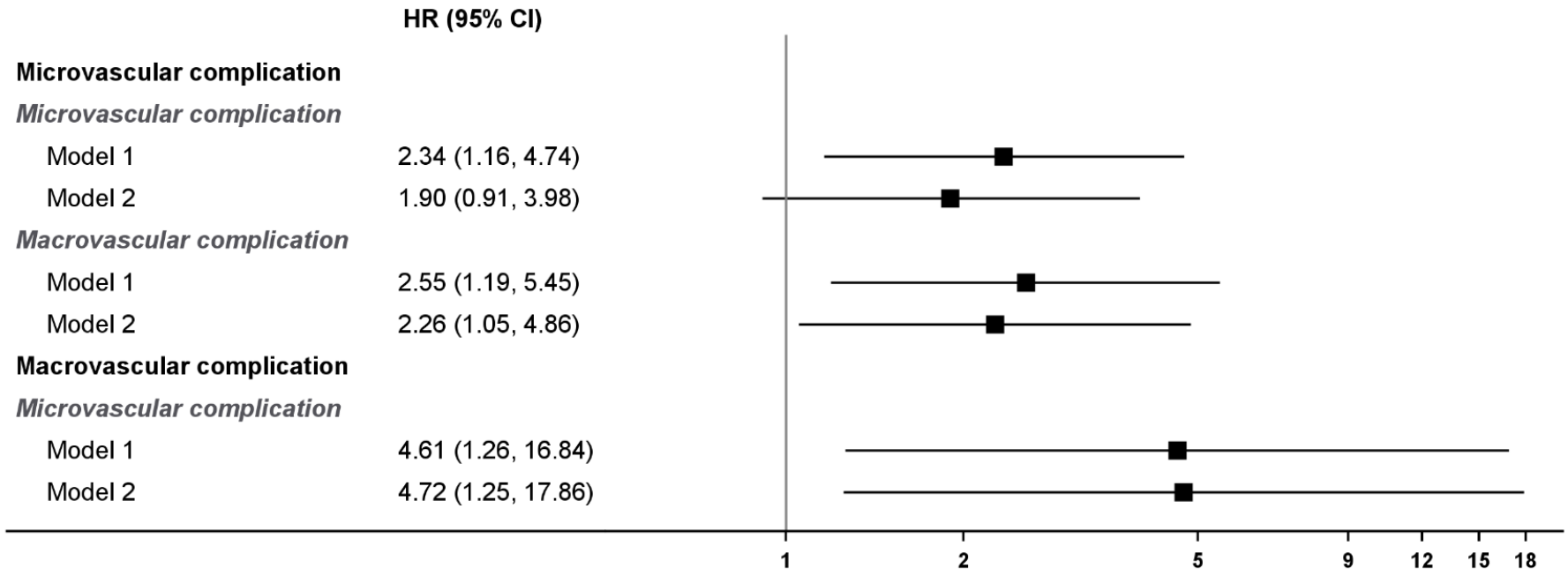

Figure 4.2 HRs and 95% CIs for microvascular and macrovascular complications according to complication load

Figure presents combined rounded values from the ten imputation datasets. Model 1: age, sex, and state duration. Model 2: Model 1 + education, smoking status, smoking duration, physical activity, BMI, alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia. Time-updated covariates are used according to state.

Table 4.2 HRs and 95% CIs for microvascular and macrovascular complications according to complication load, by sex

Complication load	Men	Women	P-value for interaction term
Risk of microvascular complication			
Microvascular complication			
Model 1	2.57 (1.02, 6.45)	1.77 (0.58, 5.39)	0.417
Model 2	2.26 (0.91, 5.60)	1.44 (0.42, 4.93)	0.280
Macrovascular complication			
Model 1	2.09 (0.70, 6.26)	3.23 (1.21, 8.63)	0.945
Model 2	1.59 (0.51, 4.93)	3.00 (1.13, 7.91)	0.673
Risk of macrovascular complication			
Microvascular complication			
Model 1	4.06 (0.75, 21.84)	3.73 (0.32, 43.99)	0.161
Model 2	4.40 (0.87, 22.17)	3.80 (0.26, 54.49)	0.244

Table presents combined rounded values from the ten imputation datasets

Model 1: age, sex, and state duration

Model 2: Model 1 + education, smoking status, smoking duration, physical activity, BMI, alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia

Time-updated covariates are used according to state

Table 4.3 HRs and 95% CIs for microvascular and macrovascular complications according to complication load, complete case analysis

Risk of microvascular complication	
Microvascular complication	
Model 1	4.41 (1.88, 10.33)
Model 2	3.35 (1.31, 8.53)
Macrovascular complication	
Model 1	2.14 (0.91, 5.01)
Model 2	2.05 (0.84, 4.99)
Risk of macrovascular complication	
Microvascular complication	
Model 1	8.64 (1.55, 48.12)
Model 2	16.88 (2.27, 125.49)

Table presents combined rounded values from the ten imputation datasets

Model 1: age, sex, and state duration

Model 2: Model 1 + education, smoking status, smoking duration, physical activity, BMI, alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia

Time-updated covariates are used according to state

4.2.2 Effect of selected lifestyle factors on the incidence of vascular complications investigated alone and combined with complication burden

Table 4.4 presents the associations between baseline lifestyle factors and risk of developing micro- and macrovascular complications. In multivariable models adjusted for age, sex, state duration, education, lifestyle factors, medication and prevalent conditions of hypertension and dyslipidaemia, a higher BMI and waist circumference at diabetes diagnosis were associated with an increased risk for microvascular complications (HR [95% CI]: 1.04 [1.02, 1.06] for BMI, 1.03 [1.02, 1.03] for waist circumference); whereas no association was observed for macrovascular complications (HR [95% CI]: 1.01 [0.96, 1.06] for BMI, 1.00 [0.98, 1.03] for waist circumference). Unexpectedly, physical activity appeared to have a positive relationship with microvascular complications (HR 1.03; 95% CI 1.00, 1.05), but no association was evident for macrovascular events (HR 0.99; 95% CI 0.93, 1.06; **Table 4.4**).

Consumption of coffee was associated with a reduced risk of macrovascular complications (HR 0.87; 95% CI 0.76, 0.99). There was a U-shaped relationship between red meat intake and microvascular complications. Compared with the middle tertile group (>0.23 to ≤ 0.43 of 150g portion/day), those in the lower and higher tertile group of red meat intake were at an increased risk of developing microvascular events (HR [95% CI]: 1.32 [1.03, 1.68] for the lower tertile group, 1.58 [1.23, 2.03] for the higher tertile group). In contrast, an inverse U-shaped association between red meat and macrovascular complications was observable, although the associations were not statistically significant in both lower (HR 0.77; 95% CI 0.47, 1.27) and higher tertile groups (HR 0.79; 95% CI 0.46, 1.36) when compared to the middle tertile group. Whole grain intake above the upper tertile (>0.67 of 50g portion/day) was associated with a lower risk of microvascular complications compared to the lower tertile group (≤0.19 of 50g portion/day) (HR 0.78; 95% CI 0.62, 0.99). Furthermore, a negative association was observed for whole grain consumption and macrovascular complications. However, the confidence interval was markedly large (**Table 4.4**).

Current smokers had an increased risk of developing diabetes-related complications than never-smokers, but this was more pronounced for macrovascular events (HR 4.81; 95% CI 1.47, 15.74) than microvascular events, where no clear conclusion can be drawn (HR

1.18; 95% CI 0.68, 2.05). Compared with very light alcohol consumption, higher consumption was associated with a decreased microvascular complication risk. However, an increased risk was observed for macrovascular complications, although the confidence intervals lacked precision (**Table 4.4**). Furthermore, compared with very light alcohol intake, abstinence was associated with an increased risk of vascular events.

Table 4.4 HRs and 95% CIs for microvascular and macrovascular complications according to baseline lifestyle factors

Lifestyle factor	Microvascular complication	Macrovascular complication
BMI (kg/m^2)	1.04 (1.02, 1.06)	1.01 (0.96, 1.06)
Waist circumference (cm)	1.03 (1.02, 1.03)	1.00 (0.98, 1.03)
Physical activity (h/week)	1.03 (1.00, 1.05)	0.99 (0.93, 1.06)
Coffee intake (150 g/day)	1.01 (0.96, 1.07)	0.87 (0.76, 0.99)
Red meat intake (150 g)		
≤0.23 portion/day	1.32 (1.03, 1.68)	0.77 (0.47, 1.27)
>0.23 to ≤ 0.43 portion/day	1.00 (Ref.)	1.00 (Ref.)
>0.43 portion/day	1.58 (1.23, 2.03)	0.79 (0.46, 1.36)
Whole grain intake (50 g)		
≤0.19 portion/day	1.00 (Ref.)	1.00 (Ref.)
>0.19 to ≤0.67 portion/day	0.82 (0.65, 1.04)	0.84 (0.47, 1.50)
>0.67 portion/day	0.78 (0.62, 0.99)	0.90 (0.53, 1.52)
Smoking status		
Never-smoker	1.00 (Ref.)	1.00 (Ref.)
Former smoker	1.03 (0.72, 1.45)	1.96 (0.95, 4.04)
Current smoker	1.18 (0.68, 2.05)	4.81 (1.47, 15.74)
Alcohol intake[a]		
Non-drinker	1.14 (0.67, 1.94)	2.89 (0.77, 10.82)
Very light user	1.00 (Ref.)	1.00 (Ref.)
Below the limit	0.84 (0.61, 1.16)	2.08 (0.78, 5.56)
Above the limit	0.72 (0.50, 1.02)	2.05 (0.71, 5.89)

Table presents combined rounded values from the ten imputation datasets

Models were adjusted for age, sex, state duration, education, smoking status, smoking duration, physical activity, BMI (not for waist circumference), coffee, red meat, whole grain and alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia

[a] Alcohol intake categories: non-drinker (lifetime non-user and former user); very light user (men/women ≤2/≤1 g/day); below the limit (men/women >2 to ≤24/>1 to ≤12 g/day); above the limit (men/women >24/>12 g/day)

4.2.2.1 Time-updated lifestyle factors and microvascular complications

The observed associations between lifestyle and complications were consistent when time-updated lifestyle factors were investigated. The overall effects of time-updated BMI and waist circumference were positively related to microvascular complications and were not modified by complication load (*p* for LRT=0.438 for BMI, 0.321 for waist circumference; **Table 4.5**). Time-updated physical activity was positively associated with microvascular events in the total population and participants without prior complication burden. The association was attenuated among participants with a previous micro- or macrovascular complication (**Table 4.5**).

Coffee intake was not associated with microvascular events in the total population, while a negative non-significant association was observed for participants with a complication burden. Nevertheless, the differences were not statistically significant (*p* for LRT=0.741). There was a significant interaction between complication burden and time-updated red meat intake (*p* for LRT=0.015). A U-shaped association was identified in the total population and among participants without a prior complication but was not apparent among participants with a complication load. There was a significant negative association between higher consumption of whole grain consumption and microvascular complications, compared with low intake (≤0.19 of 50g portion/day), in the total population and those without preceding vascular disease. However, the association was not clear for participants with a complication burden (**Table 4.5**).

Current smokers had a higher risk of developing microvascular complications regardless of existing complication burden, but associations did not reach statistical significance. Higher alcohol intake indicated a negative association with microvascular events when compared with very light users, except for participants with a previous microvascular complication, where a positive non-significant association was observed (**Table 4.5**).

Table 4.5 HR and 95% CIs for microvascular complications according to time-updated lifestyle factors, by complication load

Lifestyle factor	Overall	None	Microvascular complication	Macrovascular complication	LRT *p*-value
BMI (kg/m^2)	1.04 (1.02, 1.06)	1.04 (1.01, 1.06)	1.05 (1.00, 1.10)	1.07 (0.95, 1.20)	0.438
Waist circumference (cm)	1.03 (1.02, 1.04)	1.03 (1.02, 1.03)	1.03 (1.01, 1.05)	1.05 (1.00, 1.09)	0.321
Physical activity (h/week)	1.03 (1.00, 1.05)	1.04 (1.01, 1.07)	1.00 (0.97, 1.03)	0.99 (0.80, 1.23)	0.282
Coffee intake (150 g/day)[a]	0.98 (0.92, 1.05)	1.01 (0.94, 1.09)	0.87 (0.71, 1.07)	0.47 (0.20, 1.09)	0.741
Red meat intake (150 g)[a]					
≤0.23 portion/day	1.30 (0.99, 1.72)	1.40 (1.02, 1.91)	0.98 (0.48, 1.99)	1.38 (0.38, 5.03)	0.015
>0.23 to ≤ 0.43 portion/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
>0.43 portion/day	1.35 (1.01, 1.80)	1.59 (1.14, 2.22)	0.88 (0.49, 1.57)	0.67 (0.18, 4.47)	
Whole grain intake (50 g)[a]					
≤0.19 portion/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	0.333
>0.19 to ≤0.67 portion/day	0.69 (0.51, 0.93)	0.58 (0.41, 0.83)	0.91 (0.45, 1.84)	2.30 (0.59, 8.96)	
>0.67 portion/day	0.67 (0.50, 0.89)	0.63 (0.46, 0.86)	0.89 (0.41, 1.95)	1.67 (0.39, 7.21)	
Smoking status					
Never-smoker	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	0.752
Former smoker	1.06 (0.75, 1.50)	1.07 (0.75, 1.53)	0.90 (0.48, 1.70)	1.04 (0.33, 3.27)	
Current smoker	1.52 (0.87, 2.63)	1.41 (0.80, 2.49)	2.39 (0.99, 5.80)	2.50 (0.70, 8.99)	
Alcohol intake[b]					
Non-user	1.25 (0.78, 2.01)	1.19 (0.64, 2.21)	1.40 (0.63, 3.10)	0.83 (0.21, 3.23)	0.325

Continued

Table 4.5 continued

Lifestyle factor	Overall	None	Microvascular complication	Macrovascular complication	LRT *p*-value
Very light user	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Below the limit	0.94 (0.68, 1.29)	0.92 (0.63, 1.33)	1.26 (0.65, 2.45)	0.28 (0.11, 0.69)	
Above the limit	0.84 (0.59, 1.21)	0.79 (0.53, 1.20)	1.73 (0.76, 3.93)	0.21 (0.07, 0.65)	

Table presents combined rounded values from the ten imputation datasets

Models were adjusted for age, sex, state duration, education, smoking status, smoking duration, physical activity, BMI (not for waist circumference), coffee, red meat, whole grain and alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia

[a] Results among 714 participants with diabetes diagnosis between the two food frequency questionnaire applications

[b] Alcohol intake categories: non-drinker (lifetime non-user and former user); very light user (men/women ≤2/≤1 g/day); below the limit (men/women >2 to ≤24/>1 to ≤12 g/day); above the limit (men/women >24/>12 g/day)

LRT, Likelihood ratio test; BMI, Body mass index

4.2.2.2 Time-updated lifestyle factors and macrovascular complications

There was no association between time-updated adiposity measurers and macrovascular complications regardless of the several complication profiles (*p* for LRT=0.556 for BMI, 0.660 for waist circumference; **Table 4.6**). Time-updated physical activity and coffee intake showed a non-significant inverse association with macrovascular complications, which was not modified by complication load (*p* for LRT=0.556 for physical activity, 0.660 for coffee intake; **Table 4.6**). As before, an inverse U-shaped relationship between time-updated red meat intake and macrovascular complications was detected; however, confidence intervals were considerably wide for all associations. Whole grain intake did not appear to be associated with macrovascular complications in any of the complication profiles.

A significant interaction between complication status and smoking status was observed (*p* for LRT=0.002; **Table 4.6**). Compared with never-smokers, former and current smoking increased the risk of macrovascular complications by twofold and sixfold, respectively, in the total population and those without complications. However, among participants with a microvascular complication, past smoking history was non-significantly inversely associated with macrovascular complications, while current smoking showed a non-significant positive association. Finally, a significant interaction between complication burden and time-updated alcohol intake was present (*p* for LRT=0.008). Compared with very light alcohol consumption, consumption below and above the limit was associated with increased risk of macrovascular complications in the total population and participants without complication burden. An inverse association was observed among individuals with a preceding microvascular event. None of the associations, however, were statistically significant (**Table 4.6**).

Table 4.6 HRs and 95% CIs for macrovascular complications according to time-updated lifestyle factors, by complication load

Lifestyle factor	Overall	None	Microvascular complication	LRT *p*-value
BMI (kg/m^2)	1.00 (0.95, 1.05)	1.00 (0.94, 1.06)	1.03 (0.94, 1.13)	0.556
WC (cm)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.99 (0.94, 1.04)	0.660
Physical activity (h/week)	0.96 (0.89, 1.03)	0.96 (0.90, 1.03)	0.66 (0.41, 1.06)	0.158
Coffee intake (150 g/day)[a]	0.85 (0.72, 1.01)	0.86 (0.71, 1.04)	0.83 (0.60, 1.14)	0.751
Red meat intake (150 g)[a]				
≤0.23 portion/day	0.70 (0.36, 1.35)	0.61 (0.30, 1.26)	0.59 (0.28, 1.26)	0.152
>0.23 to ≤ 0.43 portion/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
>0.43 portion/day	0.59 (0.28, 1.26)	0.69 (0.32, 1.49)	0.41 (0.03, 5.42)	
Whole grain intake (50 g)[a]				
≤0.19 portion/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	0.072
>0.19 to ≤0.67 portion/day	0.77 (0.33, 1.82)	1.03 (0.44, 2.44)	—[b]	
>0.67 portion/day	1.03 (0.53, 2.01)	1.08 (0.54, 2.19)	0.32 (0.05, 2.11)	
Smoking status				
Never-smoker	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Former smoker	2.08 (1.03, 4.20)	2.66 (1.26, 5.63)	0.17 (0.02, 1.46)	0.002
Current smoker	6.37 (2.04, 19.9)	6.65 (2.01, 21.99)	2.60 (0.42, 16.08)	
Alcohol intake[c]				
Non-user	1.42 (0.46, 4.41)	2.66 (0.60, 11.84)	0.48 (0.05, 4.96)	0.008

Continued

Table 4.6 continued

Lifestyle factor	Overall	None	Microvascular complication	LRT *p*-value
Very light user	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Below the limit	1.06 (0.51, 2.20)	2.20 (0.74, 6.53)	0.12 (0.02, 0.72)	
Above the limit	1.25 (0.57, 2.76)	2.43 (0.78, 7.61)	0.24 (0.04, 1.32)	

Table presents combined rounded values from the ten imputation datasets

Models were adjusted for age, sex, state duration, education, smoking status, smoking duration, physical activity, BMI (not for waist circumference), coffee, red meat, whole grain and alcohol intake, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia

[a] Results among 714 participants with diabetes diagnosis between the two food frequency questionnaire applications

[b] HR (95% CI) are not reported due to small numbers

[c] Alcohol intake categories: non-drinker (lifetime non-user and former user); very light user (men/women ≤2/≤1 g/day); below the limit (men/women >2 to ≤24/>1 to ≤12 g/day); above the limit (men/women >24/>12 g/day)

LRT, Likelihood ratio test; BMI, Body mass index

4.3 BMI, BMI change and risk of vascular complications[13]

Out of 1,083 participants, 587 (54.2%) were men, and there were 85 (7.8%) macrovascular events, 347 (32.0%) total microvascular events, 207 (19.1%) kidney disease cases, and 211 (19.5%) neuropathy cases. The median (25^{th}–75^{th} percentile) follow-up time was 10.8 (8.2–13.8) years for total complications, 11.6 (9.0–14.6) years for macrovascular complications, 11.1 (8.5–14.0) years for microvascular complications, 11.4 (8.9–14.4) years for kidney disease and 11.4 (9.0–14.4) years for neuropathy.

Baseline characteristics are presented in **Table 4.7**. The median BMI was 29.9 kg/m^2 (25^{th}–75^{th} percentile 27.4–33.2). The median age at baseline was 60.4 years (25^{th}–75^{th} percentile 53.5–65.3) and was the lowest in the highest BMI category (57.8 years, 25^{th}–75^{th} percentile 51.2–64.1). Participants with a lower BMI reported higher alcohol intake, were more likely to be current smokers and to have a university degree. Higher BMI was associated with a higher prevalence of hypertension and a family history of diabetes. Median relative annual BMI change after diabetes diagnosis was –0.4% (25^{th}–75^{th} percentile –2.1 to 0.9), and higher pre-diagnosis BMI was associated with a higher decrease.

Appendices 10 and 11 report baseline characteristics by sex. Overall, women were diagnosed with diabetes at an older age than men, consumed less alcohol and were more likely to have a family history of diabetes and CVD. Furthermore, the majority of women were never-smokers, while men reported more often past or current smoking and were more likely to have a university degree.

[13] Data presented in this section were published by POLEMITI, E., BAUDRY, J., KUXHAUS, O., JÄGER, S., BERGMANN, M. M., WEIKERT, C. & SCHULZE, M. B. 2021. BMI and BMI change following incident type 2 diabetes and risk of microvascular and macrovascular complications: the EPIC-Potsdam study. Diabetologia, 64, 814-25.

Table 4.7 Characteristics of study participants according to pre-diagnosis BMI categories [extracted from (Polemiti et al., 2021)]

Characteristic	Total n=1083	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155
Pre-diagnosis BMI, kg/m^2, median (25th–75th pct)	29.9 (27.4–33.2)	23.8 (22.8–24.5)	28.0 (26.7–29.1)	32.1 (30.9–33.5)	37.6 (36.1–40.6)
Relative annual BMI change (%), median (25th–75th pct)[a,b]	−0.4 (−2.1 to 0.9)	−0.0 (−2.0 to 1.1)	−0.3 (−1.7 to 0.9)	−0.5 (−2.2 to 0.8)	−0.6 (−2.5 to 0.8)
Relative annual BMI change, categories, n (%)[a]					
>1% BMI loss	420 (39.3)	37 (37.5)	162 (36.1)	153 (41.3)	69 (45.1)
No change	402 (37.6)	35 (36.41)	179 (40.0)	133 (36.0)	55 (36.3)
>1% BMI gain	247 (23.1)	26 (26.2)	107 (23.9)	85 (23.0)	29 (19.0)
Relative BMI change before pre-diagnosis fup (%), median (25th–75th pct)[c]	0.3 (−1.0 to 1.5)	0 (−1.2 to 0.9)	0.1 (−1.1 to 1.3)	0.5 (−0.8 to 1.7)	1.0 (−0.3 to 2.5)
Demographics					
Male sex, n (%)	587 (54.2)	46 (46.7)	268 (59.2)	215 (56.8)	58 (37.5)
Age at pre-diagnosis BMI measurement, years, median (25th–75th pct)	59.1 (52.2–64.4)	57.8 (51.0–63.3)	60.2 (54.6–64.8)	58.8 (51.4–64.2)	57.0 (50.3–63.0)
Age at diabetes diagnosis, years, median (25th–75th pct)	60.4 (53.5–65.3)	58.9 (52.4–64.5)	61.5 (56.0–66.0)	60.0 (52.3–65.1)	57.8 (51.2–64.1)
Education, n (%)					
No vocational training/vocational training	490 (45.2)	35 (34.7)	187 (41.4)	184 (48.7)	84 (53.9)
Technical college degree	274 (25.3)	28 (28.6)	116 (25.6)	89 (23.7)	40 (25.9)
University degree	320 (29.6)	36 (36.7)	149 (33.0)	104 (27.5)	31 (20.1)
Pre-diagnosis lifestyle					
Physical activity, h/week, median (25th–75th pct)	1.0 (0–3.2)	1.0 (0–3.5)	1.0 (0–3.5)	1.0 (0–3.0)	0.6 (0–3.0)
Alcohol intake, g/day, median (25th–75th pct)	9.0 (2.8–21.7)	10.1 (2.5–18.6)	10.2 (3.6–22.5)	8.3 (2.9–23.5)	5.8 (1.8–16.3)

Continued

Table 4.7 continued

Characteristic	Total n=1083	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155
MedPyramid score, units, median (25th–75th pct)	6.7 (5.8–7.5)	6.7 (5.8–7.5)	6.8 (5.8–7.5)	6.6 (5.8–7.5)	6.8 (5.8–7.7)
Smoking status, n (%)					
Never-smoker	428 (39.5)	41 (41.7)	172 (38.0)	147 (38.9)	68 (43.7)
Former smoker	474 (43.7)	35 (34.7)	200 (44.2)	175 (46.3)	65 (41.9)
Current smoker	182 (16.8)	24 (23.7)	80 (17.7)	56 (14.9)	22 (14.3)
Smoking duration, years, median (25th–75th pct)	24.0 (15.0–33.0)	24.0 (11.5–34.0)	25.0 (15.0–35.0)	23.0 (15.0–32.3)	26.9 (14.0–31.0)
Medical information					
Family history of diabetes, n (%)	483 (44.6)	43 (43.4)	197 (43.5)	169 (44.8)	76 (49.0)
Family history of myocardial infarction, n (%)	180 (16.6)	13 (12.8)	78 (17.2)	65 (17.2)	26 (16.8)
Family history of stroke, n (%)	222 (20.5)	22 (22.5)	99 (21.8)	70 (18.5)	30 (19.4)
Hypertension, n (%)	870 (80.3)	64 (64.8)	343 (75.8)	317 (84.0)	145 (93.6)
Dyslipidaemia, n (%)	795 (73.4)	64 (64.1)	347 (76.8)	285 (75.5)	100 (64.5)
Insulin use at diabetes diagnosis, n (%)	85 (7.8)	9 (9.2)	29 (6.4)	39 (10.3)	7 (4.5)

Table presents combined rounded values from the ten imputation datasets

[a] 14 participants did not have follow-up after diabetes diagnosis

[b] Mean (±standard deviation) for relative BMI change for the total population was –0.6 (±2.8)

[c] 197 participants did not have follow-up before pre-diagnosis time point.

BMI, Body mass index; Pct, percentile; Fup, follow-up

4.3.1 BMI and risk of vascular complications

In age and sex-adjusted Cox models, each additional 5 kg/m^2 BMI higher was associated with 1.17 times higher incidence (95% CI 1.05, 1.30) of total vascular complications (**Table 4.8**, model 1). The association did not change markedly in multivariable models further adjusted for education, lifestyle, and family health history (HR 1.18; 95% CI 1.06, 1.31; **Table 4.8**, model 2). Restricted cubic spline analyses did not indicate a departure from linearity (*p* for nonlinearity=0.55; **Figure 4.3**, panel a). Compared to participants with normal weight (18.5–24.9 kg/m^2), the multivariable-adjusted HR was 1.29 (95% CI 0.81, 2.04) for participants in the overweight category (25.0–29.9 kg/m^2), 1.57 (95% CI 0.99, 2.50) in obese I category (30.0–34.9 kg/m^2), and 1.97 (95% CI 1.20, 3.24) in obese II category (≥35.0 kg/m^2) (**Table 4.8**, model 2).

When micro- and macrovascular complications were evaluated separately, a positive association was observed for microvascular complications (multivariable-adjusted HR per 5 kg/m^2 BMI increment: 1.21; 95% CI 1.07, 1.36; **Table 4.8**, model 2) and no deviation from linearity was detected (*p* for nonlinearity=0.36; **Figure 4.3**, panel c). The HRs were 1.41 (95% CI 0.84, 2.37) for persons in the overweight category, 1.76 (95% CI 1.06, 2.95) in obese I and 2.50 (95% CI 1.44, 4.36) in obese II category, compared to individuals with normal weight (**Table 4.8**, model 2). No association between BMI and macrovascular complications was detected in continuous (HR per 5 kg/m^2 BMI increment: 1.05; 95% CI 0.81, 1.36, model 2) or categorical analyses (HR [95% CI] was 0.94 [0.40, 2.19] for individuals in the overweight category, 1.09 [0.45, 2.60] in obese I and 0.77 [0.26, 2.25] in obese II category; **Table 4.8**, model 2).

Positive linear associations were observed with further subdivision of microvascular complications into kidney disease (multivariable-adjusted HR per 5 kg/m^2 BMI increment: 1.39; 95% CI 1.21, 1.60; *p* for nonlinearity=0.46) and neuropathy (HR 1.12; 95% CI 0.96, 1.31; *p* for nonlinearity=0.86) (**Table 4.8**, model 2; **Figure 4.3**, panel d and e). Findings were corroborated in analyses using BMI categories, where for every increasing BMI category the incidence of kidney disease and neuropathy increased, compared with individuals in the normal weight category (**Table 4.8**).

After further adjustment for dyslipidaemia and hypertension, the magnitude of the associations remained unchanged for microvascular complications (per 5 kg/m^2 BMI increment: HR 1.24; 95% CI 1.09, 1.40), kidney disease (HR 1.42; 95% CI 1.22, 1.66) and neuropathy (HR 1.11; 95% CI 0.94, 1.31) (**Table 4.8**, model 3).

Table 4.8 HRs and 95% CIs for microvascular and macrovascular complications according to pre-diagnosis BMI (categories and per 5 kg/m^2) [extracted from (Polemiti et al., 2021)]

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=1083
	18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155	
Total vascular complications					
No. of cases / person-years	24 / 1073.9	159 / 4844.6	147 / 4047.2	66 / 1663.1	395 / 11,623.9
Age- and sex-adjusted model	1.00 (Ref.)	1.28 (0.81, 2.00)	1.51 (0.97, 2.36)	1.86 (1.15, 3.01)	1.17 (1.05, 1.30)
Model 2	1.00 (Ref.)	1.29 (0.81, 2.04)	1.57 (0.99, 2.50)	1.97 (1.20, 3.24)	1.18 (1.06, 1.31)
Model 3	1.00 (Ref.)	1.23 (0.77, 1.98)	1.51 (0.95, 2.42)	2.05 (1.23, 3.41)	1.19 (1.07, 1.34)
Macrovascular complications					
No. of cases / person-years	7 / 1107.3	38 / 5204.7	32 / 4376.5	8 / 1831.9	85 / 12,516.7
Age- and sex-adjusted model	1.00 (Ref.)	0.91 (0.39, 2.11)	1.02 (0.44, 2.36)	0.70 (0.24, 2.03)	1.01 (0.78, 1.32)
Model 2	1.00 (Ref.)	0.94 (0.40, 2.19)	1.09 (0.45, 2.60)	0.77 (0.26, 2.25)	1.05 (0.81, 1.36)
Model 3	1.00 (Ref.)	0.89 (0.38, 2.11)	0.99 (0.41, 2.40)	0.68 (0.23, 2.04)	1.00 (0.76, 1.31)
Microvascular complications					
No. of cases / person-years	19 / 1108.1	138 / 5082.4	129 / 4218.1	62 / 1707.6	347 / 12,122.7
Age- and sex-adjusted model	1.00 (Ref.)	1.43 (0.86, 2.37)	1.71 (1.04, 2.83)	2.38 (1.39, 4.06)	1.20 (1.07, 1.35)
Model 2	1.00 (Ref.)	1.41 (0.84, 2.37)	1.76 (1.06, 2.95)	2.50 (1.44, 4.36)	1.21 (1.07, 1.36)
Model 3	1.00 (Ref.)	1.33 (0.78, 2.26)	1.69 (1.00, 2.85)	2.70 (1.53, 4.76)	1.24 (1.09, 1.40)

Continued

Table 4.8 continued

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=1083
	18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155	
Kidney disease					
No. of cases/ person-years	11 / 1130.1	74 / 5309.4	80 / 4386.7	42 / 1778.1	207 / 12,607.7
Age- and sex-adjusted model	1.00 (Ref.)	1.42 (0.73, 2.75)	2.01 (1.04, 3.87)	3.10 (1.57, 6.13)	1.38 (1.20, 1.58)
Model 2	1.00 (Ref.)	1.45 (0.74, 2.82)	2.09 (1.07, 4.07)	3.36 (1.67, 6.79)	1.39 (1.21, 1.60)
Model 3	1.00 (Ref.)	1.37 (0.70, 2.70)	2.02 (1.02, 3.97)	3.57 (1.72, 7.41)	1.42 (1.22, 1.66)
Neuropathy					
No. of cases / person-years	10 / 1118.7	90 / 5250.6	75 / 4417.1	35 / 1794.0	211 / 12,591.1
Age- and sex-adjusted model	1.00 (Ref.)	1.47 (0.75, 2.88)	1.54 (0.79, 2.98)	2.10 (1.03, 4.27)	1.12 (0.96, 1.31)
Model 2	1.00 (Ref.)	1.43 (0.71, 2.87)	1.55 (0.78, 3.10)	2.18 (1.05, 4.54)	1.12 (0.96, 1.31)
Model 3	1.00 (Ref.)	1.32 (0.66, 2.65)	1.41 (0.71, 2.80)	2.14 (1.04, 4.43)	1.11 (0.94, 1.31)

Table presents combined rounded values from the ten imputation datasets

Model 2: age- and sex-adjusted model + education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke

Model 3: Model 2 + prevalent conditions of hypertension and dyslipidaemia

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

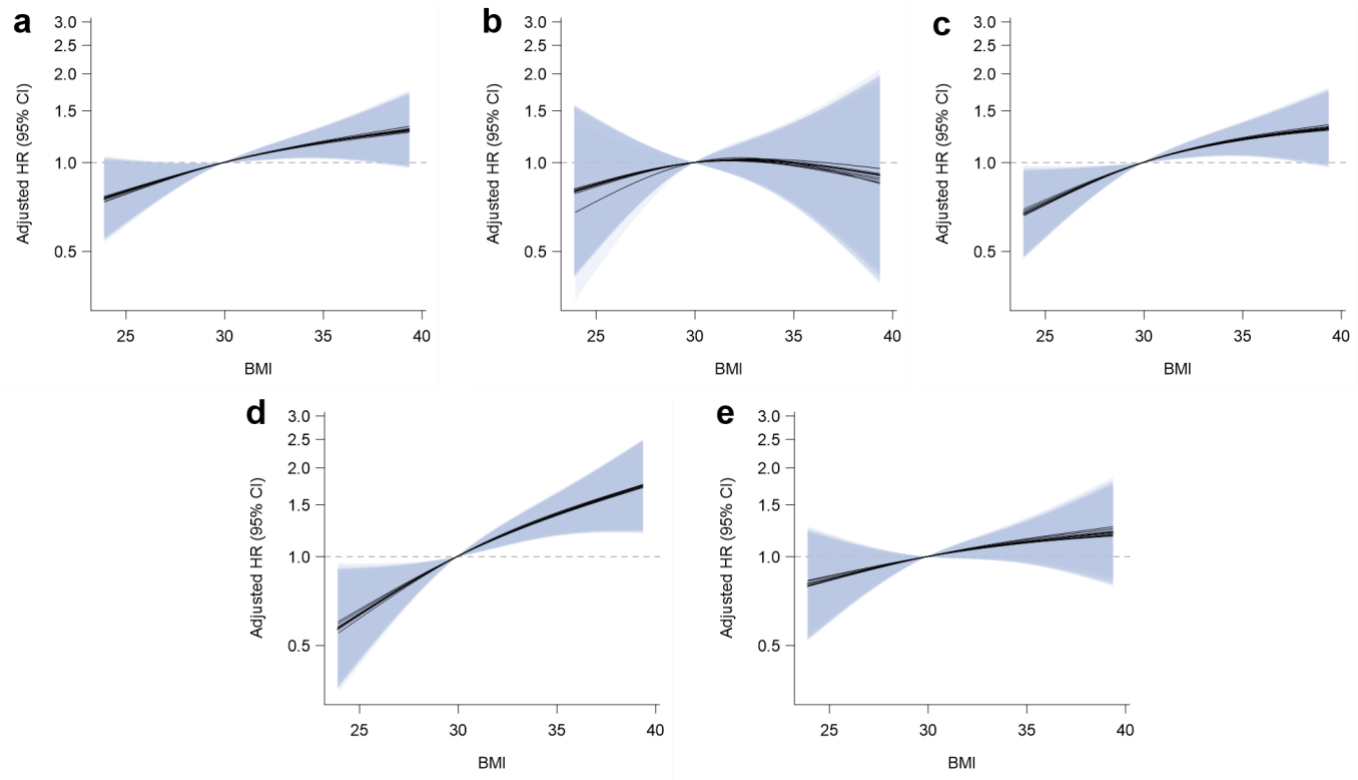

Figure 4.3 Association between pre-diagnosis BMI and risk of microvascular and macrovascular complications of diabetes [extracted from (Polemiti et al., 2021)]

(a) Total vascular complications. (b) Macrovascular complications. (c) Microvascular complications. (d) Kidney disease. (e) Neuropathy. Pre-diagnosis BMI was assessed as a continuous variable using restricted cubic spline regression, adjusted for age, sex, education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke. Splines (black lines) and 95% CIs (blue shading) from ten imputation datasets are shown. Knot placement was 5th, 50th and 95th percentile. Median BMI of 29.9 kg/m^2 served as reference. Test for non-linearity: total complications, p=0.55; macrovascular complications, p=0.64; microvascular complications, p=0.36; kidney disease, p=0.46; neuropathy, p=0.86. HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index.

Sensitivity analyses

Sex-stratified analyses did not reveal substantial differences in associations, except for neuropathy, where a stronger association was present in women (HR 1.22; 95% CI 0.96, 1.54; **Table 4.9**, model 2) than in men (HR 1.03; 95% CI 0.81, 1.31). Nevertheless, this difference was not statistically significant (*p* for LRT=0.30). Among never-smokers, a nonlinear association was observed for macrovascular complications (*p* for nonlinearity=0.02), indicating a positive association with a higher BMI up to about 32.5 kg/m^2 (**Appendix 12**). However, a positive linear association among never-smokers was still evident for microvascular complications (HR 1.16; 95% CI 0.94, 1.43), kidney disease (HR 1.20; 95% CI 0.93, 1.58) and neuropathy (HR 1.12; 95% CI 0.84, 1.49) (**Table 4.9**, model 2).

In analyses stratified by age of diabetes diagnosis associations appear consistent. Still, for neuropathy, a more pronounced association was detected among participants who were diagnosed with diabetes at 65 or older than those diagnosed younger (HR [95% CI]: 1.42 [1.02, 1.99] for age group ≥65 years, 1.06 [0.89, 1.27] for age group <65 years; **Table 4.9**, model 2). However, this difference was not statistically significant (*p* for LRT=0.93; **Table 4.9**). Results did not differ substantially from primary analyses after exclusion of participants treated with insulin at diabetes diagnosis or exclusion of individuals who developed a vascular event in the first two years of follow-up (**Table 4.9**).

Findings did not differ when only first in order complications were used as endpoints. The corresponding HRs (95% CIs) per 5 kg/m^2 BMI increment were 1.03 (0.78, 1.37) for macrovascular complications, 1.21 (1.08, 1.37) for microvascular complications, 1.39 (1.18, 1.64) for kidney disease and 1.07 (0.90, 1.28) for neuropathy (**Table 4.10**, model 2). Finally, results obtained from the complete case analysis were similar to those from multiple imputation, except for macrovascular complications, where estimates were higher in the complete case analysis (per 5 kg/m^2 BMI increment: HR 1.19, 95% CI 0.86, 1.67; **Table 4.11**, model 2). Nevertheless, the confidence interval was relatively wide to alter the conclusions drawn.

Table 4.9 HRs and 95% CIs for microvascular and macrovascular complications according to pre-diagnosis BMI (per 5 kg/m^2), by subgroups and sensitivity analyses [extracted from (Polemiti et al., 2021)]

	Total complications	Macrovascular	Microvascular	Kidney disease	Neuropathy
Men					
No. of cases / person-years	241 / 6354.6	57 / 6878.4	206 / 6579.4	124 / 6864.6	119 / 6868.6
Age- and sex- adjusted model	1.14 (0.99, 1.32)	1.05 (0.75, 1.49)	1.17 (1.00, 1.38)	1.38 (1.12, 1.69)	0.99 (0.79, 1.24)
Model 2	1.17 (1.00, 1.36)	1.06 (0.74, 1.51)	1.22 (1.02, 1.45)	1.50 (1.21, 1.87)	1.03 (0.81, 1.31)
Women					
No. of cases / person-years	155 / 5270.4	28 / 5638.8	142 / 5389.3	83 / 5589.2	92 / 5570.4
Age- and sex- adjusted model	1.18 (0.99, 1.40)	0.93 (0.60, 1.45)	1.22 (1.02, 1.46)	1.32 (1.05, 1.64)	1.23 (0.98, 1.56)
Model 2	1.21 (1.00, 1.45)	1.02 (0.63, 1.67)	1.24 (1.02, 1.51)	1.32 (1.01, 1.73)	1.22 (0.96, 1.54)
Never-smoker					
No. of cases / person-years	136 / 4671.6	22 / 4982.3	127 / 4801.0	77 / 4955.4	77 / 4983.5
Age- and sex- adjusted model	1.19 (0.97, 1.45)	—[a]	1.17 (0.95, 1.44)	1.24 (0.96, 1.60)	1.16 (0.88, 1.53)
Model 2	1.20 (0.98, 1.46)	—[a]	1.16 (0.94, 1.43)	1.20 (0.93, 1.58)	1.12 (0.84, 1.49)
Former smoker					
No. of cases / person-years	185 / 5157.3	42 / 5584.1	157 / 5399.1	98 / 5624.8	94 / 5626.7
Age- and sex- adjusted model	1.21 (1.02, 1.43)	—[a]	1.29 (1.08, 1.55)	1.51 (1.24, 1.85)	1.16 (0.92, 1.47)
Model 2	1.20 (1.00, 1.44)	—[a]	1.31 (1.07, 1.61)	1.64 (1.30, 2.06)	1.18 (0.91, 1.52)
Current smoker					
No. of cases / person-years	75 / 1794.6	21 / 1953.2	65 / 1920.6	32 / 2026.4	41 / 1980.5

Continued

Table 4.9 continued

	Total complications	Macrovascular	Microvascular	Kidney disease	Neuropathy
Age- and sex- adjusted model	1.10 (0.85, 1.42)	1.21 (0.75, 1.97)	1.08 (0.81, 1.45)	1.52 (1.05, 2.20)	1.04 (0.72, 1.50)
Model 2	1.21 (0.87, 1.67)	1.38 (0.57, 3.31)	1.19 (0.85, 1.66)	1.77 (1.08, 2.90)	1.31 (0.81, 2.13)
Age at diagnosis <65 years					
No. of cases / person-years	276 / 8960.6	51 / 9612.6	247 / 9294.9	140 / 9671.8	155 / 9608.6
Age- and sex- adjusted model	1.19 (1.05, 1.34)	1.00 (0.72, 1.37)	1.20 (1.05, 1.38)	1.47 (1.25, 1.74)	1.07 (0.89, 1.29)
Model 2	1.18 (1.05, 1.33)	1.03 (0.74, 1.44)	1.20 (1.04, 1.37)	1.50 (1.26, 1.79)	1.06 (0.89, 1.27)
Age at diagnosis ≥65 years					
No. of cases / person-years	119 / 2664.9	34 / 2904.0	101 / 2828.2	67 / 2935.0	57 / 2982.5
Age- and sex- adjusted model	1.14 (0.91, 1.43)	1.05 (0.65, 1.69)	1.23 (0.97, 1.55)	1.18 (0.91, 1.55)	1.32 (0.98, 1.78)
Model 2	1.17 (0.92, 1.48)	1.14 (0.68, 1.89)	1.25 (0.97, 1.61)	1.23 (0.91, 1.67)	1.42 (1.02, 1.99)
Exclusion of early outcomes					
No. of cases / person-years	369 / 11,595.3	70 / 12,504.8	333 / 11,953.9	199 / 12,599.7	205 / 12,581.7
Age- and sex- adjusted model	1.17 (1.05, 1.31)	1.01 (0.76, 1.36)	1.20 (1.06, 1.35)	1.38 (1.20, 1.59)	1.11 (0.94, 1.30)
Model 2	1.19 (1.06, 1.32)	1.05 (0.79, 1.40)	1.21 (1.07, 1.37)	1.40 (1.21, 1.61)	1.12 (0.96, 1.32)
Exclusion of insulin users					
No. of cases / person-years	351 / 10,816.9	77 / 11,601.6	306 / 11,273.3	186 / 11,685.0	181 / 11,693.7
Age- and sex- adjusted model	1.14 (1.02, 1.28)	1.03 (0.78, 1.37)	1.18 (1.04, 1.33)	1.29 (1.11, 1.49)	1.09 (0.93, 1.28)
Model 2	1.15 (1.03, 1.29)	1.07 (0.81, 1.42)	1.18 (1.04, 1.34)	1.30 (1.11, 1.52)	1.10 (0.94, 1.30)

Table presents combined rounded values from the ten imputation datasets

Model 2: age- and sex-adjusted model + education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke

[a] HR (95% CI) was not reported where violation of linearity assumption was found

Likelihood ratio test for interaction term for sex: Total complications: p=0.96; Macrovascular complications: p=0.48; Microvascular complications: p=0.86; Kidney disease: p=0.64; Neuropathy: p=0.30. Likelihood ratio test for interaction term for smoking status: Total complications: p=0.76; Microvascular complications: p=0.72; Microvascular complications: p=0.48; Kidney disease: p=0.24; Neuropathy: p=0.99. Likelihood ratio test for interaction term for age at diabetes diagnosis: Total complications: p=0.36; Macrovascular complications: p=0.74; Microvascular complications: p=0.82; Kidney disease: p=0.93; Neuropathy: p=0.93

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

Table 4.10 HRs and 95% CIs for microvascular and macrovascular complications according to pre-diagnosis BMI (categories and per 5 kg/m^2), censored at first event [extracted from (Polemiti et al., 2021)]

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=1083
	18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155	
Macrovascular complications					
No. of cases / person-years	6 / 1073.9	34 / 4844.6	26 / 4047.2	8 / 1663.1	74 / 11,623.9
Age- and sex-adjusted model	1.00 (Ref.)	0.95 (0.39, 2.30)	0.97 (0.40, 2.39)	0.82 (0.27, 2.47)	1.03 (0.78, 1.37)
Model 2	1.00 (Ref.)	0.99 (0.41, 2.42)	1.00 (0.39, 2.53)	0.86 (0.29, 2.61)	1.03 (0.78, 1.37)
Model 3	1.00 (Ref.)	0.94 (0.38, 2.32)	0.90 (0.35, 2.32)	0.75 (0.24, 2.33)	0.97 (0.72, 1.31)
Microvascular complications					
No. of cases / person-years	18 / 1073.9	125 / 4844.6	121 / 4047.2	58 / 1663.1	321 / 11,623.9
Age- and sex-adjusted model	1.00 (Ref.)	1.39 (0.82, 2.34)	1.70 (1.01, 2.86)	2.26 (1.30, 3.93)	1.20 (1.07, 1.36)
Model 2	1.00 (Ref.)	1.39 (0.81, 2.38)	1.76 (1.03, 3.02)	2.42 (1.36, 4.31)	1.21 (1.08, 1.37)
Model 3	1.00 (Ref.)	1.32 (0.76, 2.29)	1.71 (0.98, 2.96)	2.68 (1.48, 4.83)	1.26 (1.11, 1.42)
Kidney disease					
No. of cases/ person-years	8 / 1073.9	56 / 4844.6	63 / 4047.2	31 / 1663.1	157 / 11,623.9
Age- and sex-adjusted model	1.00 (Ref.)	1.52 (0.72, 3.19)	2.11 (1.01, 4.41)	2.92 (1.3, 6.54)	1.36 (1.16, 1.60)
Model 2	1.00 (Ref.)	1.63 (0.76, 3.48)	2.36 (1.10, 5.06)	3.44 (1.47, 8.03)	1.39 (1.18, 1.64)
Model 3	1.00 (Ref.)	1.55 (0.71, 3.38)	2.26 (1.04, 4.92)	3.68 (1.52, 8.90)	1.43 (1.20, 1.69)
Neuropathy					

Continued

Table 4.10 continued

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=1083
	18.5–24.9 kg/m^2 n=99	25.0–29.9 kg/m^2 n=452	30.0–34.9 kg/m^2 n=377	≥35.0 kg/m^2 n=155	
No. of cases / person-years	9 / 1073.9	67 / 4844.6	54 / 4047.2	24 / 1663.1	154 / 11,623.9
Age- and sex-adjusted model	1.00 (Ref.)	1.34 (0.64, 2.79)	1.48 (0.72, 3.05)	1.76 (0.80, 3.87)	1.07 (0.90, 1.27)
Model 2	1.00 (Ref.)	1.29 (0.60, 2.81)	1.49 (0.69, 3.19)	1.79 (0.79, 4.10)	1.07 (0.90, 1.28)
Model 3	1.00 (Ref.)	1.22 (0.56, 2.66)	1.43 (0.67, 3.07)	1.95 (0.86, 4.43)	1.09 (0.91, 1.31)

Table presents combined rounded values from the ten imputation datasets

Model 2: age- and sex-adjusted model + education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke

Model 3: Model 2 + prevalent conditions of hypertension and dyslipidaemia

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

Table 4.11 HRs and 95% CIs for microvascular and macrovascular complications according to pre-diagnosis BMI categories and per 5 BMI kg/m^2, complete case analysis

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=831
	18.5–24.9 kg/m^2 n=74	25.0–29.9 kg/m^2 n=361	30.0–34.9 kg/m^2 n=295	≥35.0 kg/m^2 n=101	
Total vascular complications					
No. of cases / person-years	16 / 843.4	115 / 3987.6	108 / 3224.5	39 / 1147.4	278 / 9202.97
Age- and sex-adjusted model	1.00 (Ref.)	1.31 (0.78, 2.21)	1.76 (1.05, 2.94)	1.92 (1.07, 3.44)	1.20 (1.05, 1.37)
Model 2	1.00 (Ref.)	1.32 (0.77, 2.27)	1.81 (1.06, 3.09)	1.95 (1.06, 3.58)	1.21 (1.05, 1.39)
Model 3	1.00 (Ref.)	1.29 (0.75, 2.23)	1.75 (1.02, 3.00)	2.04 (1.10, 3.77)	1.23 (1.06, 1.42)
Macrovascular complications					
No. of cases / person-years	2 / 870.2	23 / 4250.7	21 / 3478.9	5 / 1244.4	51 / 9844.2
Age- and sex-adjusted model	1.00 (Ref.)	1.83 (0.47, 7.24)	2.34 (0.60, 9.20)	1.93 (0.40, 9.29)	1.21 (0.88, 1.68)
Model 2	1.00 (Ref.)	1.90 (0.54, 6.72)	2.23 (0.61, 8.11)	1.84 (0.40, 8.38)	1.19 (0.86, 1.67)
Model 3	1.00 (Ref.)	1.86 (0.53, 6.49)	2.12 (0.59, 7.66)	1.66 (0.37, 7.52)	1.13 (0.79, 1.62)
Microvascular complications					
No. of cases / person-years	15 / 852.0	102 / 4107.8	94 / 3315.6	37 / 1168.3	248 / 9443.6
Age- and sex-adjusted model	1.00 (Ref.)	1.29 (0.73, 2.29)	1.71 (0.96, 3.01)	2.10 (1.11, 3.96)	1.21 (1.05, 1.40)
Model 2	1.00 (Ref.)	1.30 (0.72, 2.37)	1.75 (0.96, 3.17)	2.17 (1.12, 4.23)	1.22 (1.05, 1.42)
Model 3	1.00 (Ref.)	1.24 (0.68, 2.27)	1.65 (0.91, 3.01)	2.34 (1.20, 4.57)	1.26 (1.07, 1.47)

Continued

Table 4.11 continued

Diabetes complication	BMI category				Continuous BMI, per 5 kg/m^2 n=831
	18.5–24.9 kg/m^2 n=74	25.0–29.9 kg/m^2 n=361	30.0–34.9 kg/m^2 n=295	≥35.0 kg/m^2 n=101	
Kidney disease					
No. of cases/ person-years	8 / 869.8	56 / 4262.8	58 / 3431.8	21 / 1221.0	143 / 9785.3
Age- and sex-adjusted model	1.00 (Ref.)	1.36 (0.62, 3.00)	2.04 (0.93, 4.46)	2.31 (0.97, 5.48)	1.29 (1.07, 1.55)
Model 2	1.00 (Ref.)	1.43 (0.63, 3.26)	2.12 (0.93, 4.83)	2.31 (0.92, 5.82)	1.30 (1.06, 1.60)
Model 3	1.00 (Ref.)	1.38 (0.60, 3.15)	2.04 (0.90, 4.65)	2.47 (0.96, 6.38)	1.35 (1.08, 1.68)
Neuropathy					
No. of cases / person-years	8 / 860.1	70 / 4225.0	60 / 3467.7	21 / 1219.8	159 / 9772.6
Age- and sex-adjusted model	1.00 (Ref.)	1.51 (0.70, 3.24)	1.75 (0.82, 3.72)	2.05 (0.89, 4.74)	1.13 (0.95, 1.35)
Model 2	1.00 (Ref.)	1.55 (0.69, 3.46)	1.84 (0.83, 4.07)	2.19 (0.92, 5.26)	1.13 (0.94, 1.36)
Model 3	1.00 (Ref.)	1.45 (0.65, 3.22)	1.68 (0.77, 3.68)	2.20 (0.94, 5.19)	1.13 (0.94, 1.36)

Model 2: age- and sex-adjusted model + education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke

Model 3: Model 2 + prevalent conditions of hypertension and dyslipidaemia

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

4.3.2 BMI change and risk of vascular complications

In models adjusted for age, sex and pre-diagnosis BMI, BMI loss of >1% per year was associated with a lower hazard of total complications in comparison to stable BMI (HR 0.73; 95% CI 0.58, 0.94), while no clear association was observed for >1% BMI gain (HR 0.92; 95% CI 0.71, 1.20) (**Table 4.12**, model 1). Further adjustment for lifestyle and medication did not markedly change the results (HR for BMI loss: 0.69; 95% CI 0.54, 0.89; HR for BMI gain 0.86; 95% CI 0.65, 1.14, model 2). A linear trend was observed (*p* for nonlinearity=0.73; **Figure 4.4**, panel a) when modelling BMI change as a continuous variable per 1% increment; however, it resulted in a positive non-significant association (HR 1.03; 95% CI 0.99, 1.07; **Table 4.12**, model 2).

A clearer positive association emerged when microvascular complications were evaluated. The HR (95% CI) of microvascular complications was 1.05 (1.01, 1.10) per 1% increment in BMI change in the final multivariable-adjusted model (**Table 4.12**, model 2) and the association was linear (*p* for nonlinearity=0.89; **Figure 4.4**, panel c). This finding was corroborated by the categorical analysis where participants with BMI loss were at lower risk of microvascular complications than those with stable BMI (HR 0.62; 95% CI 0.47, 0.80; **Table 4.12**, model 2). Similarly, a 1% increment in BMI change showed a positive association with both kidney disease (HR 1.06; 95% CI 1.00, 1.13; **Table 4.12**, model 2; *p* for nonlinearity=0.66; **Figure 4.4**, panel d) and neuropathy (HR 1.05; 95% CI 0.99, 1.11; **Table 4.12**, model 2; *p* for nonlinearity=0.18; **Figure 4.4**, panel e). Furthermore, a decreased hazard was observed for BMI loss (HR [95% CI]: 0.57 [0.40, 0.81] for kidney disease, 0.73 [0.52, 1.03] for neuropathy; **Table 4.12**, model 2). No clear association between BMI change and macrovascular risk was observable. Spline regression, categorical and continuous analyses indicated a modest inverse non-significant association (HR per 1% BMI change 0.95; 95% CI 0.87, 1.03, model 2; *p* for nonlinearity=0.37).

Table 4.12 HRs and 95% CIs for microvascular and macrovascular complications according to relative annual BMI change (categories and per 1%) [extracted from (Polemiti et al., 2021)]

Diabetes complication	BMI change category			Continuous BMI change, per 1% increment n=1069
	>1% BMI loss n=420	Stable BMI[a] n=402	>1% BMI gain n=247	
Total vascular complications				
No. of cases / person-years	141 / 4709.4	158 / 4223.7	82 / 2632.3	380 / 11,568.7
Model 1	0.73 (0.58, 0.94)	1.00 (Ref.)	0.92 (0.71, 1.20)	1.03 (0.99, 1.08)
Model 2	0.69 (0.54, 0.89)	1.00 (Ref.)	0.86 (0.65, 1.14)	1.03 (0.99, 1.07)
Macrovascular complications				
No. of cases / person-years	34 / 4984.6	29 / 4610.2	14 / 2857.9	76/ 12,445.7
Model 1	1.15 (0.69, 1.92)	1.00 (Ref.)	0.80 (0.40, 1.60)	0.93 (0.85, 1.02)
Model 2	1.04 (0.62, 1.74)	1.00 (Ref.)	0.82 (0.42, 1.63)	0.95 (0.87, 1.03)
Microvascular complications				
No. of cases / person-years	120 / 4856.5	147 / 4482.3	75 / 2730.4	341 / 12,068.6
Model 1	0.67 (0.52, 0.86)	1.00 (Ref.)	0.99 (0.75, 1.30)	1.06 (1.02, 1.11)
Model 2	0.62 (0.47, 0.80)	1.00 (Ref.)	0.90 (0.67, 1.21)	1.05 (1.01, 1.10)
Kidney disease				
No. of cases / person-years	66 / 5022.1	88 / 4706.7	48 / 2823.4	202 / 12,551.5
Model 1	0.62 (0.44, 0.86)	1.00 (Ref.)	1.14 (0.80, 1.64)	1.07 (1.01, 1.14)
Model 2	0.57 (0.40, 0.81)	1.00 (Ref.)	1.03 (0.71, 1.50)	1.06 (1.00, 1.13)

Continued

Table 4.12 continued

Diabetes complication	BMI change category			Continuous BMI change, per 1% increment n=1069
	>1% BMI loss n=420	Stable BMI[a] n=402	>1% BMI gain n=247	
Neuropathy				
No. of cases / person-years	74 / 4994.5	94 / 4652.6	42 / 2883.9	209 / 12,530.2
Model 1	0.74 (0.54, 1.03)	1.00 (Ref.)	0.86 (0.60, 1.24)	1.06 (1.01, 1.11)
Model 2	0.73 (0.52, 1.03)	1.00 (Ref.)	0.82 (0.56, 1.20)	1.05 (0.99, 1.11)

Table presents combined rounded values from the ten imputation datasets

Fourteen participants did not have a follow-up after diabetes diagnosis. The number of participants excluded from each model because they developed a complication between diabetes diagnosis and post-diagnosis BMI measurement was as follows: 11 for total complications; 7 for macrovascular complications; 4 for microvascular complications; 3 for kidney disease; 2 for neuropathy

[a] Stable BMI was defined as ≤1% BMI gain/loss

Model 1: adjusted for age, sex and pre-diagnosis BMI

Model 2: Model 1 + education, smoking status change, smoking duration at pre-diagnosis, smoking duration change, physical activity at pre-diagnosis, physical activity change, alcohol consumption at pre-diagnosis, alcohol consumption change, MedPyramid score, lipid-lowering medication, antihypertensive medication and glucose-lowering medication

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

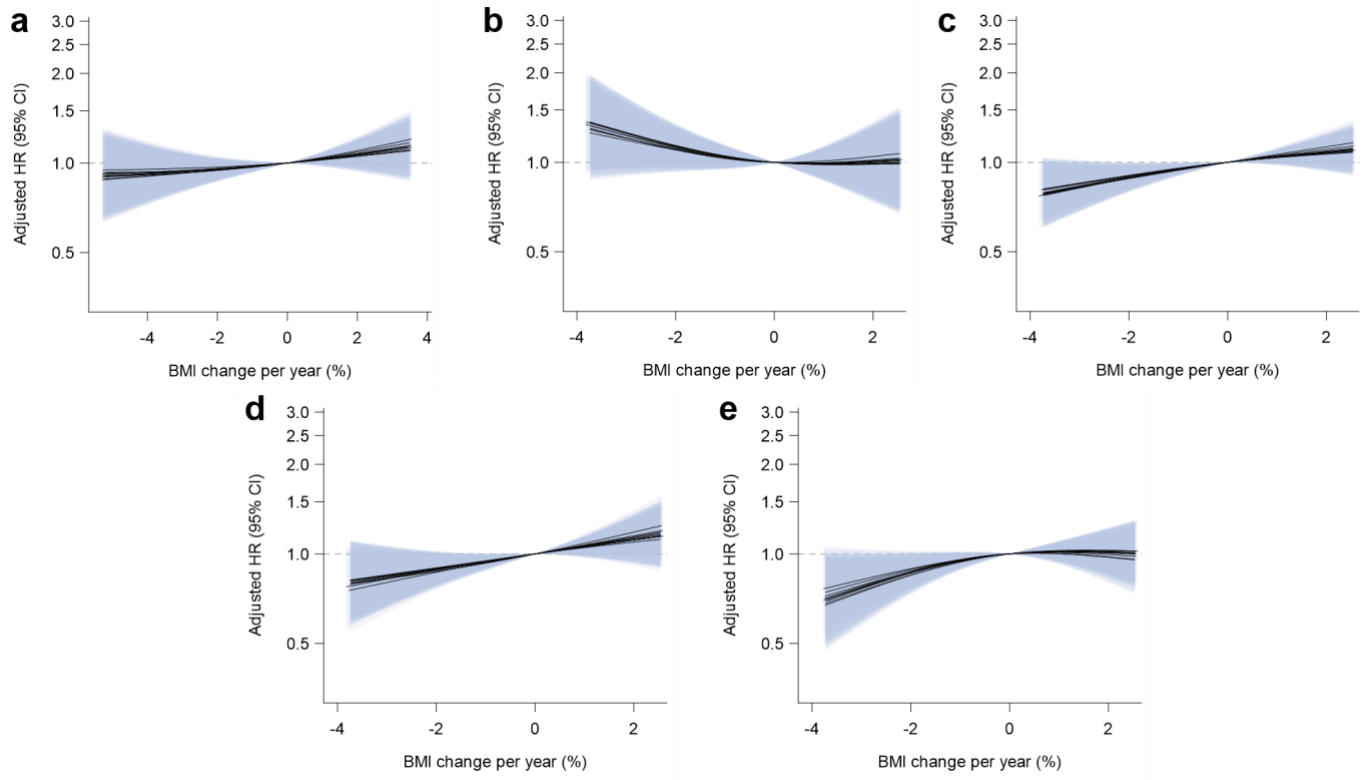

Figure 4.4 Association between relative annual BMI change and risk of microvascular and macrovascular complications of diabetes [extracted from (Polemiti et al., 2021)]

(a) Total vascular complications. (b) Macrovascular complications. (c) Microvascular complications. (d) Kidney disease. (e) Neuropathy. Relative annual BMI change was assessed using restricted cubic spline regression, adjusted for age, sex, BMI at diabetes diagnosis, education, smoking status change, smoking duration at pre-diagnosis, smoking duration change, physical activity at pre-diagnosis, physical activity change, alcohol consumption at pre-diagnosis, alcohol consumption change, MedPyramid score, lipid-lowering medication, antihypertensive medication, glucose-lowering medication. Splines (black lines) and 95% CIs (blue shading) from ten imputation datasets are shown. Knot placement was 5th, 50th and 95th percentile. BMI change of 0% served as reference. Test for

nonlinearity: Total complications, p=0.73; Macrovascular complications, p=0.37; Microvascular complications, p=0.89; Kidney disease, p=0.66; Neuropathy, p=0.18.

Sensitivity analyses

Sex-stratified analyses showed similar associations, except for macrovascular complications, where an inverse association appeared to be present among women (HR 0.85; 95% CI 0.73, 1.00; **Table 4.13**, model 2), while no meaningful association was observed in men (HR 0.98; 95% CI 0.87, 1.11) (p for LRT<0.001; **Table 4.13**). Associations were more prominent for all outcomes among never-smokers. The HRs (95% CIs) per 1% increment in BMI change were 1.09 (1.01, 1.18) for total complications, 0.78 (0.62, 0.97) for macrovascular complications, 1.15 (1.06, 1.25) for microvascular complications, 1.13 (1.02, 1.25) for kidney disease and 1.16 (1.04, 1.29) for neuropathy (**Table 4.13**, model 2). No substantial differences in associations between BMI change and vascular complications across strata of age at diabetes diagnosis, pre-diagnosis BMI or medication and in analyses excluding insulin users were detected (**Table 4.13**).

Findings from analyses where only first events were used as final endpoints were consistent with the main analysis, although confidence intervals were slightly less precise (HR 0.94; 95% CI 0.85, 1.03 for macrovascular complications, HR 1.05; 95% 1.00, 1.10 for microvascular complications, HR 1.05; 95% CI 0.97, 1.13 for kidney disease, HR 1.04; 95% CI 0.98, 1.11; **Table 4.14**, model 2). Finally, estimates from complete case analysis did not differ substantively from those obtained with the multiple imputation (**Table 4.15**).

Table 4.13 HRs and 95% CIs for microvascular and macrovascular complications per 1% relative annual BMI change, by subgroups and sensitivity analyses [extracted from (Polemiti et al., 2021)]

	Total complications	Macrovascular	Microvascular	Kidney disease	Neuropathy
Men					
No. of cases / person-years	235 / 6319.0	55 / 6841.7	203 / 6644.4	122 / 6925.9	118 / 6936.1
Model 1	1.03 (0.98, 1.09)	0.96 (0.85, 1.07)	1.06 (1.01, 1.12)	1.07 (1.00, 1.16)	1.07 (1.00, 1.14)
Model 2	1.03 (0.97, 1.08)	0.98 (0.87, 1.11)	1.05 (0.99, 1.12)	1.07 (0.98, 1.15)	1.06 (0.99, 1.14)
Women					
No. of cases / person-years	145 / 5249.3	22 / 5606.8	139 / 5423.3	80 / 5624.8	91 / 5590.7
Model 1	1.04 (0.97, 1.12)	0.86 (0.74, 0.99)	1.07 (0.99, 1.16)	1.06 (0.95, 1.18)	1.09 (1.00, 1.18)
Model 2	1.05 (0.98, 1.13)	0.85 (0.73, 1.00)	1.06 (0.98, 1.15)	1.04 (0.93, 1.16)	1.09 (0.99, 1.19)
Never-smoker[a]					
No. of cases / person-years	128 / 4650.0	18 / 4652.1	123 / 4734.8	73 / 4889.7	76 / 4906.1
Model 1	1.10 (1.01, 1.19)	0.84 (0.68, 1.03)	1.16 (1.07, 1.26)	1.15 (1.04, 1.28)	1.16 (1.04, 1.29)
Model 2	1.09 (1.01, 1.18)	0.78 (0.62, 0.97)	1.15 (1.06, 1.25)	1.13 (1.02, 1.25)	1.16 (1.04, 1.29)
Former smoker[a]					
No. of cases / person-years	174 / 5032.2	38 / 5033.6	149 / 5373.0	93 / 5415.8	91 / 5419.4
Model 1	1.01 (0.96, 1.07)	0.96 (0.84, 1.10)	1.03 (0.97, 1.10)	1.10 (1.00, 1.22)	1.02 (0.94, 1.10)
Model 2	1.00 (0.94, 1.07)	0.94 (0.83, 1.06)	1.02 (0.95, 1.09)	1.08 (0.98, 1.20)	1.01 (0.93, 1.11)
Current smoker[a]					
No. of cases / person-years	58 / 1787.1	19 / 1369.7	49 / 1465.4	23 / 1543.7	33 / 1507.5

Continued

Table 4.13 continued

	Total complications	Macrovascular	Microvascular	Kidney disease	Neuropathy
Model 1	0.91 (0.78, 1.06)	1.05 (0.84, 1.32)	0.86 (0.69, 1.06)	0.85 (0.68, 1.06)	0.86 (0.66, 1.12)
Model 2	0.89 (0.74, 1.07)	—[b]	0.78 (0.61, 1.01)	—[b]	—[b]
Age at diagnosis <65y					
No. of cases / person-years	271 / 8949.8	49 / 9605.6	244 / 9285.7	138 / 9664.4	153 / 9603.9
Model 1	1.02 (0.97, 1.07)	0.87 (0.80, 0.95)	1.06 (1.01, 1.11)	1.05 (0.98, 1.13)	1.06 (1.00, 1.12)
Model 2	1.03 (0.95, 1.12)	0.89 (0.81, 0.98)	1.05 (1.00, 1.11)	1.04 (0.97, 1.12)	1.05 (0.98, 1.11)
Age at diagnosis ≥65y					
No. of cases / person-years	109 / 2617.3	28 / 2840.0	97 / 2784.3	64 / 2887.1	56 / 2926.6
Model 1	1.08 (1.00, 1.16)	1.08 (0.91, 1.27)	1.07 (0.99, 1.17)	1.13 (1.01, 1.26)	1.06 (0.97, 1.16)
Model 2	1.02 (0.94, 1.11)	0.99 (0.84, 1.16)	1.03 (0.94, 1.13)	1.08 (0.95, 1.23)	1.11 (1.00, 1.22)
Pre-diagnosis BMI <30.0 kg/m^2					
No. of cases / person-years	176 / 5899.7	40 / 6290.1	156 / 6182.0	83 / 6428.7	101 / 6352.6
Model 1	1.05 (0.99, 1.12)	0.96 (0.83, 1.12)	1.09 (1.02, 1.16)	1.14 (1.04, 1.25)	1.06 (0.99, 1.14)
Model 2	1.05 (0.98, 1.12)	0.97 (0.86, 1.11)	1.09 (1.01, 1.17)	1.15 (1.03, 1.29)	1.06 (0.98, 1.14)
Pre-diagnosis BMI ≥30.0 kg/m^2					
No. of cases / person-years	204 / 5665.7	37 / 6154.7	185 / 5884.6	118 / 6117.0	108 / 6167.9
Model 1	1.03 (0.98, 1.09)	0.90 (0.82, 0.99)	1.06 (1.00, 1.13)	1.04 (0.96, 1.12)	1.11 (1.02, 1.20)
Model 2	1.02 (0.97, 1.08)	0.95 (0.84, 1.06)	1.05 (0.99, 1.11)	1.04 (0.96, 1.12)	1.08 (0.99, 1.17)
No glucose-lowering medication					

Continued

Table 4.13 continued

	Total complications	Macrovascular	Microvascular	Kidney disease	Neuropathy
No. of cases / person-years	96 / 3616.2	16 / 3843.2	85 / 3780.9	56 / 3895.5	45 / 3894.5
Model 1	1.05 (0.96, 1.14)	0.85 (0.68, 1.05)	1.09 (0.99, 1.20)	1.12 (0.97, 1.29)	—[c]
Model 2	1.06 (0.98, 1.16)	0.74 (0.55, 0.99)	1.12 (1.02, 1.23)	1.13 (0.99, 1.29)	—[c]
Glucose-lowering medication[d]					
No. of cases / person-years	242 / 7156.0	53 / 7697.6	216 / 7450.4	126 / 7742.9	135 / 7746.5
Model 1	1.00 (0.95, 1.06)	0.94 (0.84, 1.05)	1.03 (0.97, 1.09)	1.05 (0.98, 1.13)	1.04 (0.97, 1.11)
Model 2	1.00 (0.95, 1.06)	0.95 (0.86, 1.05)	1.02 (0.96, 1.08)	1.05 (0.98, 1.14)	1.03 (0.96, 1.11)
Exclusion of insulin users					
No. of cases / person-years	338 / 10,769.5	69 / 11,538.6	300 / 11,230.5	182 / 11,637.7	180 / 11,641.0
Model 1	1.03 (0.98, 1.07)	0.92 (0.83, 1.01)	1.06 (1.01, 1.11)	1.07 (1.00, 1.14)	1.05 (1.00, 1.11)
Model 2	1.02 (0.98, 1.06)	0.94 (0.86, 1.03)	1.05 (1.00, 1.10)	1.07 (1.00, 1.14)	1.04 (0.98, 1.10)

Table presents combined rounded values from the ten imputation datasets

Fourteen participants did not have a follow-up after diabetes diagnosis. The number of participants excluded from each model because they developed a complication between diabetes diagnosis and post-diagnosis BMI measurement was as follows: 11 for total complications; 7 for macrovascular complications; 4 for microvascular complications; 3 for kidney disease; 2 for neuropathy

Model 1: adjusted for age, sex and BMI at diabetes diagnosis

Model 2: Model 1 + education, smoking status change, smoking duration at pre-diagnosis, smoking duration change, physical activity at pre-diagnosis, physical activity change, alcohol consumption at pre-diagnosis, alcohol consumption change, MedPyramid score, lipid-lowering medication, antihypertensive medication, glucose-lowering medication

[a] Participants who changed smoking status were excluded

[b] HR (95% CI) was not reported due to small numbers

[c] HR (95% CI) was not reported where violation of linearity assumption was found

[d] Insulin users were excluded

Likelihood ratio test for interaction for smoking status: Total complications: *p*=0.09; Macrovascular complications: *p*=0.74; Microvascular complications: *p*=0.02; Kidney disease: p=0.34; Neuropathy: *p*=0.04. Likelihood ratio test for interaction for age at diabetes diagnosis: Total complications: *p*=0.04; Macrovascular complications: *p*=0.35; Microvascular complications: *p*=0.11; Kidney disease: *p*=0.001; Neuropathy: *p*=0.75. Likelihood ratio test for interaction term for pre-diagnosis BMI: Total complications: p=0.44; Macrovascular complications: p=0.67; Microvascular complications: p=0.05; Kidney disease: p=0.03; Neuropathy: p=0.83. Likelihood ratio test for interaction term for glucose-lowering medication at diabetes diagnosis: Total complications: p=0.27; Macrovascular complications: p=0.53; Microvascular complications: p=0.26; Kidney disease: p=0.28; Neuropathy: p=0.86

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

Table 4.14 HRs and 95% CIs for microvascular and macrovascular complications according to relative annual BMI change (categories and per 1%), censored at first event [extracted from (Polemiti et al., 2021)]

Diabetes complication	BMI change category			Continuous BMI change, per 1% increment n=1069
	>1% BMI loss n=420	Stable BMI[a] n=402	>1% BMI gain n=247	
Macrovascular complications				
No. of cases / person-years	31 / 4709.4	23 / 4223.7	12 / 2632.3	66 / 11,568.7
Model 1	1.27 (0.72, 2.23)	1.00 (Ref.)	0.81 (0.38, 1.70)	0.92 (0.83, 1.02)
Model 2	1.23 (0.69, 2.21)	1.00 (Ref.)	0.84 (0.40, 1.77)	0.94 (0.85, 1.03)
Microvascular complications				
No. of cases / person-years	110 / 4709.4	134 / 4223.7	70 / 2632.3	314 / 11,568.7
Model 1	0.65 (0.50, 0.84)	1.00 (Ref.)	0.95 (0.71, 1.26)	1.06 (1.02, 1.11)
Model 2	0.61 (0.46, 0.80)	1.00 (Ref.)	0.87 (0.64, 1.18)	1.05 (1.00, 1.10)
Kidney disease				
No. of cases / person-years	49 / 4709.4	67 / 4223.7	37 / 2632.3	153 / 11,568.7
Model 1	0.56 (0.38, 0.82)	1.00 (Ref.)	1.00 (0.65, 1.52)	1.06 (0.99, 1.14)
Model 2	0.52 (0.35, 0.79)	1.00 (Ref.)	0.91 (0.58, 1.42)	1.05 (0.97, 1.13)
Neuropathy				
No. of cases / person-years	57 / 4709.4	66 / 4223.7	29 / 2632.3	152 / 11,568.7
Model 1	0.72 (0.49, 1.05)	1.00 (Ref.)	0.80 (0.52, 1.22)	1.05 (0.99, 1.11)
Model 2	0.69 (0.47, 1.01)	1.00 (Ref.)	0.77 (0.49, 1.20)	1.04 (0.98, 1.11)

Table presents combined rounded values from the ten imputation datasets

Fourteen participants did not have a follow-up after diabetes diagnosis. The number of participants excluded from each model because they developed a complication between diabetes diagnosis and post-diagnosis BMI measurement was as follows: 11 for total complications; 7 for macrovascular complications; 4 for microvascular complications; 3 for kidney disease; 2 for neuropathy

Model 1: adjusted for age, sex and pre-diagnosis BMI

Model 2: Model 1 + education, smoking status change, smoking duration at pre-diagnosis, smoking duration change, physical activity at pre-diagnosis, physical activity change, alcohol consumption at pre-diagnosis, alcohol consumption change, MedPyramid score, lipid-lowering medication, antihypertensive medication, glucose-lowering medication

[a] Stable BMI was defined as ≤1% BMI gain/loss

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

Table 4.15 HRs and 95% CIs for microvascular and macrovascular complications according to relative annual BMI change (categories and per 1%), complete case analysis

Diabetes complication	BMI change category			Continuous BMI change, per 1% increment n=824
	>1% BMI loss n=324	Stable BMI[a] n=314	>1% BMI gain n=186	
Total vascular complications				
No. of cases / person-years	98 / 3711.6	115 / 3407.0	58 / 2079.2	271 / 9197.8
Model 1	0.72 (0.55, 0.96)	1.00 (Ref.)	0.93 (0.68, 1.26)	1.03 (0.98, 1.09)
Model 2	0.69 (0.52, 0.92)	1.00 (Ref.)	0.88 (0.64, 1.21)	1.03 (0.98, 1.09)
Macrovascular complications				
No. of cases / person-years	21 / 3901.6	18 / 3698.1	7 / 2241.9	46 / 9841.6
Model 1	1.09 (0.57, 2.08)	1.00 (Ref.)	0.65 (0.26, 1.64)	0.90 (0.82, 1.00)
Model 2	1.12 (0.58, 2.18)	1.00 (Ref.)	0.72 (0.29, 1.83)	0.91 (0.82, 1.01)
Microvascular complications				
No. of cases / person-years	84 / 3801.2	108 / 3518.6	54 / 2121.4	246 / 9441.2
Model 1	0.67 (0.52, 0.86)	1.00 (Ref.)	0.97 (0.70, 1.34)	1.06 (1.01, 1.12)
Model 2	0.63 (0.47, 0.85)	1.00 (Ref.)	0.91 (0.65, 1.28)	1.06 (1.00, 1.12)
Kidney disease				
No. of cases / person-years	44 / 3905.2	65 / 3676.8	33 / 2201.6	142 / 9783.6
Model 1	0.55 (0.37, 0.82)	1.00 (Ref.)	0.96 (0.63, 1.47)	1.06 (0.99, 1.14)
Model 2	0.54 (0.36, 0.81)	1.00 (Ref.)	0.89 (0.57, 1.38)	1.06 (0.98, 1.13)

Continued

Table 4.15 continued

Diabetes complication	BMI change category			Continuous BMI change, per 1% increment n=824
	>1% BMI loss n=324	Stable BMI[a] n=314	>1% BMI gain n=186	
Neuropathy				
No. of cases / person-years	73 / 3649.5	54 / 3901.8	32 / 2208.7	159 / 9760.0
Model 1	0.73 (0.50, 1.06)	1.00 (Ref.)	0.86 (0.58, 1.29)	1.07 (1.01, 1.15)
Model 2	0.70 (0.48, 1.02)	1.00 (Ref.)	0.83 (0.55, 1.24)	1.07 (1.00, 1.14)

Table presents combined rounded values from the ten imputation datasets

Seven participants did not have a follow-up after diabetes diagnosis. The number of participants excluded from each model because they developed a complication between diabetes diagnosis and post-diagnosis BMI measurement was as follows: 7 for total complications; 5 for macrovascular complications; 2 for microvascular complications; 1 for kidney disease; 1 for neuropathy

[a] Stable BMI was defined as ≤1% BMI gain/loss

Model 1: adjusted for age, sex and pre-diagnosis BMI

Model 2: Model 1 + education, smoking status change, smoking duration at pre-diagnosis, smoking duration change, physical activity at pre-diagnosis, physical activity change, alcohol consumption at pre-diagnosis, alcohol consumption change, MedPyramid score, lipid-lowering medication, antihypertensive medication and glucose-lowering medication

HRs, Hazard ratios; CIs, Confidence intervals; BMI, Body mass index

4.4 Application of the German diabetes risk score and cardiovascular disease risk score for prediction of vascular complications

A total of 1226 individuals were included in this analysis, out of which 101 (8.3%) developed macrovascular complications and 394 (32.1%) microvascular complications, comprising 228 kidney disease cases, 239 neuropathy cases and 43 retinopathy cases. **Table 4.16** shows the follow-up time according to the time point of scores' calculation and vascular complication occurrence. The median follow-up was slightly higher than 17 years for all endpoints when risk scores were calculated at the recruitment of EPIC-Potsdam study, and approximately ten years for scores assessed at the closest follow-up to diabetes diagnosis.

Characteristics of participants and components of GDRS assessed before diabetes diagnosis according to categories of a 5-year probability of developing type 2 diabetes are presented in **Table 4.17**. The percentage of men was higher in the categories with a higher risk score. Furthermore, as anticipated by the score's definition, participants with a higher score were older, had higher waist circumference, were more often heavier current or former smokers, and were more likely to report a family history of diabetes than individuals with a lower score.

Table 4.16 Follow-up time according to time point of scores' calculation and complication occurrence, in years

	Median (25th–75th percentile)
Nonclinical scores at diabetes diagnosis	
Total complications	10.6 (8.0–13.7)
Macrovascular complications	11.4 (8.7–14.4)
Microvascular complications	10.8 (8.3–13.8)
Kidney disease	11.2 (8.6–14.2)
Neuropathy	11.3 (8.7–14.2)
Retinopathy	11.5 (9.0–14.5)
Nonclinical scores at recruitment	
Total complications	17.3 (14.9–18.7)
Macrovascular complications	17.9 (16.6–19.1)
Microvascular complications	17.4 (15.5–18.8)
Kidney disease	17.8 (16.4–19.0)
Neuropathy	17.8 (16.4–19.0)
Retinopathy	18.0 (16.7–19.1)
Clinical scores at recruitment	
Total complications	17.2 (14.7–18.8)
Macrovascular complications	18.1 (16.5–19.1)
Microvascular complications	17.3 (15.3–18.8)
Kidney disease	17.8 (13.3–19.0)
Neuropathy	17.9 (16.4–19.0)
Retinopathy	18.1 (16.6–19.1)

Table 4.17 Characteristics of study participants and components of the nonclinical GDRS according to score categories, at diabetes diagnosis

Characteristic	Total	Risk score categories (~) (5-year probability of developing type 2 diabetes)		
		<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
n (%)	1226	377 (30.8)	310 (25.3)	538 (43.9)
Male sex, n (%)	649 (52.9)	149 (39.6)	164 (52.9)	335 (62.3)
Age, years, median (25^{th}–75^{th} pct)	60.8 (54.2–65.9)	57.8 (51.6–62.7)	61.6 (54.9–66.1)	62.4 (56.2–67.4)
Height, cm, median (25^{th}–75^{th} pct)				
Men	174.0 (168.9–178.5)	176.2 (170.5–179.5)	173.2 (168.9–178.0)	172.8 (168.5–177.8)
Women	161.5 (157.5–165.9)	162 (157.9–166.8)	160.7 (157.0–164.7)	161.0 (157.5–165.7)
Waist circumference, cm, median (25^{th}–75^{th} pct)				
Men	103.0 (97.0–110.5)	95.0 (89.4–99.0)	100.5 (97.0–104.0)	109.5 (103.6–116.0)
Women	95.0 (87.0–103.0)	86 (80.2–91.0)	95.5 (90.0–99.0)	105.0 (100.0–114.6)
Prevalent hypertension, n (%)	987 (80.5)	229 (60.4)	259 (82.9)	501 (93.1)
Physical activity, h/week, median (25^{th}–75^{th} pct)	1.0 (0–3.0)	1.5 (0–4.0)	1.0 (0–4.0)	1.0 (0–3.0)
Smoking status, n (%)				
Former smoker (<20 units/day)	318 (25.9)	96 (25.4)	92 (29.7)	130 (24.1)
Former smoker (≥20 units/day)	220 (17.9)	37 (9.8)	49 (15.5)	135 (25.1)
Current smoker (<20 units/day)	126 (10.3)	52 (13.7)	27 (8.7)	47 (8.8)
Current smoker (≥20 units/day)	78 (6.4)	11 (2.9)	13 (4.2)	54 (10.0)

Continued

Table 4.17 continued

Characteristic	Total	Risk score categories (~) (5-year probability of developing type 2 diabetes)		
		<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
Coffee, 150 g/day, median (25th–75th pct)	2.7 (1.5–3.5)	2.7 (2.0–4.0)	2.7 (1.4–3.5)	2.7 (1.5–3.0)
Red meat, 150 g/day, median (25th–75th pct)	0.3 (0.2–0.5)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.4 (0.2–0.6)
Whole grain, 50 g/day, median (25th–75th pct)	0.4 (0.1–1.0)	0.5 (0.2–1.2)	0.4 (0.2–1.0)	0.4 (0.1–0.9)
Family history of diabetes, n (%)				
One parent	406 (33.1)	87 (23.1)	96 (30.9)	222 (41.3)
Both Parents	83 (6.7)	16 (4.1)	14 (4.5)	53 (9.9)
At least one sibling	149 (12.2)	29 (7.6)	28 (9.1)	92 (17.1)

Pct, Percentile

4.4.1 Association of the risk scores with vascular complications

In crude Cox models, an elevated risk of micro- and macrovascular complications was observed with a higher clinical or nonclinical GDRS, regardless of the time point at which the score was examined (**Table 4.18**). Furthermore, there was no indication of nonlinearity of associations, as assessed by restricted cubic splines. Per 50 units increase in $GDRS_{REC}$, the HRs ranged from 1.15 (95% CI 1.09, 1.21) for neuropathy to 1.21 (95% CI 1.07, 1.37) for retinopathy. For an increment of 50 units of nonclinical $GDRS_{T2D}$, the elevated risk of incident complications ranged from 13% for neuropathy and retinopathy to 18% for kidney disease, and from 11% for kidney disease to 21% for retinopathy for each 50-unit increment in the clinical GDRS. Additional adjustment for age and sex slightly attenuated the findings (**Table 4.18**, model 2). The associations remained positive and statistically significant, except the association of nonclinical $GDRS_{T2D}$ with macrovascular complications and retinopathy (per 50 units increment: HR 1.06; 95% CI 0.97, 1.16; HR 1.13; 95% CI 0.99, 1.29, respectively). Findings were corroborated by analyses where risk scores were modelled categorically, where individuals in the higher risk score categories showed an increased risk for complications, compared with those in the lowest risk category, although the confidence intervals for macrovascular complications and retinopathy were fairly wide (**Appendix 13–15**). Lastly, results from the complete case analysis did not materially differ from those based on the imputed data (**Appendix 16**).

A linear positive association was observed between the nonclinical and clinical CVDRS and vascular complications, except for retinopathy, where no clear association was observed (**Table 4.19**). In unadjusted Cox models, the increased risk ranged from 25% for total microvascular complications and neuropathy to 43% for macrovascular complications for each 50-unit increase in the nonclinical $CVDRS_{T2D}$. Furthermore, per 50 units increment of nonclinical $CVDRS_{REC}$ and clinical CVDRS the HRs ranged from 1.20 (95% CI 1.12, 1.30) and 1.28 (95% CI 1.14, 1.44) for neuropathy to 1.40 (95% CI 1.22, 1.62) and 1.41 (95% CI 1.13, 1.77) for macrovascular complications, respectively (**Table 4.19**, crude model). Results remained largely unchanged after adjustment for age and sex (**Table 4.19**, model 2). Categorical analysis showed similar results, although confidence intervals were large and

crossed the null for some associations (**Appendix 17–19**). Results from complete case analysis were consistent with the main findings but lacked precision (**Appendix 20**).

Table 4.18 HRs and 95% CIs for microvascular and macrovascular complications per 50 units of the nonclinical and clinical GDRS calculated at diabetes diagnosis and EPIC-Potsdam recruitment

Complication	Nonclinical $GDRS_{T2D}$ n=1226	Nonclinical $GDRS_{REC}$ n=1226	Clinical GDRS n=655
Total complications			
Cases / person-years	453 / 12,895.6	453 / 20,008.5	256 / 10,601.7
Crude model	1.14 (1.10, 1.19)	1.17 (1.12, 1.21)	1.13 (1.08, 1.17)
Model 2	1.10 (1.05, 1.15)	1.13 (1.08, 1.18)	1.11 (1.06, 1.16)
Macrovascular complications			
Cases / person-years	101 / 13,880.5	101 / 20,996.4	55 / 11,188.8
Crude model	1.15 (1.06, 1.24)	1.19 (1.09, 1.29)	1.12 (1.04, 1.21)
Model 2	1.06 (0.97, 1.16)	1.11 (1.01, 1.22)	1.09 (1.00, 1.19)
Microvascular complications			
Cases / person-years	394 / 13,261.5	394 / 20,376.2	222 / 10,824.2
Crude model	1.15 (1.10, 1.20)	1.17 (1.12, 1.21)	1.13 (1.08, 1.18)
Model 2	1.11 (1.06, 1.16)	1.13 (1.08, 1.18)	1.11 (1.06, 1.17)
Kidney disease			
Cases / person-years	228 / 13,801.7	228 / 20,917.7	132 / 11,153.1
Crude model	1.18 (1.12, 1.24)	1.20 (1.14, 1.27)	1.11 (1.06, 1.16)
Model 2	1.14 (1.08, 1.21)	1.16 (1.10, 1.23)	1.09 (1.03, 1.15)
Neuropathy			
Cases / person-years	239 / 13,781.1	239 / 20,892.6	130/ 11,122.7
Crude model	1.13 (1.07, 1.19)	1.15 (1.09, 1.21)	1.13 (1.07, 1.19)
Model 2	1.10 (1.04, 1.17)	1.12 (1.06, 1.19)	1.12 (1.06, 1.19)
Retinopathy			
Cases / person-years	43 / 14,193.8	43 / 21,310.0	32/ 11,371.3
Crude model	1.13 (1.00, 1.29)	1.21 (1.07, 1.37)	1.21 (1.11, 1.31)
Model 2	1.13 (0.99, 1.29)	1.20 (1.06, 1.37)	1.20 (1.10, 1.32)

Table presents combined rounded values from the ten imputation datasets

Model 2: age- and sex-adjusted model

HRs, Hazard ratios; CIs, Confidence intervals; GDRS, German diabetes risk score

Table 4.19 HRs and 95% CIs for microvascular and macrovascular complications per 50 units of the nonclinical and clinical CVDRS calculated at diabetes diagnosis and EPIC-Potsdam recruitment

Complication	Nonclinical $CVDRS_{T2D}$ n=1226	Nonclinical $CVDRS_{REC}$ n=1226	Clinical CVDRS n=669
Total complications			
Cases / person-years	453 / 12,895.6	453 / 20,008.5	262 / 10,788.6
Crude model	1.27 (1.19, 1.34)	1.23 (1.16, 1.31)	1.30 (1.19, 1.42)
Model 2	1.21 (1.11, 1.33)	1.23 (1.13, 1.33)	1.26 (1.12, 1.42)
Macrovascular complications			
Cases / person-years	101 / 13,880.5	101/ 20,996.4	57 / 11,388.7
Crude model	1.43 (1.25, 1.63)	1.40 (1.22, 1.62)	1.41 (1.13, 1.77)
Model 2	1.41 (1.17, 1.71)	1.40 (1.15, 1.71)	1.37 (1.01, 1.85)
Microvascular complications			
Cases / person-years	394 / 13,261.5	394 / 20,376.2	226 / 11,011.6
Crude model	1.25 (1.17, 1.33)	1.21 (1.14, 1.28)	1.30 (1.18, 1.43)
Model 2	1.18 (1.08, 1.29)	1.19 (1.09, 1.29)	1.26 (1.11, 1.42)
Kidney disease			
Cases / person-years	228 / 13,801.7	228 / 20,917.7	137 / 11,337.9
Crude model	1.32 (1.22, 1.43)	1.26 (1.17, 1.36)	1.39 (1.23, 1.58)
Model 2	1.23 (1.09, 1.38)	1.20 (1.08, 1.33)	1.27 (1.08, 1.49)
Neuropathy			
Cases / person-years	239 / 13,781.1	239 / 20,892.6	132 / 11,315.7
Crude model	1.25 (1.16, 1.35)	1.20 (1.12, 1.30)	1.28 (1.14, 1.44)
Model 2	1.17 (1.05, 1.32)	1.19 (1.07, 1.32)	1.24 (1.06, 1.45)
Retinopathy			
Cases / person-years	43 / 14,193.8	43 / 21,310.0	32 / 11,571.5
Crude model	1.00 (0.82, 1.21)	1.08 (0.90, 1.29)	1.03 (0.81, 1.32)
Model 2	0.92 (0.67, 1.25)	1.04 (0.81, 1.35)	0.98 (0.73, 1.32)

Table presents combined rounded values from the ten imputation datasets

Model 2: age- and sex-adjusted model

HRs, Hazard ratios; CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score

4.4.2 Predictive performance of risk scores for vascular complications

The predictive value of the nonclinical and clinical GDRS was low for vascular complication risk. The C-index of the nonclinical $GDRS_{T2D}$ ranged from 0.56 (95% CI 0.27, 0.83) for retinopathy to 0.62 (0.50, 0.73) for kidney disease (**Figure 4.5**, panel a). The nonclinical $GDRS_{REC}$ had the lowest C-index for retinopathy and neuropathy (0.59 [95% CI 0.35, 81], 0.59 [95% CI 0.48, 0.70], respectively) and the highest for kidney disease (0.62 [95% CI 0.51, 0.73]; **Figure 4.5**, panel b). The clinical GDRS C-index was higher for all outcomes but remained poor, ranging from 0.60 (95% CI 0.40, 0.79) for macrovascular complications to 0.64 (95% CI 0.36, 0.89) for retinopathy (**Figure 4.5**, panel c).

Nonclinical and clinical CVDRS also exhibited a poor discriminatory ability for vascular complications. A consistently higher C-index was found for macrovascular complications as opposed to other vascular events but was still poor (0.66; 95% CI 0.50, 080 for nonclinical $CVDRS_{T2D}$; 0.64; 95% CI 0.49, 0.78 for nonclinical $CVDRS_{REC}$; 0.62; 95% CI 0.42, 0.81 for clinical CVDRS; **Figure 4.6**, panel a–c). Regarding total microvascular complications, the C-index ranged from 0.60 (95% CI 0.51, 0.68) for nonclinical $CVDRS_{REC}$ to 0.62 (95% CI 0.53, 0.71) for nonclinical $CVDRS_{T2D}$; and was the highest for kidney disease across the two risk scores and time points, ranging from 0.62 (95% CI 0.51, 0.72) for nonclinical $CVDRS_{REC}$ to 0.64 (95% CI 0.52, 0.76) for nonclinical $CVDRS_{T2D}$. The CVDRS failed to discriminate for retinopathy, with the C-index ranging between 0.51 to 0.54 across time points and versions (**Figure 4.6**, panel a–c).

Complete case analysis showed overall similar findings as the main analysis for both GDRS and CVDRS, but C-indices were consistently higher for retinopathy. Nevertheless, the discrimination ability remained low and confidence intervals were large (**Appendix 21**).

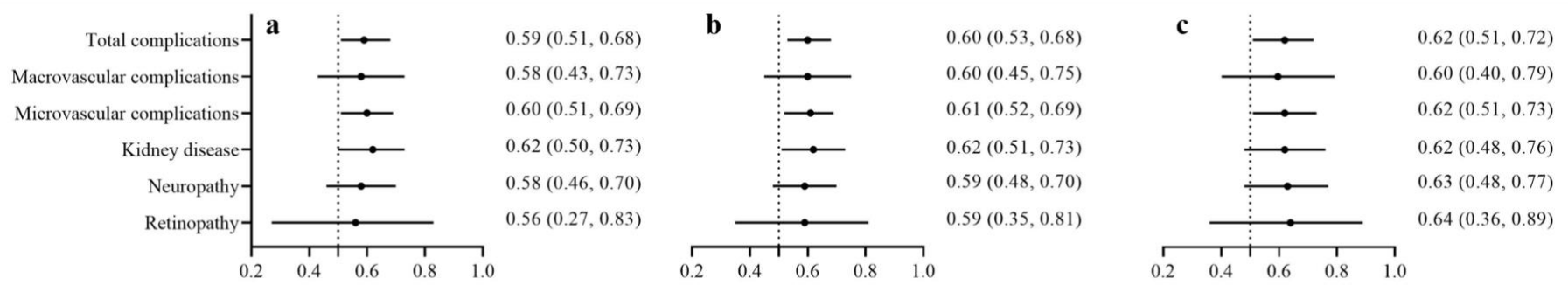

Figure 4.5 C-indices and 95% CIs of the nonclinical and clinical GDRS according to complication

(a) Nonclinical $GDRS_{T2D}$. (b) Nonclinical $GDRS_{REC}$. (c) Clinical GDRS. Figure presents combined rounded values from the ten imputation datasets. CIs, Confidence intervals; GDRS, German diabetes risk score.

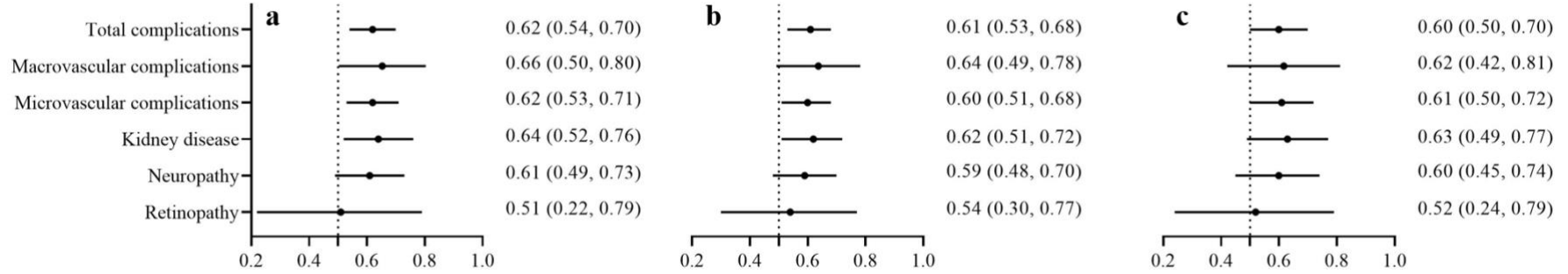

Figure 4.6 C-indices and 95% CIs of the nonclinical and clinical CVDRS according to complication

(a) Nonclinical $CVDRS_{T2D}$. (b) Nonclinical $CVDRS_{REC}$. (c) Clinical CVDRS. Figure presents combined rounded values from the ten imputation datasets. CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score.

5.
Discussion

5.1 Overview of the chapter

The chapter starts with a summary of the main findings (section 5.2). Next, the results of this work are discussed and a comparison with existing literature as well as potential mechanisms underlining the associations are provided (section 5.3). Thereafter, the study methods and potential sources of bias are discussed (section 5.4). Finally, the overall conclusions and future perspectives are provided (section 5.5).

5.2 Summary of main findings

This work aimed to identify risk factors of diabetes-associated vascular complications, using a prospective cohort of individuals with incident type 2 diabetes participating in the EPIC-Potsdam study during a median follow-up time of more than ten years. Applying a multivariable-adjusted multistate model, it was observed that individuals who developed a vascular complication during the follow-up period had an increased risk of developing a further complication than persons with no complication burden. Different lifestyle factors appeared to exert different effects on micro- and macrovascular complications. There was a positive association between baseline BMI, waist circumference and physical activity with

microvascular complications, whereas a negative association was observed for baseline intake of whole grains and alcohol. A U-shaped association was observed between red meat intake and microvascular complications. Higher baseline coffee intake was associated with a decreased risk of developing a macrovascular event, while former and current smokers at diabetes diagnosis had an increased risk, compared with never-smokers. The observed associations were not substantially altered when time-updated lifestyle factors were investigated. Furthermore, concurrent complication burden did not modify the effect of most lifestyle factors on diabetes complications.

The effect of BMI and BMI change on diabetes complications was investigated in individuals free of cancer, cardiovascular and microvascular disease at diabetes diagnosis using multivariable-adjusted Cox models. A positive association was observed between BMI and microvascular complications, and this applied to both kidney disease and neuropathy. Furthermore, BMI loss shortly after diabetes diagnosis was associated with a decreased risk of total microvascular complications, kidney disease and neuropathy. The findings were consistent across different subgroups of age, sex and smoking status for BMI, whereas for BMI change the associations were strengthen among never-smokers. In contrast, no apparent association between BMI and macrovascular complications was observed, while weight loss was associated with a non-significant increased risk for macrovascular events, an association that was strengthened in analyses restricted to never-smokers.

The GDRS and CVDRS are simple tools for identifying individuals at risk of diabetes and CVD, respectively. Findings of this study suggest that among individuals destined to develop type 2 diabetes, high GDRS and CVDRS were associated with an increased risk of total macrovascular and microvascular complications, kidney disease and neuropathy, in crude and age- and sex-adjusted Cox models. Furthermore, GDRS was positively associated with retinopathy. The associations were similar when risk scores were assessed shortly before diabetes diagnosis or at EPIC-Potsdam recruitment – on average, approximately seven years before diabetes diagnosis. However, the discriminatory ability of the risk scores for diabetes complications was low.

5.3 Comparison with existing literature and potential mechanisms underlying the associations

5.3.1 Vascular complications of diabetes and risk of further complications

Earlier studies have documented an increased risk of vascular complication incidence in type 2 diabetes patients with pre-existing complications at study entry. However, most studies investigated the incidence of a single complication as a process of one transition without considering the coexistence or cooccurrence of other vascular events. Therefore, a direct comparison of previous literature with the present results is difficult. In the current study, a multistate analysis was performed to model complication state transitions in newly diagnosed type 2 diabetes patients free of prevalent vascular disease, controlling for diabetes duration, state duration as well as transition-specific covariates. Thus, allowing to study several transitions over time within the same model and excluding individuals with an accrual of chronic health conditions, which might have resulted in spurious associations.

In the present work, participants who develop a micro- or a macrovascular complication had an approximately two-fold increased risk of a subsequent microvascular event, compared with participants without a complication burden, suggesting that both conditions may play a role in (further) microvasculature injury. In addition, the hazard of developing a macrovascular complication was five times higher among those with a prior microvascular event. A disadvantage of multistate models, however, is that as the number of states increases over the follow-up period, late states might result in small sample sizes. In this study, after excluding 138 participants with prevalent vascular complications, seven composite complication states were observed. Nevertheless, analyses were performed in a five-state model due to the limited cell size in the final two states. Thus, it was not possible to investigate the effect of cumulative states or isolated vascular complications on subsequent vascular events.

Multistate models fitted separately for each of the three types of microvascular complications and without distinguishing states by order of complication occurrence were applied in individuals with type 1 diabetes enrolled at the SDCC (Bjerg et al., 2018a). In

agreement with the present findings, the authors observed that participants with any previous microvascular complication had an increased risk of further microvascular events (kidney disease, neuropathy, retinopathy). Furthermore, a stepwise increased risk of microvascular events was reported with the presence of a cumulative burden of microvascular complications (Bjerg et al., 2018a). Data from the CPRD and ADVANCE/ ADVANCE-ON studies in individuals with type 2 diabetes have demonstrated that the prevalence of a microvascular complication at study entry was associated with an approximately 1.5 times higher risk of macrovascular disease, and the accumulation of several prevalent complications further increased the risk (Brownrigg et al., 2016, Mohammedi et al., 2017). Moreover, an elevated risk of microvascular complications was observed in persons with baseline macrovascular or microvascular disease in the ADVANCE/ ADVANCE-ON study. Those with both conditions at study entry showed the highest risk (Mohammedi et al., 2017). In like fashion, the 3-year incidence of micro- and macrovascular was elevated in people with type 2 diabetes initiating second-line glucose-lowering therapy (Arnold et al., 2022).

Several mechanisms have been suggested to explain the pathogenesis of diabetes vascular complications. As described in section 1.3.5, hyperglycaemia leads to overproduction of ROS within the endothelial cells of both small and large vessels, which in turn causes accelerated atherosclerosis, impaired angiogenesis and activates proinflammatory pathways (Giacco and Brownlee, 2010). Furthermore, hypertension and dyslipidaemia activate the endothelium resulting in inflammation at sites of diabetes complications (Forbes and Cooper, 2013). Experimental studies have demonstrated that endoplasmic reticulum stress, induced by misfolded proteins, is involved not only in the development of diabetes but also in the pathogenesis of diabetes-related complications through apoptosis initiation (Galán et al., 2012, Avogaro and Fadini, 2019). Still, mechanistically, it is unclear how one complication may lead to another.

Conceivably, the presence of one complication might be simply a marker of more advanced disease. In this analysis, the elevated risk remained after adjusting for prevalent conditions of hypertension and dyslipidaemia, diabetes duration and glucose-lowering medication. However, levels of cardiometabolic risk factors were not available at diabetes diagnosis or during follow-up, and their inclusion in the model would likely have attenuated

the observed associations. Still, the CPRD, ADVANCE/ADVANCE ON and SDCC studies reported an elevated risk of vascular complications with the presence of a previous one that could not be explained by levels of dyslipidaemia, blood pressure and hyperglycaemia; suggesting that additional pathophysiological processes are involved. In line with these findings, prospective observational studies have long reported an increased risk of CVD risk and mortality in individuals with chronic kidney disease in the general population independently of conventional cardiometabolic markers (Pavkov et al., 2018). Augmentation of other CVD risk factors in kidney disease, such as generalised endothelial dysfunction, oxidative stress and inflammation, or kidney disease-specific mechanisms (i.e., altered mineral metabolism, anaemia and accumulation of uremic toxins) might be implicated in the development of cardiovascular events (Tuttle et al., 2014, Kim-Mitsuyama et al., 2019, Lekawanvijit, 2018). In addition to the suggested common pathways of vascular injury, there are speculations that the progressive decline in vitamin D and increasing levels of cystatin C[14] during the course of kidney disease might promote the development of retinopathy (Nusinovici et al., 2019). Diabetic retinopathy is characterised by microvascular dysfunction and early neurodegenerative changes of the retinal neurons and glial, which eventually may result in localised inflammation and loss of synaptic activity and dendrites. Neurodegenerative changes may also be involved in the impairment of vascular integrity of the retina (Barrett et al., 2017). Whether there is a causative relationship between neuropathy and retinopathy remains unknown.

In general, individuals with diabetes show a range of alterations in the structure and function of the microvascular endothelium, including the coronary microcirculation, which have been suggested to be implicated in worsening of arterial hypertension, coronary atherosclerotic plaque and major adverse cardiovascular events (Taqueti and Di Carli, 2018, Avogaro and Fadini, 2019). An association between coronary microvascular dysfunction and decreased GFR was observed in cross-sectional analyses among individuals with non-obstructive coronary artery disease (Chade et al., 2006) and in a hospital-based study (Charytan et al., 2018), where increased severity of coronary microvascular dysfunction was

[14] **Cystatin C** – Protein produce by cells in the body and an early biomarker of chronic kidney disease.

also associated with a higher incidence of CVD. Thus, impairment in the several microvascular beds is involved in the pathogenesis of micro- and macrovascular complications, reflecting a link between the different vascular manifestations. Further studies are needed to elucidate whether these observations indicate, yet unidentified, pathophysiological pathways or exhibit a continuous progress of systemic vascular injury.

5.3.2 Effect of lifestyle on diabetes related vascular complications

5.3.2.1 Whole grain intake

Evidence from previous literature regarding diet and incidence of diabetes complications is scarce. Available data suggest that higher consumption of whole grain was associated with a decreased risk of diabetic kidney disease in high-risk individuals participating in the ONTARGET study (Dunkler et al., 2013). In the present study, while it was not possible to perform separate analyses for the several microvascular complications due to sample size restrictions, an inverse association was observed between whole grain consumption and total microvascular complications. The NHS study showed a reduced risk of CVD mortality with higher whole grain consumption in women with type 2 diabetes during a 26-year follow-up (He et al., 2010). Nevertheless, no clear association was observed for incidence of macrovascular complications in this work. Furthermore, the associations were not changed when time-updated whole grain intake was assessed and did not appear to be influenced by concurrent complication burden.

A protective effect of whole grain intake on diabetes complications is biologically plausible through several mechanisms. Whole grain contains an outer layer, the bran, the starchy endosperm, which comprises approximately 80% of the grain, and the germ, which refers to the embryo of the grain (Okarter and Liu, 2010). Whole grains are important sources of carbohydrate functional components such as dietary fibre, β-glycans and oligosaccharides and non-carbohydrate functional components, including carotenoids, tocopherols, flavonoids, minerals and phenolic acids (Mirmiran et al., 2014, Slavin et al., 1999). Higher concentrations of nutrients and phytochemicals are found in the outer part of the grain; thus, refined grains have reduced nutrient content. The health benefits of dietary fibre, particularly

soluble fibre, oligosaccharides and β-glycans include cholesterol-lowering effects and improved glucose response (Okarter and Liu, 2010, Slavin et al., 1999). The beneficial effects of the other phytochemicals lie in their antioxidant and anti-inflammatory activity (Okarter and Liu, 2010).

Higher whole grain intake, derived from dark bread and high-fibre and cooked cereals, was associated with increased insulin sensitivity in a cross-sectional study of individuals with normal or impaired glucose tolerance (Liese et al., 2003). Short-term randomised crossover trials (≤12 weeks) involving individuals with obesity and hyperinsulinemia (Pereira et al., 2002) or individuals with type 2 diabetes (Pick et al., 1998) showed that compared with consumption of refined grains, whole grain intake improved fasting insulin and insulin resistance and some participants reduced their dose in oral glucose-lowering medication. Body weight was maintained stable throughout the studies. In a one-month intervention among individuals with glucose intolerance, the addition of wheat barn in their usual diet showed favourable effects on blood glucose, insulin, cholesterol and triglycerides (Bosello et al., 1980). These findings should be interpreted with caution as there was no control group. The addition of wheat barn, however, did not improve glucose control or other cardiovascular risk factors in a randomised 3-month crossover trial in participants with type 2 diabetes (Jenkins et al., 2002). In contrast, two weeks of consumption of less-processed whole grain foods (wheat, oats, brown rice) improved measures of glycaemia in free-living individuals with type 2 diabetes participating in a randomised crossover trial (Åberg et al., 2020).

Observational and short-term intervention studies have shown that high consumption of whole grain and cereal fibre were associated with lower blood pressure levels (Steffen et al., 2005, Pins et al., 2002) and greater blood concentrations of adiponectin (Qi et al., 2006, Qi et al., 2005), a cytokine that improves insulin sensitivity and reduces inflammation (Liu et al., 2016). In addition, evidence from cross-sectional or short-term observational studies supports that higher consumption of whole grain was associated with lower concentrations of inflammatory markers (CRP and interleukin-6) in healthy individuals and in type 2 diabetes. These anti-inflammatory benefits were not consistently supported by short-term intervention studies (Buyken et al., 2014, Roager et al., 2019). However, pooled estimates of randomised controlled trials administering whole grain diet over 4–16 weeks showed an

inverse association between whole grain consumption and inflammatory markers (Xu et al., 2018b).

Given the suggested mechanisms, it would be expected that higher consumption of whole grain would reduce the risk of both micro- and macrovascular complications. Likely, the present study was underpowered to detect modest associations between whole grain intake and macrovascular events. Further studies are needed to verify the present findings regarding microvascular complications and clarify the role of whole grain intake on cardiovascular outcomes in type 2 diabetes. Habitual consumption of whole grain has been shown to be inversely associated with obesity and chronic weight gain (Mozaffarian, 2016, Kissock et al., 2021). Thus, BMI may be considered as a confounder and a mediating factor in the association between whole grain intake and diabetes complications. Similarly, diets rich in whole grains showed desirable effects on CVD risk factors, such as hypertension and dyslipidaemia (Wang et al., 2020). To assess whether this would apply to the present data, additional analyses excluding BMI, as well as prevalent conditions of hypertension and dyslipidaemia might have been worthwhile. Herein, whole grain assessment was mainly based on total whole grain bread and breakfast cereal. As different types of whole grain foods have heterogeneous glycaemic properties and contain various amounts of fibre and phytochemicals, they might exert differential effects on vascular complications (Mirmiran et al., 2014). Additional studies are warranted to investigate the effect of different sources of whole grain on diabetes complications.

5.3.2.2 Red meat intake

High red meat intake has been associated with an increased risk of type 2 diabetes (Schwingshackl et al., 2017a), CVD (Bechthold et al., 2019), age-related macular oedema (Dinu et al., 2019, Dighe et al., 2020) and chronic kidney disease (van Westing et al., 2020) in prospective cohort studies in the general population. Even so, prospective studies on red meat consumption and diabetes vascular complications are lacking. Among EPIC participants with prevalent diabetes, a higher intake of red meat was not associated with mortality during a median follow-up of ten years (Sluik et al., 2014). In the present cohort of individuals with newly-diagnosed type 2 diabetes, a U-shaped association was observed between red meat intake and microvascular complications, with a nadir at light-to-moderate

intake (35–65 g/day); while no clear association was evident for macrovascular complications. When time-updated red meat intake was assessed, the overall associations were not substantially modified. However, there was no association between red meat intake and microvascular complications in participants with a previous complication. Given the limited number of participants in these states, definitive conclusions cannot be drawn. High habitual consumption of red meat has been previously associated with an increased risk of obesity and hypertension (Schlesinger et al., 2019b, Schwingshackl et al., 2017b) and has been linked to dyslipidaemia (Bronzato and Durante, 2017). Therefore, future analyses would benefit from taking into account potential mediating effects by evaluating the associations without including BMI, and prevalent conditions of hypertension and dyslipidaemia.

The observed U-shaped association needs to be considered from both biological and methodological perspectives. The pathogenic role of high red meat intake on vascular complications may involve several mechanisms. Red meat is an important source of heme iron, which, in overload, leads to ROS formation, such as superoxide and hydrogen peroxide. Furthermore, iron plays a catalytic role in converting low-reactive free radicals into highly reactive ones, such as hydroxyl and superoxide radicals (Kim et al., 2015). Hyperglycaemia- and hyperlipidaemia-induced oxidative stress in diabetes may further contribute to the availability of intracellular iron that exacerbates oxidative stress and vascular injury (Swaminathan et al., 2007). Serum ferritin, a biomarker of iron stores and inflammatory marker, has been inversely associated with adiponectin, independently of other inflammatory markers, such as CRP, interleukin-6 and TNF-α (Simcox and McClain, 2013). In addition, red meat contains high levels of AGEs and is prone to new AGEs formation during cooking (Uribarri et al., 2010). Dietary AGEs are absorbed through the gastrointestinal tract and significantly increase circulating AGEs in individuals with diabetes (Feskens et al., 2013). High intake of dietary AGEs was associated with vascular stiffness and inflammation in a cross-sectional study (Di Pino et al., 2017) and short-term randomised trials, whereas their restriction suppressed inflammatory responses in diabetes (Vlassara et al., 2002).

Red meat is a protein-rich food. Clinical guidelines from nephrology associations recommend dietary protein restriction with an intake of up to 0.8 g/kg of body weight per

day or lower in patients with (diabetic or non-diabetic) kidney disease who are not undergoing haemodialysis (Ikizler et al., 2020). Nonetheless, the impact of dietary protein on kidney disease is equivocal. Large prospective cohort studies suggest, though not consistently, that chronic intake of high-protein diets may increase the risk of a severe stage of chronic kidney disease in the general population, with red meat protein appearing to be most harmful (Kamper and Strandgaard, 2017). Pooled analysis of seven randomised controlled trials in type 1 diabetes showed a non-significant reduction in renal function decline among individuals in the low protein intervention arm compared with the control group (Robertson et al., 2007). A similar effect was observed in type 2 diabetes patients participating in two six-month randomised controlled trials with follow-up of more than 28 months, where a low-protein diet did not confer a renoprotective effect as measured by GFR decline compared to the control group (normal-protein diet or dietary advice) (Koya et al., 2009, Pijls et al., 2002). In a one-year randomised trial among people with type 2 diabetes, there was no difference between the two intervention groups (low protein diet vs free protein diet) in GFR decline (Robertson et al., 2007). Pooled analyses of randomised controlled trials reported that a low-protein diet was associated with a slightly increased excursion of proteinuria but increased GFR compared to the control group in type 2 diabetes (Zhu et al., 2018, Nezu et al., 2013). Still, concerns about the duration of the trials, adherence to the diet and pre-existing renal function decline limit the conclusions. Based on the current literature and grading of the evidence by the Diabetes Nutrition Study Group (DNSG) (Pfeiffer et al., 2020), DDG guidelines suggest that protein restriction to less than 0.8 g/kg of body weight is unlikely to be beneficial in any stage of kidney impairment (Skurk et al., 2022).

In the current work, the identification of diabetes complications relied on the accurate reporting of participants' treating physicians. One could speculate that participants at the early stages of microalbuminuria were not classified as having diabetes-related kidney disease but were advised to reduce their protein intake. Therefore, the increased risk of microvascular complications observed among individuals in the lowest tertile of red meat intake potentially reflects reverse causation driven by individuals who eventually developed kidney disease. However, as described above, separate analyses for the several vascular complications were not possible to be performed. The positive association between low animal protein intake and incidence or progression of diabetic kidney disease has also been documented in

individuals with type 2 diabetes and normo- or microalbuminuria participating in the ONTARGET cohort study (Dunkler et al., 2013).

On the other hand, red meat is a source of essential amino acids, which are crucial in the preservation of skeletal muscle mass, as well as micronutrients. One of them is zinc, an essential element of superoxide dismutase, a potent enzyme that inactivates ROS (Mafra et al., 2018). Taken together, low-to-moderate consumption of unprocessed red meat can be part of a healthy diet in individuals with type 2 diabetes and without other major comorbidities. However, given the limited evidence available, larger studies are needed to understand the relationship between red meat intake and micro- and macrovascular complications. High habitual consumption of red meat has been previously associated with an increased risk of obesity and hypertension (Schlesinger et al., 2019b, Schwingshackl et al., 2017b) and has been linked to dyslipidaemia (Bronzato and Durante, 2017). Therefore, future analyses would benefit from taking into account potential mediating effects by evaluating the associations without including BMI and prevalent conditions of hypertension and dyslipidaemia.

5.3.2.3 Coffee intake

In this work, no association between coffee intake and total microvascular complications was observed. Previous literature reported a lower non-significant risk of kidney disease among individuals with diabetes, prospectively assessed, who drank higher amounts of coffee (Hu et al., 2018); while, a significantly decreased risk of renal function decline was observed among Korean women with diabetes in a cross-sectional study (Kim et al., 2013) and prospective cohort studies in the general population (van Westing et al., 2020, Herber-Gast et al., 2016, Jhee et al., 2018). Currently, studies on diabetes-related neuropathy and retinopathy are scarce. Evidence from a short-term prospective cohort study from the US indicated that coffee intake was not associated with early age-related maculopathy (Tomany et al., 2001).

With respect to macrovascular complications, a linear inverse association was observed between habitual coffee intake and macrovascular complications, which remained consistent when time-updated coffee consumption was evaluated. Similar to the present findings, coffee drinking was associated with a reduced risk of CVD mortality in a Finnish prospective cohort

among individuals with type 2 diabetes (Bidel et al., 2006). However, prospective analyses in the NHS and HPFS cohort studies showed an inverse non-significant association between high coffee consumption (≥4 cups/ day) and CVD in type 2 diabetes, compared with low coffee intake (<1 cup/ month) (Zhang et al., 2009b, Zhang et al., 2009a). One possible reason is that the NHS and HPFS studies involved individuals with prevalent diabetes. Coffee drinking is often considered an unhealthy habit by consumers (Samoggia and Riedel, 2019, Institute for Scientific Information on Coffee (ISIC), 2016). Consequently, individuals might have reduced or avoided coffee drinking after diabetes diagnosis, resulting in attenuated associations in these two cohorts.

The misconception of the adverse effects of coffee intake on health outcomes emerged from short-term clinical trials. Coffee is a complex chemical mixture containing several bioactive compounds, including caffeine, phenolic compounds, such as chlorogenic acids, flavonoids and lignans, minerals and diterpenes (cafestol and kahweol) (Farah, 2018). In several, but not all, short-term randomised controlled trials among individuals with diabetes, caffeine intake increased blood glucose levels and prolonged the period of hyperglycaemia when combined with carbohydrates (Dewar and Heuberger, 2017). The unfavourable effects of acute caffeine intake on glucose metabolism were also reported in short-term clinical studies among persons without diabetes. In contrast, data from long-term trials (2–16 weeks) found that caffeinated coffee might improve glucose metabolism and insulin sensitivity (Reis et al., 2019), corroborating, thus, prospective cohort studies that reported an inverse association between coffee intake and type 2 diabetes risk (Poole et al., 2017). In a cross-sectional analysis in the NHS, consumption of four or more cups of caffeinated coffee per day was associated with higher plasma adiponectin concentrations in women with and without diabetes (Williams et al., 2008). Similar findings have been observed in other cross-sectional studies among individuals without or at high risk of diabetes (Hang et al., 2019, Izadi et al., 2018) and in an 8-week randomised controlled trial among habitual coffee drinkers (Wedick et al., 2011). These results suggest that adiponectin concentrations may partly mediate the beneficial effects of coffee on insulin sensitivity.

Additionally, short-term randomised controlled trials have indicated that coffee consumption increases blood pressure, attributed to the acute effects of caffeine (Noordzij et al., 2005, Mesas et al., 2011). However, these findings were not supported in meta-analyses

of randomised controlled trials with longer duration (4–16 weeks) and prospective cohort studies, where no association was detected (Steffen et al., 2012). Hence, conclusions cannot be extrapolated from short-term trials, as acute caffeine effects are attenuated after prolonged coffee intake and in habitual coffee drinkers.

Concerns have been raised that high coffee intake adversely alters levels of serum lipids. Findings from a meta-analysis of randomised controlled trials showed a positive association between coffee consumption and total cholesterol, LDL cholesterol and triglycerides (Cai et al., 2012), although the associations were attenuated in trials with a duration of eight weeks or more. Similar findings were reported in cross-sectional studies in healthy individuals and with type 2 diabetes (Cornelis and van Dam, 2020, Ghavami et al., 2021). The detrimental effects of coffee intake on serum lipids have been attributed to the diterpene content of coffee. In fact, instant and filtered coffee, which has negligible amounts of diterpenes (Urgert et al., 1995), was not associated with an increase in serum lipids in stratified analyses in the aforementioned studies. Therefore, high chronic consumption of unfiltered coffee could potentially increase serum lipids and, consequently, elevate the risk of diabetes-related vascular complications. The coffee brewing method was not assessed in the present study, where habitual coffee intake was associated with a lower risk of macrovascular complications in a dose-response fashion. In Germany, filtered coffee is the main method of coffee preparation (Floegel et al., 2012). Therefore, the participants of the present cohort most likely consumed predominantly filtered coffee. In a meta-analysis of prospective cohort studies in the general population involving individuals most likely drinking filtered coffee, a U-shaped association was observed with a nadir at 3–5 cups of coffee per day, while heavy coffee consumption (≥6 cups per day) was not associated with an increased CVD risk (Ding et al., 2014). These findings do not contradict the present observations, as consumption levels were lower in the present study, with 90% of the participants consuming up to five cups of coffee per day.

In vitro and in vivo human studies have shown that the phenolic compounds of coffee may lower atherogenesis risk by inhibiting platelet aggregation, mitigating LDL oxidation and decreasing LDL cholesterol (Amarowicz and Pegg, 2017, Yukawa et al., 2004, Natella et al., 2007, Natella et al., 2008). In addition, the phenolic compounds of coffee have antioxidant properties, exert anti-inflammatory effects and favourably affect endothelial

function (Farah, 2018, Hang et al., 2019, Kempf et al., 2010, Jacobs et al., 2014). In people with diabetes, higher coffee intake was associated with lower concentrations of inflammatory markers, such as CRP levels and TNF-α, as well as E-selectin, a more specific marker of endothelial function (Williams et al., 2008, Lopez-Garcia et al., 2006, Vitale et al., 2017).

Even though the potential benefits of (filtered) coffee drinking in the endothelial function, no association was apparent between coffee intake and microvascular complications in the current data. Coffee consumption has been linked to poorer health habits, particularly smoking. Albeit adjustment for smoking status and duration was performed in the present analysis, residual confounding might still be present, overshadowing the potential modest benefits of coffee consumption on microvascular complication risk. However, the relatively small size of the cohort limited the ability to perform analysis in subgroups of smoking status.

Given the high coffee consumption worldwide, the present findings are of importance to public health. However, in view of the paucity in the current evidence, further larger prospective studies are needed to understand better the relationship between coffee intake and vascular complications of diabetes.

5.3.2.4 Obesity measures and BMI change[15]

The present data revealed a positive association between waist circumference and BMI and total microvascular complications, kidney disease and neuropathy as assessed by multistate and standard Cox models. Furthermore, multistate models showed that the observed associations were not modified by complication load. Previous longitudinal observational studies have shown inconsistent results regarding the association between BMI and microvascular complications. In line with the current findings, several studies reported a positive association (Gray et al., 2015, Nakanishi et al., 2019, Rossi et al., 2010, Schlesinger et al., 2019a, Svensson et al., 2015, Tanaka et al., 2016). In contrast, others have observed an inverse (Bentata and Abouqal, 2014, Huang et al., 2014) or no association (Chung et al.,

[15] This section was published by POLEMITI, E., BAUDRY, J., KUXHAUS, O., JÄGER, S., BERGMANN, M. M., WEIKERT, C. & SCHULZE, M. B. 2021. BMI and BMI change following incident type 2 diabetes and risk of microvascular and macrovascular complications: the EPIC-Potsdam study. *Diabetologia,* 64**,** 814-25.

2017, Klein et al., 1997, Mohsen et al., 2012). Of note, only Gray et al. included individuals with newly diagnosed type 2 diabetes (Gray et al., 2015). However, the study did not consider comorbid conditions and was based on health care claims data, making it susceptible to misclassification and confounding due to inadequate adjustment. The association between waist circumference and microvascular complications has been studied to a smaller degree. Similar to the present study, previous literature has observed analogous associations with BMI (Andersen et al., 2018, Chung et al., 2017, Schlesinger et al., 2019a).

Regarding macrovascular events, no apparent association was observable in the current data. Former studies showed discordant results by reporting positive (Costanzo et al., 2015, Eeg-Olofsson et al., 2009, Gray et al., 2015, Rådholm et al., 2018), inverse (Li et al., 2015, Owusu Adjah et al., 2019, Park et al., 2019a, Thomas et al., 2014) and U-shaped associations (Xing et al., 2019, Pagidipati et al., 2020). Furthermore, a meta-analysis on cardiovascular mortality found a possible nonlinear relationship (Zaccardi et al., 2017). Reverse causation and confounding by diabetes severity and treatment remain an issue in these studies. Few studies used BMI or waist circumference preceding type 2 diabetes diagnosis like in this work. Gray et al. found a positive association between pre-diagnosis BMI and macrovascular complications (Gray et al., 2015), whereas two other large cohort studies found inverse associations (Li et al., 2015, Owusu Adjah et al., 2019). Li et al. reported results from several stratified analyses, including smoking status, where the inverse association remained consistent (Li et al., 2015). However, it was based on data from low-income individuals and lacked information on important lifestyle factors. In contrast, the NHS and HPFS cohorts reported a significant positive association between pre-diagnosis BMI and cardiovascular mortality among never-smokers with type 2 diabetes (Tobias et al., 2014).

To overcome limitations of previous studies, a prospective study was used, embedded in a population-based cohort, investigating the association of pre-diagnosis BMI and waist circumference with the incidence of both micro- and macrovascular complications in individuals with incident type 2 diabetes. Furthermore, the impact on complication load was investigated in multistate Cox models and potential biases were accounted extensively in two-state Cox models for the association between pre-diagnosis BMI and diabetes-related complications. The use of pre-diagnosis adiposity measures protects against misclassification due to weight change by disease severity or medical treatment. Moreover, excluding

participants with pre-existing disease and cases during the first years of follow-up prevents reverse causation. In the present study, no obesity paradox was observed. Instead, a clear robust positive association was found with microvascular complications, while BMI and waist circumference were not associated with macrovascular complications.

Several mechanisms have been proposed linking obesity to endothelial dysfunction and vascular disease. Obesity increases the occurrence of conventional cardiometabolic risk factors, such as hypertension, dyslipidaemia and insulin resistance. In insulin-resistant and obese states, dyslipidaemia is characterised by an increased concentration of small, dense triacylglycerol-containing LDL particles. Small dense LDL particles are more susceptible to oxidation and glycation, enter the arterial wall more easily and promote inflammation, vascular endothelial dysfunction, production of procoagulants and atherosclerosis (Kwiterovich, 2002). In addition, adipose tissue is an active endocrine and paracrine organ altering the secretion of adipokines (i.e., upregulation of leptin and downregulation of adiponectin) and increasing the release of proinflammatory cytokines, including interleukin-6, interleukin-1β and TNF-α, which subsequently elevate CRP levels. Through these pathways, the adipose tissue contributes to a proinflammatory, thrombogenic, and atherosclerotic vascular environment, exacerbating systemic insulin resistance and development of vascular complications (Van Gaal et al., 2006, Herder et al., 2015, Forbes and Cooper, 2013).

Several factors could explain the lack of a relationship between obesity and macrovascular complications observed in the present study. First, participants with overweight or obesity may be treated more intensively for dyslipidaemia, hypertension, or hyperglycaemia than counterparts with a normal weight. Measurements of these markers were not available, and therefore their changes over time were not possible to be assessed. Adjusting for prevalent hypertension and dyslipidaemia and excluding participants treated with insulin, all representing risk factors for microvascular complications positively associated with BMI, did not change the association. Thus, better treatment of risk factors among obese individuals is unlikely to explain the difference observed for macrovascular versus microvascular complications. Second, sarcopenia may be prevalent among older leaner persons with diabetes, which might predispose to higher CVD events (Hamasaki et al., 2017). Nonetheless, the association did not change after performing a stratified analysis

by age at diabetes diagnosis. It is also unlikely that weight loss before diabetes diagnosis could explain these findings as it did not differ meaningfully between BMI categories. Third, suboptimal control for smoking status may lead to spurious results. Restricting the analysis among never-smokers did not change the initial associations for microvascular complications. Yet, the association for macrovascular disease remained uncertain, possibly due to the limited number of macrovascular events.

Whether BMI change after diabetes diagnosis may influence subsequent vascular complications was also evaluated, as a weight loss of ≥5% is routinely recommended in individuals with overweight or obesity at type 2 diabetes diagnosis (American Diabetes Association, 2020). A decreased risk was observed for total microvascular complications, kidney disease, and neuropathy with BMI loss shortly after diabetes diagnosis. A limitation of the present analyses is that it was not possible to determine whether weight loss was intentional and to what extent weight changes are attributable to different glucose-lowering medications. Still, weight loss was associated with a lower risk of total microvascular complications, kidney disease and neuropathy, independent of baseline BMI. In line with these data, a link between intentional weight loss and a lower risk of kidney disease in type 2 diabetes has been previously reported (Holland et al., 2019).

Behavioural lifestyle weight reduction has shown to be an effective intervention to improve conventional cardiometabolic risk factors and inflammation, measured as CRP, in individuals at high risk of diabetes and with established type 2 diabetes (Delahanty et al., 2014, Look Ahead Research Group, 2010, Espeland et al., 2013, Haffner et al., 2005). Nevertheless, whether weight loss after diabetes diagnosis is beneficial in terms of CVD risk has been debated. Secondary analysis of the DCGP and ACCORD data found that weight loss was linked with a non-significant increase in CVD events (Køster-Rasmussen et al., 2016, Xing et al., 2019). A large Scottish study did not find an association between weight change within two years of diabetes diagnosis and 5-year CVD incidence (Aucott et al., 2016), while secondary results of the ADDITION-Cambridge and the Look AHEAD studies observed that weight loss (≥5% and 10%, respectively) decreased risk for a 10-year CVD incident (Gregg et al., 2016a, Strelitz et al., 2019b). In this work, an increased risk of macrovascular complications with weight loss was observed, although this association was

not significant in the main analysis. Nevertheless, it was not explained by reverse causation or confounding by smoking in sensitivity analyses.

The present study underpins the importance of weight management in preventing diabetes-associated microvascular complications and the need for well-designed studies for macrovascular complications.

5.3.2.5 Physical activity

Physical activity is advocated in the management of type 2 diabetes (American Diabetes Association, 2019b). Meta-analyses of randomised controlled intervention studies showed that exercise improved insulin sensitivity (Sampath Kumar et al., 2019), glycaemic control (Gao et al., 2021, Shah et al., 2021), blood pressure and lipidemic profile (Pan et al., 2018) in individuals with type 2 diabetes. Furthermore, exercise reduced inflammatory cytokines, such as CRP, TNF-α and interleukin-6 (Chen et al., 2020), oxidative stress (Vasconcelos Gouveia et al., 2021, Gordon et al., 2008, de Oliveira et al., 2012, Farabi et al., 2015, Vinetti et al., 2015, Haxhi et al., 2016) and improved levels of soluble receptor for AGEs[16] (Choi et al., 2012). Therefore, physical activity can modulate underlying mechanisms that lead to diabetes complications. Randomised controlled trials showing that physical activity per se reduces the risk of diabetes-related complications are lacking (Hemmingsen et al., 2017). Still, physical activity delayed peripheral neuropathy progression, reduced neuropathic symptoms (Zilliox and Russell, 2019, Gholami et al., 2018), improved renal function (Cai et al., 2021), cardiorespiratory fitness (Liu et al., 2019b) and carotid intima-media thickness (Magalhães et al., 2019) in individuals with diabetes in clinical trials.

In agreement with the evidence derived from clinical trials, prospective observational studies in type 2 diabetes, although sparse, showed that the risk of micro- and macrovascular complications declined among participants engaging in higher levels of physical activity. In a secondary analysis of the ADVANCE study, moderate to vigorous physical activity was associated with a reduced risk of total microvascular complications and macrovascular

[16] **Soluble receptor for AGEs** – a secretory slice isoform of RAGE, that act as decoy receptors of AGEs contributing to the removal of circulating ligands (GEROLDI, D., FALCONE, C. & EMANUELE, E. 2006. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. *Curr Med Chem,* 13**,** 1971-8.).

complications compared to no or mild physical activity during a median 5-year follow-up (Blomster et al., 2013). Similarly, a meta-analysis of six prospective studies showed that higher levels of physical activity were associated with reduced risk of macrovascular complications (Kodama et al., 2013). Participants of the ONTARGET study who were physically active every day had a reduced incidence of kidney disease compared to those who lived a sedentary life after 5.5 years of follow-up (Dunkler et al., 2015b). Another US study among Medicare beneficiaries observed a decreased risk of kidney disease over a 5-year follow-up among individuals who had regular physical activity compared to no regular physical activity (Chen et al., 2015). However, the last two studies did not control for smoking status (Chen et al., 2015, Dunkler et al., 2015b). Evidence on the association between physical activity and retinopathy remains unclear as there is high heterogeneity between studies in a meta-analysis of prospective studies; among which, three involve individuals with type 2 diabetes (Ren et al., 2019).

The findings of the present study contradict previous literature as higher physical activity was associated with an increased risk of total microvascular complications in a linear fashion. The positive association remained when time-updated physical activity was assessed in the total study population as well as in individuals without a prior diagnosis of diabetes complications. The associations were attenuated in individuals with a prior micro- or a macrovascular complication, which may be explained by the limited sample size. Whilst previous literature might have been biased by the 'healthy exerciser effect', the present findings are unexpected. A possible explanation is reverse causality. To minimise the likelihood of reverse causality, individuals with existing chronic disease (cardiovascular or microvascular disease) at diabetes diagnosis were excluded from the analyses. Nevertheless, reverse causality might have affected the observed associations since participants with comorbidities, e.g., hypertension or dyslipidaemia, may have been advised to increase physical activity. The participants of the present study dedicated limited time to leisure physical activity (median time of 1 hour per week), which may not be sufficient to exert health benefits. Previous studies that reported a protective effect of exercise on health outcomes had considered greater levels of physical activity.

Consequently, the aforementioned comorbidities may act as both mediators and confounders in the association between physical activity and complications. Subgroup

analysis among those without comorbidities was not possible as the majority of this population with incident diabetes was afflicted with comorbid conditions. Prevalent conditions of hypertension and dyslipidaemia were included in the regression models, but residual confounding might have influenced the findings as concentrations of blood lipids and measurements of blood pressure were not available.

The measurement of physical activity was carried out through self-reported questionnaires, and exercise intensity was not assessed. In an effort to avoid reporting bias, information on physical activity was obtained from questionnaires closely before diabetes diagnosis in the first part of the analysis. Nevertheless, some degree of misclassification is inevitable in observational study designs. Any misclassification would be expected to be non-differential and, thus, bias the results toward the null. However, differential misclassification cannot be excluded in view of the positive associations. The impact of selective misreporting due to lifestyle and phenotypic traits should have been mitigated by statistically adjusting for these factors. Still, participants with more severe comorbidities, hence higher risk of complications, might have misreported higher levels of activity.

Levels of pre-diagnosis physical activity were not associated with the incidence of macrovascular complications, whereas time-updated physical activity showed an inverse non-significant association. Here, too, the limited sample size and the uncertainties in the assessment of physical activity constrain concrete conclusions. Nevertheless, the opposite directions in the observed associations between micro- and macrovascular complications raise the question of whether they could be explained by the speculated biases described above. Given the limitations of the present study, further studies are needed to best understand the effect of physical activity on diabetes-related complications.

5.3.2.6 Smoking

There is consensus that smoking is a risk factor for macrovascular complications in diabetes. A meta-analysis of 16 prospective cohort studies on individuals with type 2 diabetes (except one study which included people with type 1 diabetes) showed that active smoking was associated with 44% and 55% increased risk of macrovascular events compared to no smoking and never-smoking, respectively (Pan et al., 2015). The positive association persisted in all strata of subgroup analyses according to study and population characteristics

and study quality. Similar findings were reported from the NHS and HPF studies (Liu et al., 2018) as well as in terms of cardiovascular mortality based on 13 prospective cohorts (Pan et al., 2015). Smoking is often clustered with other unhealthy lifestyle factors, such as poor diet, excessive alcohol intake and physical inactivity (Chiolero et al., 2006, Masood et al., 2015). Nevertheless, most of the included studies did not adjust for these lifestyle factors or BMI, allowing a high potential of residual confounding. These confounding factors are essential in studying lifestyle-related diseases, such as type 2 diabetes. Furthermore, most of the studies involved participants with prevalent diabetes.

Herein, individuals with newly diagnosed type 2 diabetes who reported current smoking had almost five times greater risk of developing a macrovascular complication than never-smokers after controlling for lifestyle factors, glucose-lowering medication and prevalent conditions of hypertension and dyslipidaemia. The strong positive association remained (HR≈6.0) when time-updated smoking status was examined in the total population and those without a complication load. In individuals with a prior microvascular complication, a positive non-significant association was observed, which may be attributed to the small sample size. In addition, former smokers had about twice the risk of macrovascular events compared with never-smokers at both time-points of assessment. These findings suggest that, although former smokers exhibited a significantly higher risk of macrovascular complications than never-smokers, smoking cessation may have substantial benefits for people with diabetes in reducing or delaying the risk of developing a CVD event. A similar pattern emerged in the meta-analysis by Pan and colleagues and in a large prospective Finnish study (Pan et al., 2015, Barengo et al., 2017).

Individuals with diabetes are at excess risk of all-cause mortality, cardiovascular mortality and CVD events, in comparison to the general population (Rawshani et al., 2017). Smoking in diabetes is linked to higher levels of HbA1c and a more disadvantageous lipid profile compared to non-smokers (Kar et al., 2016), which may, in turn, further heighten the risk of vascular complications (Rawshani et al., 2018, Barengo et al., 2017). Therefore, smoking is particularly problematic in individuals with diabetes and sustained smoking cessation is a major public health goal (American Diabetes Association, 2019b). Nevertheless, a degree of concern has been raised for people with diabetes as quitting smoking is often accompanied by body weight gain (Aubin et al., 2012, Tian et al., 2015)

and deterioration in glycaemic control that lasted for three years, independent of post-cessation weight gain (Lycett et al., 2015). While the mechanisms behind the effects of smoking cessation on glycaemic levels remain unclear, quitting smoking shows cardioprotective effects in individuals with diabetes, as shown by the present work and others (Pan et al., 2015, Barengo et al., 2017, Clair et al., 2013, Choi et al., 2017). Furthermore, although weight gain may weaken the reduction in macrovascular complications risk, especially among those who gained more than 5 kg, they still exhibited lower risk than continuing smokers (Liu et al., 2020, Luo et al., 2013).

The relationship between smoking and microvascular complications has been studied predominantly in type 1 diabetes, where smoking appears to increase the risk for kidney disease, neuropathy and retinopathy (Campagna et al., 2019). The evidence for type 2 diabetes is inconclusive, as available data are of doubtful reliability and studies are not entirely consistent. The pooled estimate of four prospective cohort studies showed a significant increase in the risk of developing proteinuria in ever-smokers with type 2 diabetes compared to non-smokers (Xu et al., 2018a). Small-scale prospective studies also reported an increased rate of kidney function decline among smokers compared to non-smokers (Kar et al., 2019, Rossing et al., 2004). Notably, the analyses in most studies cited above were either crude, insufficiently adjusted or did not report information on which confounders were selected. Among participants of the ONTARGET study, smoking was not associated with kidney disease progression, defined as a GFR decline of more than 5% per year, progression to end-stage renal disease, microalbuminuria or macroalbuminuria during 5.5 years of follow-up (Dunkler et al., 2015b). Similar findings were reported from a nested case-control study, although the estimates were minimally adjusted (Bruno et al., 2003). Nonetheless, small-scale studies (35 to 193 participants) indicated that smoking cessation improved microalbuminuria at the end of the follow-up period in people with type 2 diabetes and existing microalbuminuria, followed for 24 weeks (Chuahirun et al., 2004), 12 months (Voulgari et al., 2011, Hieshima et al., 2018) and five years (Phisitkul et al., 2008).

One of the first substantive studies to investigate the association between smoking and retinopathy in type 2 diabetes was the UKPDS 50 study, in which, paradoxically, current smoking appeared to be a protective factor for the incidence and progression of retinopathy compared to never-smoking (Stratton et al., 2001). Since then, several studies have been

published that seem to support this association, including a meta-analysis of 21 longitudinal cohort studies (Cai et al., 2018) and a recent retrospective study of more than 70 thousand newly diagnosed type 2 diabetes patients privately insured and without prevalent retinopathy at baseline (Gange et al., 2021). In contrast, a small cross-sectional study in persons with type 2 diabetes without clinically evident retinopathy indicated that smoking is a risk factor of early modifications of the retinal microvasculature (Lee et al., 2018b). More specifically, current smoking was associated with lower vascular density in deep capillary plexus[17] in age- and sex-adjusted analyses. Correspondingly, in multivariable-adjusted models involving individuals with and without retinopathy at recruitment, smoking was associated with a reduced capillary density index[18] during a follow-up of one month (Ting et al., 2017).

Cross-sectional studies have demonstrated a positive link between smoking and peripheral neuropathy in type 2 diabetes (Clair et al., 2015, Abdissa et al., 2020, Mathiyalagen et al., 2021, Jaiswal et al., 2017) and prediabetes (van der Velde et al., 2020). Contradictory results were reported from a meta-analysis of three early prospective cohort studies, where an inverse non-significant association was observed (Clair et al., 2015). Yet again, two of the included studies were unadjusted or minimally adjusted, and the follow-up duration in all studies was relatively short (≤5 years). The study with a better level of adjustment reported a significant inverse association between smoking and neuropathy incidence (Gerrits et al., 2008). A protective effect of smoking has also been reported in a population of US veterans, 92% of whom had type 2 diabetes (Adler et al., 1997).

A large global prospective study reported an elevated 3-year incidence of total microvascular complications among current smokers (Arnold et al., 2022). However, the study was limited as it had a short follow-up, did not control for socioeconomic and lifestyle factors, included participants with prevalent diabetes, and one-fourth of them had pre-existing complications at baseline. The present work observed an increased risk for total microvascular complications among current smokers compared to never smokers, assessed

[17] Using optical coherence tomographic angiography to visualise retinal vessels, the **deep capillary plexus** includes flow signals of the intermediate and deep inner retinal vasculature. DANSINGANI, K. K., INOUE, M., ENGELBERT, M. & FREUND, K. B. 2015. Optical coherence tomographic angiography shows reduced deep capillary flow in paracentral acute middle maculopathy. *Eye (Lond),* 29**,** 1620-4.

[18] **Capillary density index** – a measure of retinal vascular density. Retinal vascular density describes the proportion of vessel area through which blood flows over the measured area.

at diabetes diagnosis and entry at each state. Participants who smoked and with complication load had approximately 1.7 times higher risk of developing a further microvascular complication than smokers without a complication. Nevertheless, none of the observed associations reached statistical significance. Former smokers also appeared to have an increased risk for microvascular complications, yet lower than current smokers, although the findings were not statistically significant. Given the uncertainty and opposing associations reported in previous literature, it would be valuable to investigate the associations for the several microvascular complications separately. However, it was not possible due to sample size limitations.

The lack of statistical significance in the observed association can be partly explained by selection bias. Smokers might have disproportionally experienced loss to follow-up prior to the collection of microvascular endpoints, hence ameliorating the effects of smoking on microvascular complications. Even though a strong positive association was observed for macrovascular complications, selection bias might have particularly affected observations for microvascular complications due to differences in the ascertainment process of the two endpoints. Diabetes-related micro- and macrovascular complications were collected through standardised forms completed by participants' treating physicians in 2014 – at least five years after the fifth follow-up of the EPIC-Potsdam study. Macrovascular events were also collected throughout the regular follow-up of the participants, combining various data sources, i.e., self-reports, death certificates and health records, and ultimately, verification from treating physicians. Treating physicians' records is an objective and reliable source of outcome data. Nevertheless, a level of inaccuracy cannot be opted out for microvascular complications. In fact, individuals for whom information on vascular complications could not be retrieved from the standardised forms were more likely to be lost to follow-up (see **Appendix 4**). Furthermore, non-responders were more likely to be deceased by 2014, be current smokers and have longer smoking duration at recruitment and diabetes diagnosis.

In the population used for analysis only nine fatal macrovascular events were observed, defined as death within 28 days of macrovascular event occurrence. Nevertheless, competing risk bias cannot be precluded as active smoking increases mortality risk from several other causes. Another concern is that the assessment of smoking habits might lack accuracy as the

number of cigarettes smoked per day was not assessed. Nonetheless, the associations were controlled for years of smoking.

Exposure to cigarette smoking triggers vascular damage, endothelial dysfunction, oxidative stress, activation of pro-inflammatory and prothrombotic cascades, dyslipidaemia, in addition to reduced insulin secretion and increased insulin resistance in the general population (Sliwinska-Mosson and Milnerowicz, 2017, Golbidi et al., 2020). Similar biological mechanisms of vascular injury have been identified in people with type 2 diabetes. Compared to healthy individuals, people with type 2 diabetes were more susceptible to the acute effects of nicotine (one of the components of cigarette smoke) on insulin resistance, as demonstrated by a small randomised controlled trial (Axelsson et al., 2001). Results from cross-sectional and case-control studies indicate that smoking aggravates insulin resistance in people with type 2 diabetes (Anan et al., 2006, Targher et al., 1997, Kong et al., 2001). Compared to never-smokers a dose- and time-dependent relationship was observed between smoking and insulin resistance when smoking was assessed as number of cigarettes per day or pack-years (Ohkuma et al., 2015). Likewise, active smoking increased levels of HbA1c progressively (Ohkuma et al., 2015) and the risk of poor glycaemic control compared to non-smokers (Peng et al., 2018). Furthermore, tobacco use appears to increase products of lipid peroxidation and oxidative stress and has a negative impact on circulating levels of adipokines and CRP (Ohkuma et al., 2015, Morrow et al., 1995, Pilz et al., 2000, Anusruti et al., 2020).

The exact mechanisms of how smoking may affect microvascular complications are still uncovered. It has been suggested that smoking might induce renal function decline through damage to the glomerular structure, such as thickening of the glomerular basement membrane (Baggio et al., 2002) or via an elevation in blood pressure (Cooper, 2006). A negative correlation has been observed between smoking and volume of dorsal root ganglion, a sensory neural structure involved in pain transmission (Deer et al., 2020), implying that smokers with diabetes may be at increased risk of diabetic neuropathy (Jende et al., 2020). Furthermore, an in vitro study of human diabetic macular oedema showed that nicotine alters the integrity of the outer blood-retinal barrier by upregulating hypoxia-inducible factors and VEGF (Maugeri et al., 2017).

While further studies are needed to elucidate the role of smoking on microvascular complications, its harmful impact on cardiovascular health is prominent. Thereby, smoking cessation treatment should be encouraged and supported by interventions of post-cessation weight management in order to maximise the beneficial effects of quitting smoking.

5.3.2.7 Alcohol intake

The association between alcohol consumption and CVD risk in type 2 diabetes was evaluated post hoc among participants of the ADVANCE trial, where alcohol consumption was assessed in three categories: abstainers, moderate and heavy users. Compared with abstainers, the study showed a reduced risk of total macrovascular complications in individuals who reported moderate alcohol use, defined as ≤21 drinks for men and ≤14 for women per week (Blomster et al., 2014). Furthermore, a possible U-shaped association was observable, suggesting that heavy drinking may reverse any protective effect. However, the number of heavy drinkers was somewhat limited to draw definitive conclusions.

The comparability of the ADVANCE study with the present study is restricted. The participants of the ADVANCE study had a mean diabetes duration of seven years, and about one-third of them or more had a history of major macro- or microvascular disease. Considering that participants with prevalent disease might have changed their habitual alcohol intake after diagnosis, potentially distorting the results, only incident diabetes cases without a vascular disease at baseline were included in the present study. To further limit reverse causality, very light alcohol drinkers were used as the comparison group. Taking abstainers as the reference category may have overestimated the protective effect of alcohol on vascular complications observed in the ADVANCE study because it might have captured people that quit drinking due to health issues. Lifelong abstainers should also be a cause of concern, as they may differ systematically from people who drink in ways that may not be observed in the data but still be linked to the aetiology of the outcome. Furthermore, the participants of the present study were predominantly light to moderate alcohol users. No clear association was observable between alcohol intake and macrovascular complications. Consumption of alcohol below (men/women >2 to ≤24/>1 to ≤12 g/day) or above the limit (men/women >24/>12 g/day) were positively but non-significantly associated with macrovascular complications compared with very light alcohol users. In additional analyses

assessing alcohol intake continuously, per 1 g/day increase, there was an absence of an association or any dose-response effect (HR=1.00). Yet, a similar effect was observed in the ADVANCE study, as dose-response analysis (per drink/week) among moderate alcohol users showed no association with cardiovascular events.

The NHS and HPFS studies reported that light to moderate alcohol consumption halved the risk of coronary heart disease in a dose-response pattern in health professionals with prevalent type 2 diabetes compared with non-drinkers (Tanasescu et al., 2001, Solomon et al., 2000). The findings were supported by a combined analysis of 83 prospective studies from the Emerging Risk Factors Collaboration, EPIC-CVD and the UK Biobank involving current drinkers from the general population. The authors reported a dose-response inverse relationship between alcohol intake and myocardial infraction (Wood et al., 2018). A matching relationship to myocardial infarction would be expected for ischemic stroke, given the similarities in risk factors and disease pathways. However, a roughly linear positive association was observed between alcohol intake and stroke. The opposite directionality of the associations in the CVD subtypes may explain the lack of association observed in the present work between alcohol intake and total macrovascular complications.

Alcohol consumption was also assessed after diabetes diagnosis among participants who developed more than one vascular complication. Individuals who developed a microvascular complication exhibited a decreased risk of further macrovascular complications with below and above the limit of alcohol drinking, although the latter category was not statistically significant. The reasons for this observation are difficult to conceive. Possibly the limited sample size and bias due to reverse causality influenced the results, or the cases of myocardial infarction drove the total associations. Thus, studies with a larger population and assessment of the associations separately for the several CVD subtypes are needed.

Reducing alcohol intake by two or more units per week within a year of type 2 diabetes diagnosis was associated with 44% reduced 10-year total CVD risk compared to maintaining alcohol intake in the ADDITION-Cambridge study (Strelitz et al., 2019a). There are limited studies assessing the effect of changing alcohol intake on the incidence of vascular complications. Furthermore, the mechanisms by which alcohol intake impacts CVD are still under investigation. Though, it has been suggested that alcohol consumption affects

cardiometabolic risk factors. Among healthy individuals, one-month abstinence from alcohol showed improvements in insulin resistance, weight, systolic and diastolic blood pressure, which were not associated with changes in diet, smoking or physical activity (Mehta et al., 2018). In alcohol-abstaining people with well-controlled type 2 diabetes, moderate red wine consumption did not affect blood pressure levels in a 2-year randomised controlled trial (Gepner et al., 2015). However, a positive dose-risk relationship was observed between categories of alcohol intake and the degree of prevalent hypertension in people with type 2 diabetes participating in the ACCORD study (Mayl et al., 2020).

The detrimental effects of alcohol intake on anthropometric and blood pressure measures have been documented in several Mendelian randomisation studies (van de Luitgaarden et al., 2021). Contrastingly, beneficial effects were observed on lipids; increased levels of HDL cholesterol while lowered LDL cholesterol. Alcohol also appeared to have adverse effects on triglyceride levels, although studies were inconsistent. The associations were broadly similar in people with diabetes (Taylor et al., 2015). The findings of the favourable effect of alcohol on HDL cholesterol were corroborated in a meta-analysis of 44 interventional studies in individuals without known CVD (Brien et al., 2011). The authors also reported a reduction in fibrinogen[19], while adiponectin levels were elevated. However, no association was observed between alcohol intake and total and LDL cholesterol or triglycerides. A 2-years randomised controlled trial in alcohol-abstainers with type 2 diabetes reported that moderate red wine intake and Mediterranean diet initiation increased HDL and apolipoprotein A-I[20] levels while decreased total cholesterol and triglycerides compared to the control group treated with Mediterranean diet and water. A similar effect on triglycerides was observed in the white wine arm compared to the control group (Gepner et al., 2015). Another randomised controlled trial in individuals with type 2 diabetes reported an improvement in inflammatory markers, such as CRP, interleukin-6, interleukin-18 and

[19] **Fibrinogen** – an essential protein involved in the coagulation cascade and a major determinant of blood viscosity. KAMATH, S. & LIP, G. Y. 2003. Fibrinogen: biochemistry, epidemiology and determinants. *QJM,* 96**,** 711-29.

[20] **Apolipoprotein A-I (apoA-I)** – the main protein component of HDL. Small HDL particles and apoA-I transport cholesterol from peripheral cells to the liver for redistribution or excretion by the gallbladder, a process called 'reverse cholesterol transport'. ANASTASIUS, M., KOCKX, M., JESSUP, W., SULLIVAN, D., RYE, K. A. & KRITHARIDES, L. 2016. Cholesterol efflux capacity: An introduction for clinicians. *Am Heart J,* 180**,** 54-63.

TNF-α after a one-year red wine intervention compared with the control group (Marfella et al., 2006).

Mediation analysis performed by Wood and colleagues suggested that mechanisms behind the opposite associations of alcohol consumption with subtypes of CVD are due to the effects of systolic blood pressure for stroke (partly mediated) and HDL cholesterol for myocardial infarction (fully mediated) (Wood et al., 2018). The causal role of HDL in coronary heart disease reduction has been challenged in randomised controlled trials and Mendelian randomisation studies (Voight et al., 2012, Holmes et al., 2015, Kaur et al., 2014). Furthermore, HDL did not have a protective effect for incident CVD in individuals with diabetes (Tohidi et al., 2010). But, pathways related to HDL, such as the cholesterol efflux capacity[21], may contribute to the reduction of cardiovascular events independently of HDL concentrations (Qiu et al., 2017). Moderate alcohol intake (15 to 40 g/day) increased cholesterol efflux capacity in healthy individuals participating in short-term randomised controlled trials (Sanllorente et al., 2021). Nevertheless, while pooled estimates of 84 prospective studies showed a protective effect of alcohol intake on coronary heart disease (Ronksley et al., 2011), data from Mendelian randomisation studies support either a null or a positive association between genetically predicted alcohol consumption and total CVD, stroke or coronary heart disease (van de Luitgaarden et al., 2021).

Presumably, similar mechanisms, such as those described for macrovascular complications, are involved in the effect of alcohol on microvascular complications. However, the present data showed an opposite direction of the association between alcohol intake and microvascular complications than that of macrovascular complications. Compared with very light drinking, a decreased risk of total microvascular complications was observed in the present study with light to moderate alcohol intake. Although a dose-response relationship was apparent, the associations did not reach statistical significance. Furthermore, assessment of time-updated alcohol intake revealed a strong inverse association between alcohol intake and microvascular complications compared to very light drinking among individuals who had developed a macrovascular complication. Further studies are needed to determine whether this observation is attributable to alcohol intake or

[21] **Cholesterol efflux capacity** – the first step of the reverse cholesterol transport process.

rather due to methodological sources of bias, such as reverse causation. That is, participants who reported very light drinking after diabetes diagnosis might have more severe health concerns that resulted in limiting, but not ceasing, their alcohol consumption. Nevertheless, this observation was not present in individuals who developed a microvascular complication as the first event.

There are only a few prospective studies investigating the association between alcohol intake and diabetes-related microvascular complications, and there is great variability in alcohol intake definition. Furthermore, divergent associations have been observed for the individual types of microvascular complications. Compared to non-drinkers, the ADVANCE study reported an inverse association between moderate alcohol intake and total microvascular complications, whereas there was no evident association with heavy drinking (Blomster et al., 2014). There was no association between alcohol use, continuously assessed, and incidence and progression of retinopathy in the WESDR study (Moss et al., 1994). However, a more recent study demonstrated that current alcohol drinking and occasional consumption (≤2days/week) lowered the risk of developing retinopathy, compared with non-drinkers and frequent users, respectively (Gupta et al., 2021). In individuals with type 1 diabetes followed for more than 23 years, current alcohol drinking (yes/no) did not increase the risk of neuropathy (Braffett et al., 2020). Lastly, moderate alcohol intake was inversely associated with kidney disease in people with type 2 diabetes, compared with abstainers (Dunkler et al., 2015b). Still, dichotomisation of alcohol intake, and using abstainers as the reference categories may lead to spurious associations.

Frequency of alcohol consumption and binge drinking was not assessed in the present work, which may have resulted in the omission of important information about drinking patterns that may influence the relationship of alcohol and diabetes complications (Roerecke and Rehm, 2014). Furthermore, type of alcohol (wine, beer, or liquor) consumed was not investigated. However, previous literature did not observe substantial differences between the several types of alcoholic drinks (Ricci et al., 2018, Wood et al., 2018, Blomster et al., 2014, Tanasescu et al., 2001).

The ADA guidelines on lifestyle management in diabetes do not prohibit moderate alcohol intake in individuals who choose to consume alcohol (American Diabetes Association, 2019b). The present study did not demonstrate distinct clinical benefits or

damage of moderate alcohol intake on diabetes complications. Nevertheless, the impact of alcohol on other health outcomes, such as certain cancers, road injuries and chronic liver diseases, must be considered before making recommendations (GBD 2016 Alcohol Collaborators, 2018).

5.3.3 Risk scores

The GDRS and CVDRS are simple tools for accurately identifying people at risk of developing diabetes and CVD, respectively. A clinical and a non-clinical version are available, making it possible to screen a large number of people at a low cost in a medical context or self-administered at home. Early detection of the clinical manifestations of diabetes and CVD may lead to more effective primary prevention (Palladino et al., 2020), and economic modelling indicated that intervening in screen-detected high-risk individuals was cost-effective (Mühlenbruch et al., 2020b). The ADDITION-Europe trial showed that screening and early intensive care of the detected type 2 diabetes patients were feasible in a general practice setting. Additionally, early intensive multifactorial treatment of screen-detected people with type 2 diabetes decreased substantially cardiometabolic risk factors, while a small reduction in the incidence of cardiovascular events and mortality was observed, possibly due to the short follow-up period (Griffin et al., 2011).

Participants of a population-based screening programme for diabetes were diagnosed earlier than individuals who were clinically detected and had better health outcomes regarding CVD, renal disease and retinopathy (Feldman et al., 2017). Even though results from screening initiatives may be influenced by healthy user bias, lead time bias[22] and length time bias[23], early detection and treatment are key for improved prognosis and reduced care costs for people with diabetes. Furthermore, normoglycemic individuals who scored as high

[22] **Lead time bias** – bias introduced into screening studies if the lead time is not considered when comparing morbidity or mortality among screened and unscreened groups. Lead time is the interval between disease diagnosis through first detectable signs, i.e., at screening, and overt symptoms that normally lead to diagnosis. Such that, screened individuals erroneously appear to have better prognosis simply because their disease was detected earlier in the course of disease.

[23] **Length time bias** – the overrepresentation of slowly progressing disease, which is more likely to have a favourable outcome, among screen-detected cases. HENNEKENS, C. H. & BURING, J. E. 1987. *Epidemiology in medicine,* Philadelphia, USA, Lippincott Williams & Wilkins.

risk for diabetes via a non-invasive screening tool were benefited from a lower incidence of cardiovascular events when treated by general practitioners trained to provide targeted management and promotion of healthy lifestyles compared to those who received routine care. The effect was more pronounced among those who scored higher in the accompanied cardiovascular risk assessment tool (Simmons et al., 2017).

One objective of this study was to investigate whether individuals predisposed to develop diabetes and who score high on the GDRS and CVDRS, and therefore are at high risk of developing diabetes and CVD in the following years, are also at higher risk of developing diabetes-related complications compared to their low-scoring counterparts. The non-clinical scores were calculated closely before diabetes diagnosis and at EPIC-Potsdam recruitment, while the clinical scores were calculated at EPIC-Potsdam recruitment. Regardless of the time assessed, both risk scores and versions were positively associated with total macrovascular and microvascular complications, as well as with kidney disease and neuropathy, while the GDRS was also associated with retinopathy. These findings indicate that the scores are valuable instruments for capturing future risk of diabetes-related complications over an extended period of adult life and can provide additional health-related information to their users. In addition, the associations attenuated slightly after adjustment for age and sex, suggesting that the scores offer information about future complications beyond these two components.

Major components of the risk scores are well-known modifiable risk or protective factors that can be targeted to lessen cardiometabolic and vascular disease. Within the present data, evaluation of individual components showed that abdominal obesity, smoking and high red meat intake increased the risk of either micro- or macrovascular complications, whereas coffee and whole grain intake were inversely associated (section 4.2.2). Furthermore, hypertension (Yamazaki et al., 2018), poor glycaemic control (Davies et al., 2018) and dyslipidaemia (Barrett et al., 2017) are important determinants of vascular complications. Components that were not associated with a specific diabetes complication or with the direction of associations different from those for diabetes and CVD endpoints (as evaluated during the risk scores development) may have mitigated the observed associations. For instance, physical activity contributes negatively and linearly to the GDRS, while red meat consumption positively linearly to both risk scores. Assumed the differences in the models,

time-points and populations assessed, direct comparisons cannot be made. But, a positive association was observed between physical activity and microvascular complications in the present data, while a U-shaped association was apparent for red meat intake. Nevertheless, the personalised recommendations provided by the risk scores are in line with the general lifestyle guidelines for healthy individuals and persons with diabetes (American Diabetes Association, 2019b, Rippe, 2018) and, therefore, will not be harmful with regard to vascular complications.

In a similar fashion to the present work, the association of the non-clinical GDRS with the incidence and mortality of CVD and colon, prostate and breast cancers has been evaluated in the full cohort of EPIC-Potsdam. A high GDRS score was associated with an increased risk of cardiovascular events and mortality, but its association with cancer outcomes was less clear (Heidemann et al., 2009). Another non-invasive screening tool for the prediction of type 2 diabetes established in a Finnish population (Finnish Diabetes Risk Score) was associated with increased risk of hypertension, cardiovascular disease and total mortality (Fizelova et al., 2016, Silventoinen et al., 2005). Moreover, the Cambridge risk score, developed to detect undiagnosed prevalent type 2 diabetes using non-invasive routinely available information in primary care, was associated with increases in total mortality regardless of whether or not OGTT testing showed prevalence of diabetes (Spijkerman et al., 2002).

Several risk scores have been developed to predict the probability of occurrence of cardiovascular and microvascular events in type 2 diabetes, as described in section 1.6. External validation revealed a moderate discriminatory ability (C-statistic) for macrovascular complications ranging from 0.70 for the UKPDS risk engine (Chowdhury et al., 2019) to 0.73 for the RECODe risk equation (Basu et al., 2017). Among risk scores that were validated in individuals with type 2 diabetes from the EPIC-Potsdam study, the highest discriminatory ability was observed for the Fremantle risk equation with a C-statistic equal to 0.68 for total cardiovascular events, while the UKPDS showed the highest discrimination for predicting coronary heart disease events (C-statistic=0.73) (van der Leeuw et al., 2015). Externally validated risk scores for predicting microvascular complications varied substantially in regard to their discrimination, ranging from poor to excellent. Indicatively, discrimination indices ranged as follows: early kidney disease (C-statistic=0.66–0.68 or AU-ROC=0.77) (Dunkler

et al., 2015a, Jiang et al., 2020), end-stage renal disease (C-statistic=0.51–0.88) (Cheng et al., 2020, Buchan et al., 2021, Basu et al., 2017), pressure sensation loss (C-statistic=0.69) (Basu et al., 2017) and retinopathy (C-statistic=0.57–0.82) (Scanlon et al., 2015, Basu et al., 2017, Aspelund et al., 2011).

The GDRS and CVDRS discriminated poorly for macrovascular complications (C-statistic: 0.58–0.66) and total microvascular complications (C-statistic: 0.60–0.62). The scores for the distinct microvascular complications also showed limited discriminatory power. This is not surprising, given that the scores were evaluated in a subset of individuals destined to develop diabetes. As a result, participants were more homogeneous in terms of risk and characteristics included in the scores than they would be in the general population, making the discrimination more challenging between cases and non-cases. Hence, the GDRS and CVDRS should not replace risk scores targeted to predict complications. Simple re-estimation of the scores based on a higher risk population or assessment of the scores for different follow-up lengths may have improved their performance. However, it is not expected to be substantially higher. The clinical scores, which included additionally measures of HbA1c (in GDRS), or systolic and diastolic blood pressure, total and HDL cholesterol (in CVDRS) did not or minimally improved discrimination for macro- and microvascular complications compared with the non-clinical scores assessed at the recruitment of the EPIC-Potsdam study. Combination and inclusion of traditional and complication-specific biomarkers might improve the discriminatory power of the risk scores.

To date, all available risk scores developed for diabetes-related complications include various clinical measurements. One downside is that those scores become inaccessible to persons who do not participate in screening examinations. Most common clinical predictors included systolic blood pressure, biomarker measurements for glycaemia, blood lipids and renal function markers, such as albuminuria, serum creatinine or albumin:creatinine ratio. The present study demonstrated that the application of two simple and non-invasive screening tools for diabetes and CVD might assist high-risk individuals to recognise their elevated risk, not only for cardiometabolic disease but also for vascular complications. The same individuals who would benefit from early modification of risk factors to reduce their risk.

5.4 Study methods and sources of error

The current study benefitted from the extensive characterisation of the lifestyle of participants, the long follow-up period, and the high response rate in the follow-up for complications. Moreover, multiple imputation of missing values was performed and comparative data between micro- and macrovascular complications were provided. In addition, the risk of diabetes-related complications was assessed by incorporating intermediates states of co-occurrent complications and their duration, as well as time-updated lifestyle factors and covariates. In the following, the study methods, data quality constrains as well as potential sources of bias will be discussed.

5.4.1 Statistical methods

5.4.1.1 Cox proportional hazard models

The present work applied a prospective design with a median follow-up period of over ten years. The longer an individual lives with diabetes and ages, the more likely they are to develop diabetes-related complications (Nanayakkara et al., 2021). Cox regression is a preferable model to study vascular complications, as it finely models the relationship between rates and time, allowing for rates to change constantly with time. Here, the underlying time scale in Cox models was from age at diabetes diagnosis to age at censoring, simultaneously controlling for age as well as diabetes duration.

An important assumption in Cox regression is that the effect of exposure is proportional over time. In other words, the ratio of the rate for the exposure group compared to the changing baseline rate must be constant over time. Violation of the proportional hazards assumption may result in erroneous effect estimates and reduced power due to an inferior model fit (Bellera et al., 2010). In the present analysis, to account for nonproportionality, all models were stratified by age (modelled continuously) and, in the case of multistate models, by complication stratum as well (Harrell, 2015). The proportional hazards assumption was assessed for each variable by plotting Schoenfeld residuals against survival time and was not found to be violated.

A background assumption of Cox models is the linearity of continuous covariates, which was tested with restricted cubic splines using three knots. Among exposure-outcome associations that showed linearity, four knots were also used to generate the splines, where a similar picture was presented. However, more knots were not tested to prevent overfitting, i.e., fitting the noise in the data. Where a non-linear association was evident, such as for red meat and whole grain intake, the variables were categorised using tertiles. Categorising continuous variables has the advantages of avoiding distributional assumptions about the variables and being simple and easily interpretable. The disadvantages are, however, the concealment of the information about the exposure-outcome relation, since the relation is considered constant within categories, and the loss of power due to reduced variability in the data (Frøslie et al., 2010, May and Bigelow, 2006). Therefore, the lack of significance observed in some categories may be the result of reduced power.

A multistate Cox model was applied to investigate the effect of the complication burden on the development of further complications as well as the association between several lifestyle factors, alone and combined with the current complication load (**Objective 1**). It is a flexible tool to understand disease progression better and assess transition intensities and the effects of the various covariates on the transition rates. This is an important addition to the ordinary Cox models. Different covariates may affect different transitions, and therefore the effects of important covariates may be mitigated or vanish when only two-state Cox models are used (Andersen, 1988). Furthermore, results from a simulation study suggest that compared to logistic and ordinary Cox regression models, using a multistate model provided an increase in power in scenarios where the transition intensity was low, while similar levels of power were demonstrated when the transition intensity was high. But, when the sample size was small (N=500), lower power was observed for the multistate model compared with the other two models (Smith et al., 2021). Therefore, multistate models might not be a good choice for smaller studies. Furthermore, applying a multistate model adds complexity to the analyses, which may not be worth the effort if a simple comparison of exposure levels is needed (Andersen, 1988).

To perform a multistate regression analysis, the exact transition dates are needed. In this study, the transition intervals were calculated using the dates of complication diagnosis reported by the treating physicians or, where missing, by imputation. For the same

individual, the order of complication occurrence used may differ from the actual order that the individual experienced. Analyses evaluating how a potentially misspecified sequence of complication occurrence might have affected the results were not performed. Moreover, it was assumed that the censoring patterns were independent of complication state or participants' condition, and an assessment on whether this assumption was violated was not undertaken. As the number of states increased over time, the latter states resulted in small sample sizes. Thus, it was not possible to assess the effect of more than one state on subsequent vascular events. Furthermore, vascular complications were only assessed as composite events (micro- or macrovascular complications) and not as individual outcomes, i.e., kidney disease, neuropathy, and so forth. Combining the different subtypes of vascular complications may have attenuated the results if the investigated exposures affected one subtype in an opposite direction of the other.

5.4.1.2 Multiple imputation

Assessment of the missing data indicated that the analysis would benefit from multiple imputation. A complete case analysis would discard more than 23% of the sample. The co-occurrence of missingness across variables did not reveal a particular missing data pattern. Still, participants with missing values were more likely to be smokers, have prevalent health-related conditions at diabetes diagnosis and experience vascular complications of diabetes (**Appendix 5**). Therefore, a complete case analysis may introduce bias in the results.

The missing-data mechanism (MCAR, MAR or MNAR) in the dataset is usually unknown, and most likely, it is a combination of more than one mechanism (Hendry et al., 2014). Furthermore, whether the complete case analysis or multiple imputation will bias the findings also depends on whether the missingness is related to the values of the exposure X, outcome Y or confounder Z under MAR or MNAR (Cummings, 2013). For example, under MAR, if missing values in exposure X, outcome Y or confounder Z are related to values of exposure X or outcome Y, multiple imputation will not produce biased estimates. But, when the missingness in exposure X is a function of outcome Y, the bias from a complete case analysis is heightened. When data are MNAR, both methods will lead to biased associations. Except if missingness in exposure X is related to values of exposure X, then complete case analysis of the X-Y association will not be biased, whereas bias after multiple imputation will

be more prominent. Nevertheless, in most cases, multiple imputation should reduce bias, increase study power or at least not harm (Cummings, 2013).

Unfortunately, it is not possible to determine from the data how big of a problem there may be when deciding to apply a complete case analysis or multiple imputation (Sterne et al., 2009). In the present analysis, multiple imputation was performed assuming data were MAR. Following the recommendations from the literature (White et al., 2011), all the variables needed for the analysis were incorporated in the imputation model, including the event indicators and years to event (*T*), calculated as the difference between date of diabetes and subsequent event (**Appendix 6**). This way, it is ensured that the relationships between the several variables are maintained in the imputation model and avoid bias towards the null.

Based on a simulation study (White and Royston, 2009), it is recommended to include the Nelson-Aalen estimate of cumulative hazard in the imputation model to avoid bias towards the null, which was not included in this imputation model. However, the differences between Nelson-Aalen method and the "survival outcome method" (*T*, the one used in this study) were very minimal under both MCAR and MAR assumptions and both methods showed approximately equal performance (White and Royston, 2009). Furthermore, the imputation model included auxiliary variables related to the incomplete variables, including repeated measurements (**Appendix 6**). The addition of such auxiliary variables is important for two main reasons: 1) to improve the prediction of missing values by providing additional information and 2) to make the MAR assumption more plausible (Hendry et al., 2014, Nguyen et al., 2017).

The distribution of the imputed variables remained largely intact after the application of multiple imputation (**Appendix 7**). The main discrepancies observed were for the variables: years-to-myocardial infarction, years-to-stroke and current smokers in follow-up one, where the median years and percentage, respectively, increased by one unit. Such deviations in the distribution between the observed and imputed data are expected under MAR. For instance, in these data, smokers were more likely to have incomplete data, so it is expected that the percentage of current smokers in follow-up one (where most of the missing values were observed) to be higher in the imputed data.

The analyses in this work included the investigation of interactions and non-linear associations with cubic splines. Those functions of the covariates were not included in the

imputation model, which may have created bias in the analyses (Tilling et al., 2016, Seaman et al., 2012). Furthermore, smoking units per day, soft drink and plant oil consumption were not included in the imputation model and missing values were imputed by the preceding available value. Thus, analyses including those variables may be biased, which applies to estimates of the association of the risk scores with vascular complications and calculation of C-indices (**Objective 3**). Additionally, statistical resources on how to combine confidence intervals of C-indices of the ten imputation datasets were not found in the literature. Therefore, the median of the confidence limits was reported. This method is not optimal as it does not account for the uncertainty introduced by the imputation procedure. It is, therefore, expected that the confidence intervals of the C-indices to be wider than reported here. Given the inability of the risk scores to accurately discriminate between people who developed vascular complications and those who did not, this limitation is trivial.

In addition to analyses based on the imputation datasets, complete cases analyses were also performed for all Objectives except Objective 1b. Estimates were either similar or more pronounced in the complete case analyses and, as expected, confidence intervals were wider. It is unclear whether the multiple imputation analyses biased the results towards the null or the complete case analyses overestimated the associations. Nevertheless, both methods showed the same direction of associations and the overall conclusions drawn in the present work are not altered.

5.4.2 Random error

Random error, or lack of precision, occurs as a result of sampling or measurement variability. Random sampling error may affect the precision of estimates, that is, to differ from the true population values, because of random variation from sample to sample. Furthermore, day-to-day variations in the measurements of participants, for example, in weight or dietary intake, may also result in decreased precision. Reduction of random error and thus increased precision can be achieved by increasing the sample size or reducing variability in measurements, for example, by taking repeated measurements of the exposure.

The present study had a relatively large sample size; however, it might still be underpowered to detect modest associations between some of the exposures of interest and

vascular complications. Therefore, some of the nonsignificant observed associations might be due to the limited power of the study. Nevertheless, post-hoc power analyses were not performed since it has been suggested to be analytically misleading, as they do not capture true power for detecting statistical significance (Zhang et al., 2019).

A limitation of this work is that repeated measurements were not taken into account, such as using cumulative average values to reflect long-term lifestyle. While lifestyle might have been stable in some populations, other groups of people may change lifestyle considerably over the decades, in particular those with a high risk of future disease (Micha et al., 2015, Park et al., 2020, Harrington et al., 2014, Chong et al., 2017). Hence, it is possible that the observed associations to be mitigated due to changes in the assessed lifestyle factors during the follow-up period. For instance, analyses in the HPFS and NHS studies showed that effect estimates of the associations of total and processed meat with type 2 diabetes, total and CVD mortality were attenuated when only baseline dietary data were used compared to cumulative averages from baseline to the censoring events (Pan et al., 2011, Pan et al., 2012). A similar approach was not possible to be followed in this study because the dietary intake was assessed at only two time-points (recruitment and follow-up round 3). Associations were investigated using exposure assessment either before diabetes diagnosis (baseline lifestyle-related factors) or complication diagnosis (time-updated lifestyle factors assessed before entry in complication states). However, cumulative average values of physical activity, alcohol intake and BMI would have been valuable to be investigated in regard to the risk of micro- and macrovascular complications.

Lifestyle may also be related to intermediate events, such as hypertension and dyslipidaemia, and their diagnosis may trigger lifestyle changes which, in turn, may impact the associations with the vascular complications of diabetes. In the EPIC-Potsdam study, lifestyle factors, including general and abdominal adiposity, smoking, low adherence to a healthy diet and physical inactivity, were associated with an increased risk of hypertension (Andriolo et al., 2019), which was associated with a higher risk of myocardial infarction and stroke (Heidemann et al., 2007, Weikert et al., 2007). Analytical approaches used to accommodate those events and lifestyle changes may considerably impact the observed effect estimates. Taking another example from the NHS study, women who reported hypercholesterolemia and diabetes increased their cereal fibre intake (Bernstein et al., 2011).

When intake was assessed as the cumulative average intake throughout the follow-up, the HR of coronary heart disease onset was 0.73 (95% CI 0.62, 0.87) for participants in the highest quintile of cereal fibre compared to the lowest. When the authors used cumulative average intake up to the time-point of diagnosis of an intermediate event, the HR was 0.65 (95% CI 0.55, 0.76); while the HRs were 0.81 (95% CI 0.69, 0.94) and 0.77 (95% CI 0.65, 0.91) when using baseline intake or most recent intake, respectively (Bernstein et al., 2011). Thus, efforts to reduce random measurement error using repeated assessment of exposure should also account for temporal trends and changes in exposure following intermediate events.

5.4.3 Systematic error

Systematic error, or bias, results in low internal validity of a study. Internal validity refers to the extent to which the study results accurately reflect the reality in the study sample. Systematic error is classified into three broad categories: selection bias, information bias and confounding.

5.4.3.1 Selection bias

Selection bias is less of a concern in prospective cohort studies since exposure is assessed prior to disease onset. Regardless, individuals who agree to participate in a study usually differ from non-participants. The population of this study was embedded in a population-based cohort, better representing the average population with diabetes than in trial samples (Laxy et al., 2019). However, as noted, the final study population of the EPIC-Potsdam had a more favourable socioeconomic status and health-related indicators than the source population (Boeing et al., 1999a), which limits the generalisability of the study (external validity) but not the internal validity. That is, the generalisability of the biological associations is not likely to have been impacted. However, the findings may not be generalisable to populations with a different racial/ethnic composition, as the present population was predominantly white.

A major source of bias in prospective cohort studies related to selection bias is the necessity to minimise selective losses during the follow-up period. This can be a problem if

more people in the exposure groups are more likely to be lost to follow-up than those in nonexposed groups, and the probability of loss is also related to the outcome of interest. In the EPIC-Potsdam study, the response rate of participants' treating physicians for providing information on diabetes-related complications was higher than 85%. Physicians who did not respond to the questionnaire may also be the ones not holding participants' records, either due to the participant's death or loss to follow-up before the time of collection of information on complications. In the present data, individuals for whom information on complication status could not be retrieved were more likely to be lost-to follow-up or deceased by 2014, as well as being smokers (**Appendix 4**). Therefore, findings on the association between smoking and complications may be affected by selection bias, particularly for microvascular complications, as the ascertainment of those endpoints was merely based on the standardised questionnaire filled by the treating physicians and not through other linkage sources. That is to say, if smokers who developed a microvascular complication were more likely to be lost to follow-up than non-smokers who developed a microvascular complication, then the current findings may be biased and, in particular, underestimate the true effect.

At this point, it is worth mentioning collider bias. Imagining a directed acyclic graph displaying a causal relationship between an exposure and an outcome with a directional arrow (→), a collider is a variable on a path that at least two variables collide (Tonnies et al., 2022). Collider bias can result from restricting or stratifying the analysis on a collider or adjusting for the collider in the regression model. In this study, a restriction of the EPIC-Potsdam study population to persons with incident diabetes was applied, opening the possibility of collider restriction bias – a form of selection bias. Following the structure described by Tonnies and colleagues (Tonnies et al., 2022), a simplified example from the present data is provided, utilising the unexpected positive association between physical activity and microvascular complications. Conditioning on a collider (e.g., diabetes status) may induce a non-causal association between its two causing variables, the exposure [physical activity → diabetes (Aune et al., 2015)] and an (unmeasured) third variable (variable → diabetes), that are otherwise not related. If the third variable is also associated with the outcome (variable → microvascular complication), it creates the path 'physical activity → diabetes ← variable → microvascular complication'. For this example, smoking will be considered the third variable. Restricting the population to people with diabetes leads

to an underrepresentation of people who do not smoke and are physically active, since individuals with diabetes are more likely to be smokers and have low physical activity. However, non-smokers with diabetes are more likely to be physically inactive, than people with diabetes who smoke. Since smoking increases the risk of vascular disease, it appears that physical activity increases the risk of microvascular complications. Depending on the case, collider bias distorts findings by inducing a false, strengthened or reversed associations between exposure and outcome (Sperrin et al., 2016). There is no straightforward method to correct collider bias, and the detection of potential colliders becomes complex as the number of variables included in the model increases (Tonnies et al., 2022). Whether the observed associations differ from those in the whole population may be assessed by repeating the analyses in the unselected population, adding interaction terms between the exposure and the stratifying variable (Sperrin et al., 2016).

5.4.3.2 Information bias

An overriding source of error in observational studies arises from the degree of accuracy of the information (or measurements) collected about the study participants. Accurate assessment of the exposure levels and outcome status for all participants is unlikely. The validity of the study is thus affected by the ensued mechanism of the measurement error, i.e., whether there is a differential or nondifferential error. Instances of differential measurement error are i) recall bias, where individuals with the disease recall their exposure differently from those without the disease, and ii) observer bias, if data assessors record information differently for exposed and unexposed participants.

The prospective design of the present study largely minimised differential reporting of exposure information since it is not influenced by the onset of diabetes-related complications. The dietary assessment tool (FFQ) at recruitment of the EPIC-Potsdam study showed moderate to good validity for estimating usual intake and was reasonably correlated with the FFQ during the follow-up assessment (see section 3.3.1.1). Nevertheless, some degree of measurement error is inevitable, which is expected to be nondifferential and bias the findings towards the null (Rothman, 2012). In contrast, differential exposure measurement error can bias the observed effects away from the null. Selective misreporting of dietary intake attributable to anthropometric traits is also possible when assessment relies on self-reports.

Several epidemiological studies have reported that obesity is a determinant of underreporting (Voss et al., 1997, Voss et al., 1998, Macdiarmid and Blundell, 1998, Lentjes et al., 2014). The impact of selective misreporting due to anthropometric traits should have been mitigated as a comprehensive adjustment for lifestyle, anthropometry and other phenotypic characteristics was performed.

It has been shown that categorising continuous exposure variables may transform systematic nondifferential error into differential exposure misclassification (Flegal et al., 1991). Depending on the underlying distribution of the exposure, the true exposure-outcome association and the selected cut-off points, exposure categorisation may bias the associations towards or away from the null (Brenner and Loomis, 1994). In this work, whole grain and red meat intake were categorised into three groups due to violation of the linearity assumption. The categorisation was performed using tertiles of the exposure distribution, which may still generate unbiased associations, compared to selecting predefined cut-off points (Brenner and Loomis, 1994). Assessment of the associations using restricted cubic splines showed similar relationships and the overall conclusions remain unchanged.

Other self-reported exposure variables assessed in this study, such as weight, waist circumference, physical activity and smoking status, were also likely subject to systematic measurement error (Spencer et al., 2004, Spencer et al., 2002, Connor Gorber et al., 2009), and yielded a similar pattern of misreporting as described for dietary intake. Of note, different assessment methods were used for some of the exposure variables at recruitment and during follow-up. The dietary intake was collected through two different FFQs, while weight and waist circumference were measured by trained personnel at recruitment but were self-reported during follow-up. The application of different assessment tools and methods has likely increased the noise in the present data. Furthermore, for a small percentage of participants, BMI change was calculated using the weight measured at baseline and a self-report at follow-up. While, self-reported weight is highly correlated with weight measured by interviewers, self-reporting weight measures might have been influenced by selective misreporting due to anthropometric traits and other socio-economic characteristics (Stommel and Schoenborn, 2009). Adjustments for pre-diagnosis BMI and other phenotypic characteristics have likely narrowed the impact of misreporting, but not eliminate it.

The ascertainment of diabetes-related complications was based on records from treating physicians and, in the case of macrovascular complications, linkage data were also used. Thus, measurement error was minimised compared to using self-reports. Measurement error in outcome variables might have occurred because some participants might have remained undetected, consequently underestimating prevalent and incident cases of complications. To account for prevalent cases that were not captured at baseline, analyses excluding early events were performed in Objective 2, where results did not differ substantially. Given the design of the study outcome, misclassification was most likely non-differential, thus giving attenuated risk estimates for most observed associations. However, non-differential misclassification might have occurred due to observer bias. Diagnosis of diabetes complications in a greater proportion in individuals who are obese or smoke than in lean participants or non-smokers may overestimate the impact of obesity or smoking on diabetes complications.

According to the National Disease Management Guidelines (Landgraf et al., 2019), individuals with diabetes should be screened for vascular complications every one to two years, and treating physicians have a central role in managing their care. I am not aware of a national source that provides information on the incidence of diabetes-related complications in Germany for comparison with the present data. Herein, the incidence rates for macrovascular events and kidney disease are 0.68 and 1.64 per 100 person-years, while in the Look AHEAD study (a randomised controlled trial on behavioural weight loss interventions in overweight or obese adults with type 2 diabetes) the incidence rate in the control group was 1.25 for macrovascular events and 1.26 for kidney disease per 100 person-years (Look AHEAD Research Group, 2013, Look AHEAD Research Group, 2014). However, the study participants in the Look AHEAD study are not comparable with the participants in this study, as they were ethnically more diverse, they had pre-existing cardiovascular disease, the median duration of diabetes at baseline was five years (IQR 2–10), and they had a longer follow-up for macrovascular events while they had a shorter follow-up for kidney disease. Furthermore, they are participating in a trial, and they are likely receiving better standard treatment than the general diabetes patient in Germany. Therefore, it is difficult to conclude whether the higher number of observed microvascular complications in comparison to macrovascular complications conforms to expectations.

5.4.3.3 Confounding

Confounding is a systematic error in statistical inference that occurs from mixing the effects of the exposure with the effect of other variables, compromising the interpretation of the findings. A confounder is a risk factor of the outcome – independently of the exposure, is associated with the exposure and is not an effect of the exposure. As with all observational studies, the possibility that confounding may have affected the present findings cannot be exclude. Although multivariable statistical modelling allows to investigate the strength of the relationship of interest while controlling for all potential confounders, residual confounding may remain. Furthermore, confounding by unknown and unmeasured factors cannot be ruled out.

In the first objective of this work, the associations of current complication burden, lifestyle factors and anthropometry with further diabetes complications were investigated by applying a multi-state model. A distinct advantage of the multi-state model was the possibility of including complication states, duration of those states and state-specific covariates, incorporating lifestyle changes into the model that might have been more relevant to the development or progression of complications than factors assessed in the distant past. Still, residual confounding might have crept into the analysis as a result of measurement error in the selected confounders. Furthermore, markers of metabolic and cardiovascular health were not available. The prevalence of hypertension and dyslipidaemia was included in the models; though, dyslipidaemia was self-reported and likely underreported and therefore not well adjusted for (Bergmann et al., 2004). Since meat and whole grain intake did not fulfil the requirement of linearity, they were included in the models in categories. However, probably less of a confounding was removed by adjusting for categorised variables, instead of the continuous ones (Frøslie et al., 2010).

Stratification or restriction may assist to mitigate bias due to confounding. For example, confining the analyses to non-smokers or other strata of confounding factors. Several stratified analyses to ensure robustness of findings were performed for Objective 2. The same approach was not followed for Objective 1 due to restrictions with the sample size. In order to control for diet quality in the associations between BMI, BMI change and complications a dietary score was used. Sensitivity analyses adjusting for major dietary variables instead of the score might have been helpful to assess additional confounding effects from the individual

variables. Nevertheless, they were not performed. In addition, dietary changes were not included as confounding factors in the analyses for BMI change and complications due to the limited number of repeated measurements.

5.5 Conclusions and future perspectives

The work of this dissertation enabled a better understanding of the associations of complication burden, lifestyle and weight change with diabetes-related vascular disease while providing comparative data between micro- and macrovascular complications. In the present population of adults with newly diagnosed type 2 diabetes, it was observed that individuals diagnosed with a micro- or a macrovascular complication had an increased risk of developing additional complications in the future than people who did not have a complication load. It is widely acknowledged that a healthy lifestyle is a crucial element of diabetes prevention and management. The present results suggest that optimisation of lifestyle may also play a role in preventing or delaying the onset of vascular complications. In particular, a high BMI and waist circumference, as well as higher physical activity levels, increased the risk of developing microvascular complications, whereas a reduced risk was apparent with a higher whole grain intake and moderate alcohol intake. Low-to-moderate consumption of unprocessed red meat (35–65 g/day) did not appear to elevate the risk for microvascular complications. However, a lower or higher intake of red meat was associated with an increased risk of microvascular complications. Individuals who consumed more coffee had a lower risk of developing a macrovascular disease, while former or current smoking increased the risk compared to never-smoking, and the highest risk was observed among current smokers. Of note, the effect of most lifestyle factors on diabetes complications was not substantially altered by concurrent complication burden or when time-updated lifestyle factors were investigated. The findings of this work also propose that a reduction of BMI after diabetes diagnosis may reduce microvascular complications onset, but the impact of BMI loss on macrovascular complications was not clear. In addition, the assessment of a diabetes risk score (GDRS) and CVD risk score (CVDRS) demonstrated that although their

ability to discriminate between high- and low-risk individuals for diabetes complications was low, people who had higher scores were at higher risk of developing vascular complications.

From the clinical perspective, it is essential to understand better how to optimally reduce the risk for vascular disease of type 2 diabetes. The present results prompt that particular attention should be given to regular monitoring for diabetes complications, especially among individuals with an existing vascular complication. With the exception of physical activity, this work supports existing dietary and lifestyle recommendations that emphasise weight control, high intake of whole grains, moderation in red meat and alcohol consumption and avoidance of smoking for the prevention and management of type 2 diabetes (American Diabetes Association, 2019b, American Diabetes Association, 2019c, American Diabetes Association, 2019d). The same recommendations may be followed independently of complication state. Therefore, a structured lifestyle counselling to alter unhealthy habits focusing on the specific needs of the individual can be critical in preventing diabetes complications (Lönnberg et al., 2019), and it should be integrated into primary care. The GDRS and CVDRS might provide helpful guidance to individuals to lower their complication risk by improving lifestyle and clinical factors. However, accurate and simple screening tools for diabetes-related vascular outcomes are still to be developed.

Given the limitations of the present work, further studies are needed to elucidate more precisely the associations investigated. Studies with a bigger sample size are warranted to investigate the several subtypes of complications separately and perform stratified analyses of important confounders to rule out residual confounding. The impact of lifestyle on health outcomes may weaken during a long follow-up period; therefore, additional research focusing on more recent lifestyle measures and temporal trends while incorporating intermediate events could provide valuable information. Future analyses should also consider minimising measurement error by using biomarkers or cumulative average values of exposures. The application of the multistate models in this work assumed that the censoring patterns were independent of complication state or participants' condition. The extent to which the non-informative censoring assumption might have influenced the associations is subject of further research. Exploration of underlying mechanisms using precise measurements of disease biomarkers or conducting intervention studies assessing intermediate markers as outcomes may be a promising venue for further research. Mendelian

randomisation studies could also provide more robust evidence on causal associations between lifestyle and diabetes complications, although this approach may be subject to the methodological limitations encountered in observational studies in addition to limitations specific to the genetic basis of the instrumental variable (Mukamal et al., 2020). The majority of the current evidence comes from European or North American countries. Additional prospective studies are needed from other diabetic cohorts and populations with different ethnic and genetic backgrounds to confirm the present findings. Furthermore, investigation of local lifestyle habits in other geographic regions could provide important information regarding risk or protective factors of diabetes complications, for which exposure levels are too low in European or North American populations.

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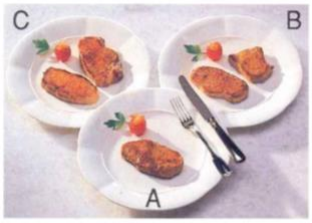

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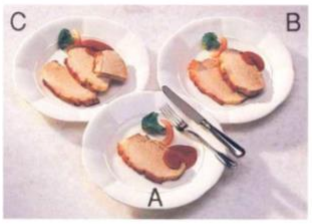

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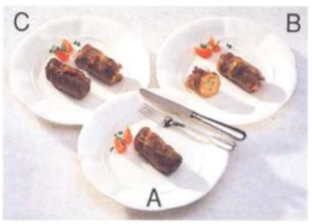

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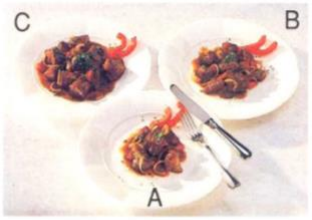

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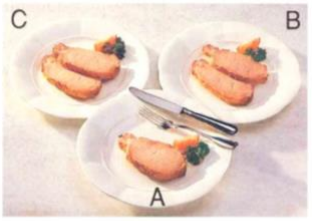

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8

Rind- und Schweinefleisch

Lebensmittel	Esse ich nicht	Vorgabe	meine Portion A	B	C	1 mal pro Monat oder weniger	2-3 mal pro Monat	1 mal pro Woche	2-3 mal pro Woche	4-6 mal pro Woche	1 mal pro Tag	2 mal pro Tag	3-4 mal pro Tag	5 mal pro Tag oder häufiger
vom Rind:														
Rindersteak, Filet, Lende	☐	Bild 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rinderbraten, Kochfleisch	☐	Bild 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rinderrouladen	☐	Bild 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Rindergulasch, Geschnetzeltes	☐	Bild 4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
vom Schwein:														
Schweineschnitzel, Kotelett, Steak, Filet, Lende	☐	Bild 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Schweinebraten	☐	Bild 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Schweinegulasch, Geschnetzeltes	☐	Bild 4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kassler, Schweinerippchen	☐	Bild 5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kochfleisch vom Schwein, Eisbein, Haxe	☐	Bild 5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Schweinebauch	☐	Bild 6	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix 2 Example page of food frequency questionnaire at follow-up assessment

Fleisch und Fisch

Schweinefleisch (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Rindfleisch (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Geflügelfleisch (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Kalbfleisch, Lammfleisch, Kaninchen, Wild (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Fisch, frisch, Konserve (z.B. Hering, Thunfisch, Lachs, Seelachs, Forelle) (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Fischzubereitung (z.B. Fischstäbchen, Schlemmerfilet) (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	
Meeresfrüchte (z.B. Shrimps, Tintenfisch, Muscheln) (1 Portion) 	○ Nie	○ 1 mal pro Monat oder seltener	○ 2-3 mal pro Monat
	○ 1-2 mal pro Woche	○ 3 mal pro Woche oder häufiger	

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Appendix 3a Components and scoring criteria for MedPyramid score [adapted from (Galbete et al., 2018)]

Component	Recommended intake	Score of 0	Score of 1
Vegetables	≥ 6 servings/day	0 servings/day	≥ 6 servings/day
Legumes	≥ 2 servings/wk	0 servings/week	≥ 2 servings/week
Fruits	3–6 servings/day	0 servings/day	3–6 servings/day
Nuts	1–2 servings/day	0 servings/day	1–2 servings/day
Cereals	3–6 servings/day	0 servings/day	3–6 servings/day
Dairy	2 servings/day	0 servings/day	1.5–2.5 servings/day
Fish	≥ 2 servings/week	0 servings/week	≥ 2 servings/week
Red meat	< 2 servings/week	≥ 4 servings/week	< 2 servings/week
Processed meat	≤ 1 servings/week	≥ 2 servings/week	≤ 1 servings/week
White meat	2 servings/week	0 servings/week	1.5–2.5 servings/week
Egg	2–4 servings/week	0 servings/week	2–4 servings/week
Potatoes	≤ 3 servings/week	≥ 6 servings/week	≤ 3 servings/week
Sweets	≤ 2 servings/week	≥ 4 servings/week	≤ 2 servings/week
Alcohol	Men: 10–50 g/day Women: 5–25 g/day	Men: > 50 g/day Women: > 25 g/day	Men: 10–50 g/day Women: 5–25 g/day
Olive oil	Principal source of dietary lipids	Non-consumers	Consumers

Appendix 3b Components of MedPyramid score and corresponding single food items derived from the food frequency questionnaire at recruitment and follow-up assessment

Component	Single food items	
	FFQ_{REC}	FFQ_{FUP}
Vegetables	Cucumber, radish, red radish, white cabbage, carrots, sprouts, bell pepper, chili pepper, tomato, raw onion, lettuce, endive, lamb's lettuce, Chinese cabbage, mixed salad, cauliflower, red cabbage, white cabbage, kohlrabi, broccoli, other cabbage vegetables, cooked tomatoes, tomato sauce, cooked bell peppers, zucchini, eggplant, spinach, leek, carrots, comfrey, celery, asparagus, peas and carrots mixed vegetables, sauerkraut, fresh and cooked mushrooms	Cucumber, white cabbage, Chinese cabbage, mixed salad, green salad, bell pepper, Sauerkraut, spinach, carrots (raw or cooked), cooked white cabbage, cauliflower, broccoli, turnip cabbage, asparagus (in season), zucchini, tomato, tomato sauce (also tinned or strained), mixed vegetables, vegetable-potato stew
Legumes	Green beans, peas, lentils-, peas-, beans stew	
Fruits	Consumed in summer/autumn: apples, pears, peaches, nectarines, cherries, plums, Mirabelle plums, grapes, strawberries, currants, raspberries, blackberries, bananas, kiwis, mangos, fresh pineapple Consumed in winter/spring: apples, oranges, grapefruit, mandarins, bananas, kiwis, mango, fresh pineapple	Any season: apples, pears, bananas Seasonal: plums, peaches, apricots, grapes, strawberries, red currant, blackberries, blueberries, oranges, mandarins, kiwis
Nuts	Nuts (e.g. peanuts, walnuts, Brazil nuts)	
Cereals	Whole grain bread, dark and whole grain bread rolls, ryebread, mixed bread, white bread, toast bread, white bread roll, crispbread, pretzel, croissant, grain flakes, grains, muesli, cornflakes, crisps, pasta, rice	Whole grain bread, whole grain bread rolls, ryebread, mixed bread, white bread, toast bread, white bread roll, crispbread, muesli, flaxseed, pasta, rice

Continued

Appendix 3b continued

Component	Single food items	
	FFQ_{REC}	FFQ_{FUP}
Dairy	Milk (3.5%, 1.5%, n.s.), milk drink (3.5%, 1.5%, n.s.), yogurt (10%, 3.5%, 1.5%, n.s.), fruit yogurt (10%, 3.5%, 1.5%, n.s.), curd (5%, 20%, 40%, n.s.), kefir, whipped cream, cream cheese, gouda, emmental, tilsit, camembert, brie, gorgonzola	Milk (3.5%, 1.5%, 0.3%, n.s.), milk drink (3.5%, 1.5%, 0.3%, n.s.), yogurt-buttermilk-soured milk-kefir (3.5%, 1.5%, 0.3%, n.s.), fruit yogurt (3.5%, 1.5%, 0.3%, n.s.), curd (n.s.), kefir, whipped cream, cream cheese, gouda, emmental, tilsit, camembert, brie, gorgonzola
Fish	Fish (e.g. tuna, pickled herring fillets, salmon, smoked trout)	Herring, tuna, soused herring, mackerel, salmon, other fish (e.g. smoked trout, fish filet, fish sticks)
Red meat	Pork schnitzel, pork cutlet, steak, filet, roast pork, pork goulash, diced pork, Kassler, spare rib, boiled pork meat, knuckle of pork, pork belly, hamburger, meat balls, meat loaf, minced meat sauce, hash, liver, calf and lamb meat, rabbit, steak, filet and loin from beef, roast beef, boiled beef, beef roulade, beef goulash, diced beef	Pork meat, beef, hamburger, meat balls, meat loaf, Bockwurst, Knackwurst, Bratwurst
Processed meat	Liver sausage, Kassler, ham, roast cold cuts, Vienna sausage, Frankfurter, Bockwurst, Knackwurst, Fleischkäse, Bierschinken, bologna sausage, Jagdwurst, salami, hard Mettwurst, Teewurst, soft Mettwurst, black pudding, blood sausage, head cheese (meat jelly), Bratwurst	Liver sausage, liver pâté, Kassler, ham, roast cold cuts, bologna sausage, Jagdwurst, salami, Teewurst, black pudding, blood sausage
White meat	Roast chicken, turkey cutlets, chicken schnitzel, chicken fricassee, duck, goose	Poultry meat
Egg	Boiled, fried, scrambled egg, omelette	Boiled or fried egg
Potatoes	Boiled, mashed, jacket potatoes, potato dumplings, Semmelknödel, fried potatoes	Potatoes, mashed potatoes, potato dumplings, fried potatoes

Continued

Appendix 3b continued

Component	Single food items	
	FFQ_{REC}	FFQ_{FUP}
Sweets	Fruitcake, shortcake, sponge cake, cupcake, yeast cake, crumcake, fruitcake, cookies, sweet biscuits, egg pancake, chocolate, pralines, sugar in coffee and tea, pudding, fruit curd, ice-cream	
Alcohol	Beer, wine, sparkling wine, champagne, spirits, cider, aperitif	Beer, white wine, red wine, sparkling wine, champagne, spirits, cider, aperitif, liqueur, dessert wine
Olive oil	Olive oil (with meat/fish, vegetables, as salad dressing)	

FFQ_{REC}, Food Frequency Questionnaire used at recruitment; FFQ_{FUP}, Food Frequency Questionnaire used at follow-up; n.s., Not specified

Appendix 4 Characteristics of responders and non-responders

Characteristic	Responders (n=1367)		Non-responders (n=234)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
Demographics				
Male sex	0 (0.0)	753 (55.1)	0 (0.0)	131 (56.0)
Age at recruitment, years	0 (0.0)	55.8 (48.8–60.6)	0 (0.0)	58.5 (51.8–62.2)
Age at diabetes diagnosis, years	0 (0.0)	61.3 (54.9–66.3)	0 (0.0)	63.1 (57.0–67.3)
Education level	0 (0.0)		0 (0.0)	
No vocational/vocational training		623 (45.6)		117 (50.0)
Technical college degree		332 (24.3)		56 (23.9)
University degree		412 (30.1)		61 (26.1)
Deceased before May 2014	0 (0.0)	154 (11.3)	0 (0.0)	109 (46.6)
Completed 5th follow-up round	0 (0.0)	1265 (92.5)	0 (0.0)	134 (57.3)
Lifestyle at recruitment				
Physical activity, h/week	0 (0.0)	0 (0–1.0)	0 (0.0)	0 (0–0.5)
Smoking duration, years[a]	27 (3.2)	24.0 (15.0–32.0)	1 (0.6)	28.3 (18.0–36.8)
Smoking status	0 (0.0)		0 (0.0)	
Never-smoker		529 (38.7)		77 (32.9)
Former smoker		557 (40.8)		98 (41.9)
Current smoker		281 (20.6)		59 (25.2)

Continued

Appendix 4 continued

Characteristic	Responders (n=1367)		Non-responders (n=234)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
Alcohol intake, g/day	0 (0.0)	8.4 (2.8–21.5)	0 (0.0)	7.1 (2.0–19.4)
Waist circumference, cm	3 (0.2)	98.5 (90.0–106.0)	0 (0.0)	99.0 (91.5–107.0)
BMI kg/m^2	13 (1.0)	29.6 (27.0–32.6)	3 (1.3)	29.3 (26.5–32.0)
Lifestyle at diabetes diagnosis				
Physical activity, h/week	12 (0.9)	1.0 (0.0–3.2)	1 (0.4)	0.5 (0–3.0)
Smoking duration, years[a]	30 (3.6)	25.0 (15.0–34.0)	2 (1.3)	29.0 (18.0–38.5)
Smoking status	7 (0.51)		7 (3.0)	
Never-smoker		524 (38.3)		77 (32.9)
Former-smoker		619 (45.3)		106 (45.2)
Current smoker		217 (15.9)		44 (18.8)
Alcohol intake, g/day	20 (1.5)	8.7 (2.6–21.4)	4 (1.7)	8.0 (2.2–19.4)
Waist circumference, cm	6 (0.4)	100.0 (92.0–107.5)	2 (0.9)	100.3 (92.5–108.0)
BMI, kg/m^2	31 (2.3)	29.9 (27.3–33.2)	8 (3.4)	29.6 (26.8–32.4)
Medical information				
Total cholesterol, mg/dL[b]	615 (45.0)	211.6 (185.2–238.3)	108 (46.2)	216.1 (193.7–246.5)
HDL-cholesterol, mg/dL[b]	615 (45.0)	46.0 (39.4–53.1)	108 (46.2)	45.1 (38.6–54.6)
Creatinine, mg/dL[b]	623 (45.6)	0.8 (0.7–1.0)	112 (47.9)	0.9 (0.8–1.1)

Continued

Appendix 4 continued

Characteristic	Responders (n=1367)		Non-responders (n=234)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
HbA1c, %[b]	629 (46.0)	6.1 (5.7–6.6)	111 (47.4)	6.1 (5.6–6.6)
Prevalent conditions at diabetes diagnosis				
Myocardial infarction	0 (0.0)	72 (5.3)	0 (0.0)	22 (9.4)
Stroke	0 (0.0)	46 (3.4)	0 (0.0)	12 (5.1)
Heart failure	0 (0.0)	42 (3.1)	0 (0.0)	18 (7.7)
Hypertension	0 (0.0)	1087 (79.5)	0 (0.0)	192 (82.1)
Dyslipidemia	0 (0.0)	745 (54.5)	0 (0.0)	131 (56.0)
Family history				
Diabetes	102 (7.5)	568 (41.6)	100 (42.7)	47 (20.1)
Myocardial infarction	102 (7.5)	244 (17.9)	100 (42.7)	30 (12.8)
Stroke	102 (7.5)	260 (19.0)	100 (42.7)	32 (13.7)
Glucose-lowering medication	0 (0.0)		0 (0.0)	
Oral medication		849 (62.1)		124 (53.0)
Insulin		78 (5.7)		21 (9.0)
Insulin and oral medication		43 (3.2)		10 (4.3)

[a]Among current and former smokers

[b]Blood collection was performed at EPIC-Potsdam recruitment evaluation

Pct, percentile; HDL, High-density lipoprotein; HbA1c, glycated haemoglobin

Appendix 5 Characteristics of participants with complete and incomplete information required for the study

Characteristic	Participants with complete data (n=1046)		Participants with incomplete data (n=321)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
Demographics				
Male sex	0 (0.0)	564 (53.9)	0 (0.0)	189 (58.9)
Age at diabetes diagnosis, years	0 (0.0)	61.5 (55.2–66.5)	0 (0.0)	60.9 (53.5–66.0)
Education level	0 (0.0)		0 (0.0)	
No vocational/vocational training		471 (45.0)		152 (47.4)
Technical college degree		255 (24.4)		77 (24.0)
University degree		320 (30.6)		92 (28.7)
Deceased before May 2014	0 (0.0)	74 (7.1)	0 (0.0)	80 (25.0)
Completed 5th follow-up round	0 (0.0)	1046 (100.0)	0 (0.0)	219 (68.2)
Lifestyle at diabetes diagnosis				
Physical activity, h/week	0 (0.0)	1.0 (0–3.5)	0 (0.0)	1.0 (0–3.0)
Smoking duration, years[a]	0 (0.0)	24.0 (14.0–33.5)	30 (13.4)	27.0 (18.0–35.5)
Smoking status	0 (0.0)		7 (2.2)	
Never-smoker		427 (40.8)		97 (30.2)
Former smoker		468 (44.7)		151 (47.0)
Current smoker		151 (14.4)		66 (20.6)
Alcohol intake, g/day	0 (0.0)	8.9 (3.0–20.9)	20 (6.2)	8.2 (2.0–22.7)

Continued

Appendix 5 continued

Characteristic	Complete information (n=1046)		Missing information (n=321)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
Waist circumference, cm	0 (0.0)	99.5 (92.0–106.5)	6 (1.9)	101.5 (94.0–112.0)
BMI kg/m^2	0 (0.0)	29.7 (27.2–32.8)	31 (9.7)	30.5 (27.8–34.2)
Medical information				
Total cholesterol, mg/dL[b]	466 (44.6)	212.1 (186.3–237.1)	149 (46.4)	211.0 (181.4–242.4)
HDL-cholesterol, mg/dL[b]	466 (44.6)	46.4 (39.2–53.4)	149 (46.4)	45.1 (39.8–51.3)
Creatinine, mg/dL[b]	471 (45.0)	0.9 (0.7–1.0)	152 (47.4)	0.8 (0.7–1.0)
HbA1c, %[b]	472 (45.1)	6.1 (5.7–6.6)	157 (48.9)	6.2 (5.7–6.9)
Prevalent conditions at diabetes diagnosis				
Myocardial infarction	0 (0.0)	49 (4.7)	0 (0.0)	23 (7.2)
Stroke	0 (0.0)	37 (3.5)	0 (0.0)	9 (2.8)
Heart failure	0 (0.0)	25 (2.4)	0 (0.0)	17 (5.3)
Nephropathy	0 (0.0)	3 (0.3)	0 (0.0)	5 (1.6)
Neuropathy	0 (0.0)	4 (0.4)	0 (0.0)	3 (0.9)
Hypertension	0 (0.0)	825 (78.9)	0 (0.0)	262 (81.6)
Dyslipidemia	0 (0.0)	575 (55.0)	0 (0.0)	170 (53.0)
Diabetes-related complications				
Myocardial infarction	0 (0.0)	35 (3.4)	0 (0.0)	21 (6.5)

Continued

Appendix 5 continued

Characteristic	Complete information (n=1046)		Missing information (n=321)	
	Missing Frequency n (%)	Median (25th–75th pct) or n (%)	Missing Frequency n (%)	Median (25th–75th pct) or n (%)
Stroke	0 (0.0)	51 (4.9)	0 (0.0)	30 (9.4)
Kidney disease	0 (0.0)	194 (18.5)	0 (0.0)	81 (25.2)
Neuropathy	0 (0.0)	201 (19.2)	0 (0.0)	75 (23.4)
Retinopathy	0 (0.0)	28 (2.7)	0 (0.0)	22 (6.9)
Family history				
Diabetes	0 (0.0)	461 (44.1)	102 (31.8)	107 (33.3)
Myocardial infarction	0 (0.0)	202 (19.3)	102 (31.8)	42 (13.1)
Stroke	0 (0.0)	218 (20.8)	102 (31.8)	42 (13.1)
Glucose-lowering medication	0 (0.0)		0 (0.0)	
Oral medication		655 (62.6)		194 (60.4)
Insulin		44 (4.2)		34 (10.6)
Insulin and oral medication		35 (3.4)		8 (2.5)

[a]Among current and former smokers

[b]Blood collection performed at EPIC-Potsdam recruitment evaluation for participants selected for the case-cohort study

Pct, percentile; HDL, High-density lipoprotein; HbA1c, glycated haemoglobin

Appendix 6 Parameters included in the imputation model

Parameter	Missing Frequency[a]
Sex	0 (0.0)
Education, 3 categories	0 (0.0)
Vital status, 3 categories[b]	0 (0.0)
Last follow-up, 6 categories[b]	0 (0.0)
Age at recruitment, years	0 (0.0)
Age at diabetes diagnosis, years	0 (0.0)
Number of children[b,c]	0 (0.0)
Age of menarche, years[b,c]	0 (0.0)
Sports at recruitment, h/week	0 (0.0)
Biking at recruitment, h/week	0 (0.0)
Gardening at recruitment, h/week	0 (0.0)
Smoking status at recruitment, 3 categories	0 (0.0)
Lifetime alcohol consumption at recruitment, 5 categories	0 (0.0)
Food items required for MedPyramid score and risk scores at recruitment	0 (0.0)
Smoking status at follow-up 4, 3 categories	0 (0.0)
Alcohol use at follow-up 5, 4 categories	0 (0.0)
Years between recruitment and last examination by treating physician[b]	0 (0.0)
Years between recruitment and diabetes diagnosis[b]	0 (0.0)
Prevalent conditions at diabetes diagnosis, yes/no	
Myocardial infarction	0 (0.0)
Stroke	0 (0.0)
Transient ischaemic attack	0 (0.0)
Heart failure	0 (0.0)
Hypertension	0 (0.0)
Dyslipidaemia	0 (0.0)
Years between transient ischaemic attack and diabetes diagnosis[b]	0 (0.0)
Years between diabetes and transient ischaemic attack diagnosis[b]	0 (0.0)
Years between stroke and type 2 diabetes diagnosis[b]	0 (0.0)
Years between diabetes and dyslipidaemia diagnosis[b]	0 (0.0)

Continued

Appendix 6 continued

Comorbid conditions at last examination by treating physician, yes/no[b]	
Arterial obstructive disease	0 (0.0)
Cancer	0 (0.0)
Coronary heart disease	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)
Dementia	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)
Carotid plaque	0 (0.0)
Conditions after type 2 diabetes diagnosis, yes/no	
Myocardial infarction	0 (0.0)
Stroke	0 (0.0)
Transient ischaemic attack[b]	0 (0.0)
Heart failure	0 (0.0)
Nephropathy	0 (0.0)
Renal replacement therapy	0 (0.0)
Neuropathy	0 (0.0)
Retinopathy	0 (0.0)
Hypertension	0 (0.0)
Dyslipidaemia	0 (0.0)
Diagnostic test for diabetes, yes/no[b]	
HbA1c	0 (0.0)
Repeated fasting plasma glucose values	0 (0.0)
Repeated postprandial glucose values	0 (0.0)
Urine glucose	0 (0.0)
Two-hour oral glucose tolerance test value	0 (0.0)
Other tests	0 (0.0)
Glucose-lowering medication at diabetes diagnosis, yes/no	
Diet	0 (0.0)
Oral medication	0 (0.0)
Insulin	0 (0.0)
Insulin and oral medication	0 (0.0)

Continued

Appendix 6 continued

Other therapy	0 (0.0)
No therapy	0 (0.0)
Glucose-lowering medication at last examination by treating physician, yes/no[b]	
Biguanide	0 (0.0)
Dipeptidyl peptidase-4 inhibitors	0 (0.0)
Glinides	0 (0.0)
Glitazones	0 (0.0)
Glucagon-like peptide-1 agonists	0 (0.0)
Sodium-glucose cotransporter 2 inhibitors	0 (0.0)
Sulfonylurea	0 (0.0)
Other	0 (0.0)
Other medication at last examination by treating physician, yes/no[b]	
Angiotensin-converting enzyme inhibitors	0 (0.0)
Beta-blocker	0 (0.0)
Other hypertensive medication	0 (0.0)
Cholesterol absorption inhibitors	0 (0.0)
Fibrates	0 (0.0)
Statins	0 (0.0)
Other lipid-lowering drugs	0 (0.0)
platelet aggregation inhibitor	0 (0.0)
Cortisone	0 (0.0)
None of the mentioned drugs	0 (0.0)
Smoking status at follow-up 3, 3 categories	1 (0.1)
Smoking status at follow-up 5, 3 categories	1 (0.1)
Years between diabetes diagnosis and renal replacement therapy[d]	1 (25.0)
Smoking status at follow-up 2, 3 categories	2 (0.1)
Weight at follow-up 5, kg	2 (0.2)
Waist circumference at recruitment, cm	3 (0.2)
Years between diabetes and stroke diagnosis[d]	3 (3.7)
Years between myocardial infarction and diabetes diagnosis[b, d]	3 (4.2)
Years between diabetes and myocardial infarction diagnosis[d]	5 (8.9)
Years between diabetes diagnosis and last follow-up examination[d]	5 (0.4)

Continued

Appendix 6 continued

Weight at recruitment, kg	6 (0.4)
Height, cm	8 (0.6)
Sports at follow-up 4, h/week	12 (0.9)
Weight at follow-up 4, kg	13 (1.0)
Waist circumference at follow-up 4, cm	14 (1.1)
Weight at follow-up 2, kg	15 (1.1)
Sports at follow-up 2, h/week	16 (1.2)
Years between diabetes and retinopathy diagnosis[d]	13 (26.5)
Biking at follow-up 2, h/week	19 (1.4)
Gardening at follow-up 2, h/week	19 (1.4)
Alcohol use at follow-up 2, 4 categories	20 (1.5)
Years between diabetes and nephropathy diagnosis[d]	26 (9.6)
Duration of smoking at recruitment, years[d]	27 (3.2)
Duration of smoking at follow-up 4, years[d]	27 (3.3)
Duration of smoking at follow-up 3, years[d]	28 (3.4)
Duration of smoking at follow-up 5, years[d]	28 (3.6)
Years between diabetes and neuropathy diagnosis[d]	28 (10.2)
Duration of smoking at follow-up 2, years[d]	29 (3.5)
Smoking status at follow-up 1, 3 categories	31 (2.3)
Weight at follow-up 3, kg	43 (3.2)
Food items required for MedPyramid score and risk scores at follow-up 3	51 (3.8)
Alcohol use at follow-up 3, 4 categories	51 (3.8)
Systolic blood pressure at last examination by treating physician, mm Hg[b]	56 (4.1)
Diastolic blood pressure at last examination by treating physician, mm Hg[b]	56 (4.1)
HbA1c at last examination by treating physician, %[b]	61 (4.5)
Weight at follow-up 1, kg	65 (4.8)
Sports at follow-up 5, h/week	75 (5.9)
Serum creatinine at last examination by treating physician, μmol/L[b]	89 (6.5)
Family history	
Diabetes	102 (7.5)
Myocardial infarction	102 (7.5)
Stroke	102 (7.5)

Continued

Appendix 6 continued

Weight at age 25 years, kg	124 (9.1)
Years between diabetes and hypertension diagnosis[b, d]	128 (9.4)
Weight at age 40 years, kg	164 (12.0)
Years between hypertension and diabetes diagnosis[b,d]	242 (17.7)
Years between dyslipidaemia and diabetes diagnosis[b, d]	262 (19.2)

[a]N (%)

[b]Only used in the imputation model

[c]Percentages were calculated among women

[d]Percentages were calculated among participants with event or behaviour

The number of participants for each follow-up was: $N_{follow\text{-}up1}$=1361, $N_{follow\text{-}up2}$=1358, $N_{follow\text{-}up3}$=1346; $N_{follow\text{-}up4}$=1329; $N_{follow\text{-}up5}$=1265

HbA1c, glycated haemoglobin

Appendix 7 Distribution of imputed parameters before and after multiple imputation and variance and efficiency information of imputation procedure

Parameter	Median (25th–75th pct) or n (%)		Relative increase in variance	Fraction missing information	Relative efficiency
	Before imputation	After imputation[a]			
Years-to-myocardial infarction[b]	3.9 (1.2–7.6)	5.1 (2.3–8.2)	0.0013	0.0013	0.9999
Years-to-stroke[b]	5.6 (2.8–9.4)	6.5 (4.1–10.0)	0.0006	0.0006	0.9999
Years-to-nephropathy[b]	10.6 (7.4–12.9)	10.6 (7.6–13.0)	0.0038	0.0038	0.9996
Years-to-renal replacement therapy[b]	7.2 (6.4–15.2)	6.8 (6.2–11.2)	0.0011	0.0011	0.9999
Years-to-neuropathy[b]	10.2 (6.9–13.1)	10.3 (7.3–13.2)	0.0014	0.0014	0.9999
Years-to-retinopathy[b]	11.3 (7.7–14.0)	11.4 (7.6–14.1)	0.0011	0.0011	0.9999
Family history, yes/no					
Diabetes	568 (44.0)	600 (43.9)	—	—	—
Myocardial infarction	244 (19.3)	260 (19.0)	—	—	—
Stroke	260 (20.6)	280 (20.5)	—	—	—
Waist (recruitment), cm	98.5 (90.0–106.0)	98.5 (90.0–106.0)	0.0002	0.0002	1.0000
Weight (recruitment), kg	84.6 (75.4–94.3)	84.7 (75.4–94.4)	0.0001	0.0001	1.0000
Height, cm	168 (161.8–174.6)	168 (161.8–174.6)	0.0023	0.0023	0.9998
Smoking status (fup 1)					
Never-smoker	522 (39.3)	525 (38.6)	—	—	—

Continued

Appendix 7 continued

Parameter	Median (25th–75th pct) or n (%)		Relative increase in variance	Fraction missing information	Relative efficiency
	Before imputation	After imputation[a]			
Former smoker	572 (43.0)	579 (42.5)	—	—	—
Current smoker	236 (17.7)	257 (18.9)	—	—	—
Weight (fup 1), kg	84.0 (75.0–93.0)	84.0 (75.0–94.0)	0.0088	0.0088	0.9991
Sports (fup 2), h/week	0 (0–1.3)	0 (0–1.2)	0.0117	0.0116	0.9988
Biking (fup 2), h/week	0.3 (0–2.5)	0.3 (0–2.3)	0.0322	0.0314	0.9969
Gardening (fup 2), h/week	2.0 (0–5.5)	2.0 (0–5.5)	0.0100	0.0099	0.9990
Smoking status (fup 2)					
Never-smoker	522 (38.5)	524 (38.6)	—	—	—
Former smoker	615 (45.4)	615 (45.3)	—	—	—
Current smoker	219 (16.2)	219 (16.1)	—	—	—
Alcohol consumption (fup 2)[c]					
Non-user	80 (6.0)	81 (6.0)	—	—	—
Very light user	238 (17.8)	243 (17.9)	—	—	—
Below the limit user	768 (57.4)	780 (57.4)	—	—	—
Above the limit user	252 (18.8)	254 (18.7)	—	—	—
Weight (fup 2), kg	85.0 (75.0–94.4)	85.0 (75.0–94.5)	0.0050	0.0050	0.9995
Smoking status (fup 3)					
Never-smoker	520 (38.7)	520 (38.6)	—	—	—

Continued

Appendix 7 continued

Parameter	Median (25th–75th pct) or n (%)		Relative increase in variance	Fraction missing information	Relative efficiency
	Before imputation	After imputation[a]			
Former smoker	646 (48.0)	647 (48.1)	—	—	—
Current smoker	179 (13.3)	179 (13.3)	—	—	—
Alcohol consumption (fup 3)[c]					
Non-user	61 (4.7)	64 (4.8)	—	—	—
Very light user	200 (15.4)	209 (15.5)	—	—	—
Below the limit user	741 (57.2)	767 (57.0)	—	—	—
Above the limit user	293 (22.6)	307 (22.8)	—	—	—
Weight (fup 3), kg	85.0 (75.0–94.5)	85.0 (75.0–94.3)	0.0065	0.0064	0.9994
Red meat consumption (fup 3), 150 g/day	0.4 (0.2–0.6)	0.4 (0.2–0.6)	0.0250	0.0245	0.9976
Whole grain bread consumption (fup 3), g/day	19.6 (9.0–37.0)	19.6 (9.0–38.1)	0.1284	0.1163	0.9885
Grain flakes, grains, muesli consumption (fup 3), g/day	0 (0–0.7)	0 (0–0.7)	0.1304	0.1180	0.9883
Coffee consumption (fup 3), 150g/day	2.7 (1.5–2.8)	2.7 (1.5–2.8)	0.0746	0.0704	0.9930
Sports (fup 4), h/week	0 (0–3.0)	0 (0–3.0)	0.0235	0.0231	0.9977
Smoking status (fup 4)					
Never-smoker	513 (38.6)	513 (38.6)	—	—	—

Continued

Appendix 7 continued

Parameter	Median (25th–75th pct) or n (%)		Relative increase in variance	Fraction missing information	Relative efficiency
	Before imputation	After imputation[a]			
Former smoker	657 (49.4)	657 (49.4)	—	—	—
Current smoker	159 (12.0)	159 (12.0)	—	—	—
Alcohol consumption (fup 5)[c]					
Waist (fup 4), cm	103.0 (96.0–112.0)	103.0 (96.0–112.0)	0.0226	0.0222	0.9978
Weight (fup 4), kg	85.0 (75.0–95.0)	85.0 (75.0–95.0)	0.0110	0.0109	0.9989
Sports (fup 5), h/week	0.5 (0–3.3)	0.5 (0–3.3)	0.0832	0.0780	0.9923
Smoking status (fup 5)					
Never-smoker	493 (39.0)	493 (39.0)	—	—	—
Former smoker	639 (50.6)	639 (50.5)	—	—	—
Current smoker	132 (10.4)	133 (10.5)	—	—	—
Weight (fup 5), kg	84.1 (74.5–94.0)	84.0 (74.5–94.0)	0.0423	0.0409	0.9959

[a]Combined rounded values from the ten imputation datasets

[b]'Years-to-event' was calculated as the difference between date of diabetes and subsequent event.

[c]Non-user: lifetime non-user or former user; Very light user: men/ women ≤2/ ≤1 g/day; Below the limit user: men/ women >2 to ≤24/ >1 to ≤12 g/day; Above the limit user: men/ women >24/1 2 g/day.

Pct, percentile; fup, follow-up

Appendix 8 Data records for fitting the five-state Cox model for one participant

						Dummy intermediate event			Time-updated covariates		
Identifier	Transition	Time in	Time out	D	Stratum	14	24	13	14	24	13
No complication	02	age_0	age_cens	0	2	0	0	0	0	0	0
	01	age_0	age_cens	0	1	0	0	0	0	0	0
	14	–	–	0	2	1	0	0	x_{14}	0	0
	24	–	–	0	1	0	1	0	0	x_{24}	0
	13	–	–	0	1	0	0	1	0	0	x_{13}
0→2	02	age_0	age_event2	1	2	0	0	0	0	0	0
	01	age_0	age_event2	0	1	0	0	0	0	0	0
	14	–	–	0	2	1	0	0	x_{14}	0	0
	24	age_event2	age_cens	0	1	0	1	0	0	x_{24}	0
	13	–	–	0	1	0	0	1	0	0	x_{13}
0→2, 2→4	02	age_0	age_event2	1	2	0	0	0	0	0	0
	01	age_0	age_event2	0	1	0	0	0	0	0	0
	14	–	–	0	2	1	0	0	x_{14}	0	0
	24	age_event2	age_event4	1	1	0	1	0	0	x_{24}	0
	13	–	–	0	1	0	0	1	0	0	x_{13}
0→1	02	age_0	age_event1	0	2	0	0	0	0	0	0
	01	age_0	age_event1	1	1	0	0	0	0	0	0
	14	age_event1	age_cens	0	2	1	0	0	x_{14}	0	0
	24	–	–	0	1	0	1	0	0	x_{24}	0
	13	age_event1	age_cens	0	1	0	0	1	0	0	x_{13}

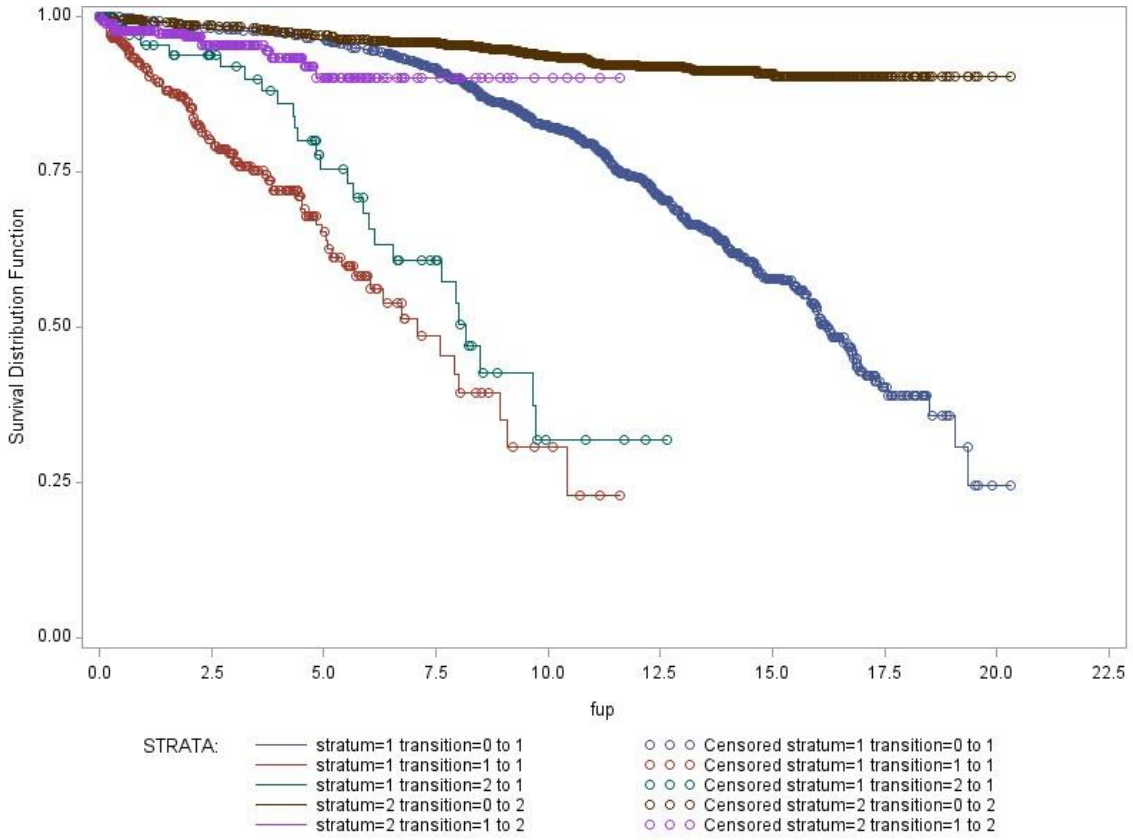
Continued

Appendix 8 continued

						Dummy intermediate event			Time-updated covariates		
Identifier	Transition	Time in	Time out	D	Stratum	14	24	13	14	24	13
0→1, 1→4	02	age_0	age_event1	0	2	0	0	0	0	0	0
	01	age_0	age_event1	1	1	0	0	0	0	0	0
	14	age_event1	age_event4	1	2	1	0	0	x_{14}	0	0
	24	–	–	0	1	0	1	0	0	x_{24}	0
	13	–	–	0	1	0	0	1	0	0	x_{13}
0→1, 1→3	02	age_0	age_event1	0	2	0	0	0	0	0	0
	01	age_0	age_event1	1	1	0	0	0	0	0	0
	14	–	–	0	2	1	0	0	x_{14}	0	0
	24	–	–	0	1	0	1	0	0	x_{24}	0
	13	age_event1	age_event3	1	1	0	0	1	0	0	x_{13}

The identification column 'Identifier' indicates the transition that the following columns will be based on. The transitions are: 0→2 (none to macrovascular complication), 0→2, 2→4 (none to macrovascular and from macrovascular to microvascular complication), 0→1 (none to microvascular complication), 0→1, 1→4 (none to microvascular and from microvascular to macrovascular complication), 0→1, 1→3 (none to microvascular and from microvascular to a second microvascular complication). For each participant the dataset contains one record for each transition. The columns 'Time in' and 'Time out' denote when the participant started and stopped being at risk for each transition (age_0 is the time at diabetes diagnosis, age_cens is the age at last examination by the treating physician and age_event1–age_event4 denote the age when the respective state was reached). The column 'D' shows whether the participant reached the state (0: no, 1: yes). Stratum denotes whether the final event was a microvascular (1) or a macrovascular complication (2). Dummies of intermediate events were included for the secondary states. There were time-updated covariates according to state. In the present model, the time-updated covariates for states 1→4 and 1→3 are identical.

Appendix 9 Kaplan-Meier estimates of the survivor function, $\boldsymbol{S(t)}$, of participants by transition status



Stratum denotes whether the final event was a microvascular (1) or a macrovascular complication (2). The transitions are: 0→2 (none to macrovascular complication), 0→2, 2→4 (none to macrovascular and from macrovascular to microvascular complication), 0→1 (none to microvascular complication), 0→1, 1→4 (none to microvascular and from microvascular to macrovascular complication), 0→1, 1→3 (none to microvascular and from microvascular to a second microvascular complication).

fup, follow-up time (in years)

Appendix 10 Characteristics of study participants according to pre-diagnosis BMI categories, among men

Characteristic	Total n=587	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=46	25.0–29.9 kg/m^2 n=268	30.0–34.9 kg/m^2 n=215	≥35.0 kg/m^2 n=58
Pre-diagnosis BMI, kg/m^2, median (25th–75th pct)	29.8 (27.5–32.5)	24.2 (23.3–24.7)	28.1 (26.9–29.1)	32.1 (30.8–33.4)	36.9 (35.8–39.6)
Relative annual BMI change (%), median (25th–75th pct)[a]	−0.4 (−1.7 to 0.9)	0.2 (−1.2 to 2.0)	−0.3 (−1.5 to 0.8)	−0.6 (−2.1 to 0.7)	−0.3 (−2.0 to 1.1)
Relative annual BMI change categories, n (%)[a]					
>1% BMI loss	222 (38.2)	12 (26.7)	95 (35.7)	92 (43.2)	23 (40.0)
No change	223 (38.5)	16 (35.6)	108 (40.7)	79 (37.1)	21 (35.7)
>1% BMI gain	135 (23.3)	17 (37.8)	62 (23.3)	42 (19.7)	14 (24.8)
Demographics					
Age at pre-diagnosis BMI measurement, years, median (25th–75th pct)	58.4 (51.9–63.4)	58.6 (51.6–62.8)	59.6 (54.2–64.2)	56.8 (51.4–63.1)	56.7 (50.7–62.1)
Age at diabetes diagnosis, years, median (25th–75th pct)	59.7 (53.1–64.9)	59.6 (52.6–63.7)	60.7 (55.4–65.3)	57.6 (52.2–64.6)	57.1 (51.0–63.3)
Education, n (%)					
No vocational training/vocational training	227 (38.7)	11 (23.9)	102 (37.9)	89 (41.4)	26 (43.7)
Technical college degree	121 (20.6)	11 (23.9)	54 (20.2)	42 (19.5)	14 (23.7)
University degree	239 (40.7)	24 (52.2)	112 (42.0)	84 (39.0)	19 (32.8)
Pre-diagnosis lifestyle					
Physical activity, h/week, median (25th–75th pct)	1.0 (0–3.0)	1.0 (0–3.0)	1.0 (0–3.0)	1.0 (0–3.0)	0.7 (0–3.0)
Alcohol intake, g/day, median (25th–75th pct)	16.1 (7.5–33.3)	15.0 (9.9–30.4)	17.0 (7.0–30.0)	16.0 (8.0–36.8)	15.2 (6.3–39.7)
MedPyr score, median (25th–75th pct)	6.7 (5.8–7.6)	6.7 (5.7–7.5)	6.8 (5.7–7.5)	6.7 (5.8–7.6)	6.6 (5.9–7.6)

Continued

Appendix 10 continued

Characteristic	Total n=587	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=46	25.0–29.9 kg/m^2 n=268	30.0–34.9 kg/m^2 n=215	≥35.0 kg/m^2 n=58
Smoking status, n (%)					
Never-smoker	136 (23.2)	10 (21.7)	64 (24.0)	47 (21.9)	15 (25.9)
Former smoker	337 (57.4)	22 (47.8)	149 (55.6)	130 (60.6)	36 (61.0)
Current smoker	114 (19.4)	14 (30.4)	55 (20.5)	38 (17.5)	8 (13.5)
Smoking duration, years, median (25th–75th pct)	24.0 (15.0–33.0)	24.5 (15.0–34.3)	25.0 (15.0–36.0)	23.0 (16.0–32.0)	24.0 (13.5–29.5)
Medical information					
Family history of diabetes, n (%)	221 (37.7)	11 (23.9)	100 (37.3)	87 (40.5)	24 (40.7)
Family history of myocardial infarction, n (%)	81 (13.8)	4 (8.5)	34 (12.8)	34 (15.9)	9 (15.5)
Family history of stroke, n (%)	101 (17.1)	8 (17.2)	48 (18.0)	36 (16.7)	9 (15.1)
Hypertension, n (%)	474 (80.8)	30 (65.2)	208 (77.7)	180 (83.7)	56 (94.9)
Dyslipidaemia, n (%)	431 (73.4)	29 (63.0)	200 (74.7)	167 (78.0)	34 (59.0)
Insulin use at diabetes diagnosis, n (%)	49 (8.4)	5 (10.9)	21 (7.9)	21 (9.8)	2 (3.5)

Table presents combined rounded values from the ten imputation datasets

[a]7 participants did not have follow-up after diabetes diagnosis

BMI, Body mass index; Pct, percentile

Appendix 11 Characteristics of study participants according to pre-diagnosis BMI categories, among women

Characteristic	Total n=497	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=53	25.0–29.9 kg/m^2 n=185	30.0–34.9 kg/m^2 n=163	≥35.0 kg/m^2 n=96
Pre-diagnosis BMI, kg/m^2, median (25th–75th pct)	30.3 (27.2–34.1)	23.7 (22.0–24.2)	27.7 (26.6–29.0)	32.2 (31.1–33.8)	38.3 (36.4–41.2)
Relative annual BMI change (%), median (25th–75th pct)[a]	–0.4 (–2.3 to 0.8)	–0.8 (–2.3 to 0.3)	–0.2 (–2.2 to 1.0)	–0.3 (–2.2 to 1.3)	–0.7 (–2.7 to 0.5)
Relative annual BMI change categories, n (%)[a]					
>1% BMI loss	199 (40.6)	24 (47.1)	67 (36.6)	62 (38.6)	46 (47.9)
No change	179 (36.5)	19 (37.3)	70 (38.7)	54 (33.9)	35 (36.7)
>1% BMI gain	112 (22.9)	9 (16.3)	45 (24.7)	44 (27.5)	15 (15.6)
Demographics					
Age at pre-diagnosis BMI measurement, years, median (25th–75th pct)	60.1 (52.3–65.0)	57.5 (50.1–63.4)	61.6 (55.2–65.4)	60.8 (52.4–65.2)	57.9 (50.3–63.2)
Age at diabetes diagnosis, years, median (25th–75th pct)	61.2 (54.0–66.3)	58.5 (50.9–64.7)	63.1 (56.6–67.2)	61.7 (54.2–66.6)	58.8 (51.4–64.6)
Education, n (%)					
No vocational training/vocational training	263 (52.9)	24 (44.3)	86 (46.5)	95 (58.4)	58 (60.0)
Technical college degree	153 (30.8)	17 (32.1)	64 (33.6)	48 (29.2)	26 (27.4)
University degree	81 (16.3)	12 (23.1)	37 (20.0)	20 (12.3)	12 (12.5)
Pre-diagnosis lifestyle					
Physical activity, h/week, median (25th–75th pct)	1.0 (0–3.5)	1.0 (0–4.0)	1.0 (0–3.5)	1.0 (0–3.6)	0.6 (0–2.6)
Alcohol intake, g/day, median (25th–75th pct)	4.3 (1.5–9.4)	5.5 (1.7–12.0)	5.5 (1.6–10.8)	3.3 (1.6–7.1)	2.9 (1.4–7.5)
MedPyramid score, median (25th–75th pct)	6.7 (5.8–7.5)	6.9 (5.9–7.6)	6.7 (6.0–7.5)	6.5 (5.8–7.3)	7.0 (5.8–7.7)

Continued

Appendix 11 continued

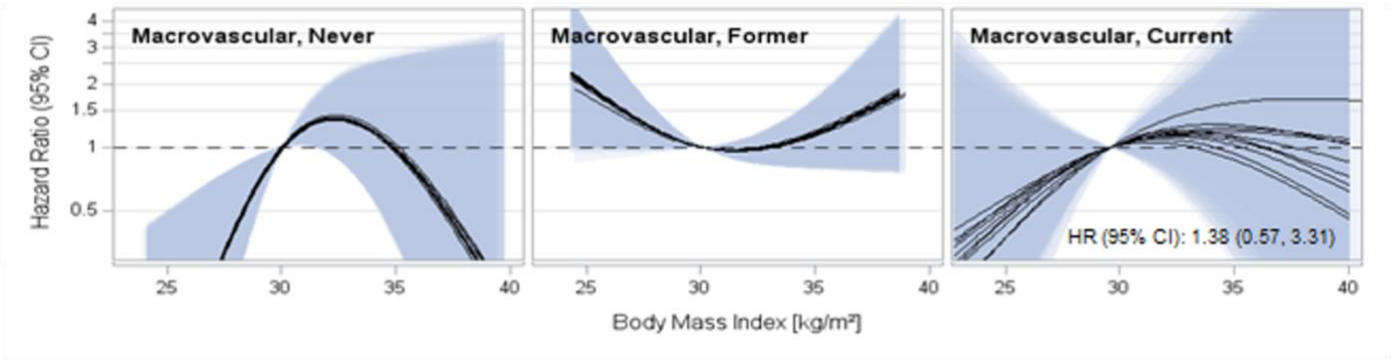
Characteristic	Total n=497	Pre-diagnosis BMI category			
		18.5–24.9 kg/m^2 n=53	25.0–29.9 kg/m^2 n=185	30.0–34.9 kg/m^2 n=163	≥35.0 kg/m^2 n=96
Smoking status, n (%)					
Never-smoker	292 (58.8)	31 (59.4)	108 (58.5)	100 (61.4)	53 (54.6)
Former smoker	137 (27.6)	12 (23.1)	51 (27.7)	44 (27.3)	29 (30.2)
Current smoker	68 (13.7)	10 (18.2)	25 (13.7)	18 (11.2)	15 (15.5)
Smoking duration, years, median (25th–75th pct)	24.0 (12.6–33.0)	20.8 (4.0–31.8)	24.0 (13.5–33.5)	20.5 (12.0–33.5)	27.5 (15.5–32.5)
Medical information					
Family history of diabetes, n (%)	262 (52.8)	32 (59.4)	96 (52.2)	83 (50.6)	53 (54.7)
Family history of myocardial infarction, n (%)	100 (20.1)	9 (16.5)	43 (23.4)	30 (18.5)	18 (18.2)
Family history of stroke, n (%)	121 (24.4)	14 (26.9)	51 (27.3)	35 (21.5)	22 (22.4)
Hypertension, n (%)	396 (79.9)	34 (63.6)	135 (73.3)	137 (84.5)	90.0 (92.8)
Dyslipidaemia, n (%)	365 (73.4)	35 (64.8)	148 (80.0)	118 (72.4)	65 (67.7)
Insulin use at diabetes diagnosis, n (%)	36 (7.2)	4 (7.7)	8 (4.4)	18 (11.0)	5 (5.2)

Table presents combined rounded values from the ten imputation datasets

[a]7 participants did not have follow-up after diabetes diagnosis

BMI, Body mass index; Pct, percentile

Appendix 12 Association between pre-diagnosis BMI and risk of macrovascular complications of diabetes, by smoking status



Pre-diagnosis BMI was assessed as a continuous variable using restricted cubic spline regression, adjusted for age, sex, education, smoking status, smoking duration, physical activity, alcohol consumption, MedPyramid score, family history of diabetes, myocardial infarction and stroke. Splines (black lines) and 95% CIs (blue shading) from ten imputation datasets are shown. Knot placement was 5th, 50th and 95th percentile. Median BMI of 29.9 kg/m^2 served as reference. Test for non-linearity: never smokers, p=0.02; former smokers, p=0.04; current smokers, p=0.43.

Appendix 13 HRs and 95% CIs for microvascular and macrovascular complications by categories of the nonclinical GDRS calculated at diabetes diagnosis, n=1226

Complication	Nonclinical $GDRS_{T2D}$ categories (~) (5-year probability of developing type 2 diabetes)		
	<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
Total complications			
Cases / person-years	106 / 4418.73	121 / 3202.75	224 / 5288.22
Crude model	1.00 (Ref.)	1.73 (1.33, 2.26)	1.96 (1.55, 2.46)
Age- and sex-adjusted model	1.00 (Ref.)	1.47 (1.12, 1.93)	1.59 (1.25, 2.03)
Macrovascular complications			
Cases / person-years	21 / 4610.0	25 / 3491.2	55 / 5787.9
Crude model	1.00 (Ref.)	1.51 (0.82, 2.78)	2.07 (1.24, 3.45)
Age- and sex-adjusted model	1.00 (Ref.)	1.14 (0.60, 2.17)	1.39 (0.81, 2.38)
Microvascular complications			
Cases / person-years	90 / 4518.0	109 / 3273.5	193 / 5482.4
Crude model	1.00 (Ref.)	1.89 (1.43, 2.51)	1.99 (1.56, 2.55)
Age- and sex-adjusted model	1.00 (Ref.)	1.66 (1.25, 2.21)	1.68 (1.30, 2.18)
Kidney disease			
Cases / person-years	45 / 4632.7	65 / 3426.6	118 / 5746.2
Crude model	1.00 (Ref.)	2.18 (1.48, 3.21)	2.38 (1.69, 3.36)

Continued

Appendix 13 continued

Complication	Nonclinical $GDRS_{T2D}$ categories (~) (5-year probability of developing type 2 diabetes)		
	<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	1.83 (1.23, 2.71)	1.95 (1.35, 2.80)
Neuropathy			
Cases / person-years	56 / 4600.9	69 / 3439.3	114 / 5744.3
Crude model	1.00 (Ref.)	1.88 (1.31, 2.68)	1.83 (1.33, 2.51)
Age- and sex-adjusted model	1.00 (Ref.)	1.66 (1.16, 2.39)	1.66 (1.16, 2.39)
Retinopathy			
Cases / person-years	10 / 4693.0	13 / 3547.4	20 / 5959.4
Crude model	1.00 (Ref.)	1.92 (0.84, 4.40)	1.70 (0.80, 3.61)
Age- and sex-adjusted model	1.00 (Ref.)	1.87 (0.80, 4.35)	1.65 (0.76, 3.57)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; GDRS, German diabetes risk score

Appendix 14 HRs and 95% CIs for microvascular and macrovascular complications by categories of the nonclinical GDRS calculated at EPIC-Potsdam recruitment, n=1226

Complication	Nonclinical $GDRS_{REC}$ categories (~) (5-year probability of developing type 2 diabetes)		
	<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
Total complications			
Cases / person-years	182 / 10,562.4	106 / 4759.1	166 / 5673.2
Crude model	1.00 (Ref.)	1.47 (1.15, 1.88)	2.01 (1.62, 2.49)
Age- and sex-adjusted model	1.00 (Ref.)	1.27 (0.99, 1.63)	1.66 (1.33, 2.09)
Macrovascular complications			
Cases / person-years	37 / 10,562.4	25 / 4759.1	40 / 5673.2
Crude model	1.00 (Ref.)	1.55 (0.92, 2.63)	2.08 (1.31, 3.31)
Age- and sex-adjusted model	1.00 (Ref.)	1.20 (0.70, 2.07)	1.51 (0.94, 2.43)
Microvascular complications			
Cases / person-years	158 / 10,364.1	92 / 4565.9	145 / 5449.1
Crude model	1.00 (Ref.)	1.47 (1.13, 1.92)	2.01 (1.60, 2.52)
Age- and sex-adjusted model	1.00 (Ref.)	1.31 (1.00, 1.71)	1.72 (1.35, 2.19)
Kidney disease			
Cases / person-years	80 / 10,564.8	57 / 4711.1	92 / 5634.4
Crude model	1.00 (Ref.)	1.73 (1.22, 2.44)	2.42 (1.79, 3.29)

Continued

Appendix 14 continued

Complication	Nonclinical GDRS$_{REC}$ categories (~) (5-year probability of developing type 2 diabetes)		
	<641 (<5%)	641 to <711 (5 to <10%)	≥711 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	1.50 (1.05, 2.14)	2.01 (1.45, 2.79)
Neuropathy			
Cases / person-years	94 / 10,532.3	62 / 4696.0	83 / 5661.0
Crude model	1.00 (Ref.)	1.62 (1.16, 2.25)	1.86 (1.38, 2.50)
Age- and sex-adjusted model	1.00 (Ref.)	1.49 (1.07, 2.07)	1.66 (1.21, 2.28)
Retinopathy			
Cases / person-years	17 / 10,687.4	9 / 4815.1	17 / 55812.9
Crude model	1.00 (Ref.)	1.22 (0.53, 2.82)	1.92 (0.97, 3.79)
Age- and sex-adjusted model	1.00 (Ref.)	1.15 (0.50, 2.64)	1.76 (0.86, 3.60)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; GDRS, German diabetes risk score

Appendix 15 HRs and 95% CIs for microvascular and macrovascular complications by categories of the clinical GDRS calculated at EPIC-Potsdam recruitment, n=655

Complication	Clinical GDRS categories (~) (5-year probability of developing type 2 diabetes)		
	<932 (<5%)	932 to <1,023 (5 to <10%)	≥1,004 (≥10%)
Total complications			
Cases / person-years	70 / 4277.6	55 / 2278.2	131 / 4033.0
Crude model	1.00 (Ref.)	1.26 (0.93, 1.7)	1.87 (1.51, 2.30)
Age- and sex-adjusted model	1.00 (Ref.)	1.14 (0.84, 1.54)	1.58 (1.27, 1.96)
Macrovascular complications			
Cases / person-years	13 / 4435.2	12 / 2421.8	30 / 4319.1
Crude model	1.00 (Ref.)	1.70 (0.78, 3.69)	2.42 (1.26, 4.66)
Age- and sex-adjusted model	1.00 (Ref.)	1.42 (0.64, 3.16)	1.85 (0.97, 3.56)
Microvascular complications			
Cases / person-years	58 / 4340.6	49 / 2320.7	115 / 4151.6
Crude model	1.00 (Ref.)	1.66 (1.12, 2.45)	2.41 (1.76, 3.30)
Age- and sex-adjusted model	1.00 (Ref.)	1.50 (1.01, 2.24)	2.08 (1.48, 2.92)
Kidney disease*			
Cases / person-years	33 / 4434.0	29 / 2407.0	70 / 4300.2
Crude model	1.00 (Ref.)	1.62 (0.98, 2.68)	2.53 (1.67, 3.83)

Continued

Appendix 15 continued

Complication	Clinical GDRS categories (~) (5-year probability of developing type 2 diabetes)		
	<932 (<5%)	932 to <1,023 (5 to <10%)	≥1,004 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	1.40 (0.84, 2.36)	2.07 (1.32, 3.24)
Neuropathy			
Cases / person-years	31 / 4418.3	33 / 2394.5	66 / 4298.4
Crude model	1.00 (Ref.)	2.03 (1.23, 3.34)	2.52 (1.64, 3.88)
Age- and sex-adjusted model	1.00 (Ref.)	1.89 (1.13, 3.16)	2.30 (1.45, 3.66)
Retinopathy			
Cases / person-years	8 / 4479.3	6 / 2465.6	19 / 4416.8
Crude model	1.00 (Ref.)	1.45 (0.45, 4.65)	2.67 (1.12, 6.34)
Age- and sex-adjusted model	1.00 (Ref.)	1.38 (0.42, 4.53)	2.46 (1.01, 6.00)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; GDRS, German diabetes risk score

Appendix 16 HRs and 95% CIs for microvascular and macrovascular complications per 50 units of the nonclinical and clinical GDRS calculated at diabetes diagnosis and EPIC-Potsdam recruitment, complete case analysis

Complication	Nonclinical $GDRS_{T2D}$ n=941	Nonclinical $GDRS_{REC}$ n=941	Clinical GDRS n=508
Total complications			
Cases / person-years	316 / 10,242.8	316 / 15,839.4	180 / 8509.2
Crude model	1.16 (1.11, 1.22)	1.17 (1.11, 1.22)	1.14 (1.09, 1.19)
Age- and sex-adjusted model	1.11 (1.06, 1.17)	1.12 (1.07, 1.18)	1.11 (1.05, 1.17)
Macrovascular complications			
Cases / person-years	60 / 10,940.5	60 / 16,548.1	34 / 8933.1
Crude model	1.17 (1.07, 1.28)	1.22 (1.11, 1.34)	1.10 (1.03, 1.18)
Age- and sex-adjusted model	1.08 (0.97, 1.20)	1.14 (1.01, 1.27)	1.05 (0.96, 1.14)
Microvascular complications			
Cases / person-years	279 / 10,406.5	279 / 16,091.3	158 / 8620.3
Crude model	1.16 (1.11, 1.22)	1.16 (1.10, 1.21)	1.15 (1.09, 1.20)
Age- and sex-adjusted model	1.12 (1.06, 1.18)	1.12 (1.06, 1.18)	1.12 (1.06, 1.19)
Kidney disease			
Cases / person-years	160 / 10,717.9	160 / 16,466.0	95 / 8790.3
Crude model	1.18 (1.11, 1.26)	1.18 (1.11, 1.25)	1.12 (1.06, 1.19)
Age- and sex-adjusted model	1.13 (1.06, 1.22)	1.13 (1.06, 1.22)	1.10 (1.02, 1.17)

Continued

Appendix 16 continued

Complication	Nonclinical $GDRS_{T2D}$ n=941	Nonclinical $GDRS_{REC}$ n=941	Clinical GDRS n=508
Neuropathy			
Cases / person-years	177 / 10,710.4	177 / 16,450.6	95 / 8837.0
Crude model	1.13 (1.07, 1.21)	1.14 (1.07, 1.21)	1.13 (1.06, 1.20)
Age- and sex-adjusted model	1.10 (1.03, 1.18)	1.11 (1.04, 1.19)	1.13 (1.05, 1.21)
Retinopathy			
Cases / person-years	22 / 11,175.3	22 / 16,771.9	13 / 9069.1
Crude model	1.17 (0.99, 1.38)	1.23 (1.04, 1.44)	1.26 (1.12, 1.43)
Age- and sex-adjusted model	1.14 (0.95, 1.39)	1.20 (1.01, 1.44)	1.25 (1.08, 1.45)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; GDRS, German diabetes risk score

Appendix 17 HRs and 95% CIs for microvascular and macrovascular complications by categories of the nonclinical CVDRS calculated at diabetes diagnosis, n=1226

Complication	Nonclinical $CVDRS_{T2D}$ categories (~) (10-year probability of developing cardiovascular disease)		
	<679 (<5%)	679 to <751 (5 to <10%)	≥751 (≥10%)
Total complications			
Cases / person-years	40 / 1,716.6	96 / 3,342.4	318 / 7,840.7
Crude model	1.00 (Ref.)	1.26 (0.88, 1.79)	2.01 (1.46, 2.76)
Age- and sex-adjusted model	1.00 (Ref.)	0.97 (0.67, 1.42)	1.18 (0.79, 1.76)
Macrovascular complications			
Cases / person-years	4 / 1,795.5	16 / 3,570.7	80 / 8,520.2
Crude model	1.00 (Ref.)	1.91 (0.64, 5.70)	3.92 (1.45, 10.62)
Age- and sex-adjusted model	1.00 (Ref.)	1.42 (0.47, 4.29)	2.12 (0.70, 6.47)
Microvascular complications			
Cases / person-years	35 / 1,737.3	84 / 3,405.7	274 / 8,122.1
Crude model	1.00 (Ref.)	1.23 (0.84, 1.79)	1.94 (1.38, 2.73)
Age- and sex-adjusted model	1.00 (Ref.)	0.95 (0.63, 1.42)	1.13 (0.73, 1.74)
Kidney disease			
Cases / person-years	15 / 1,780.2	49 / 3,554.4	165 / 8,473.4
Crude model	1.00 (Ref.)	1.59 (0.90, 2.82)	2.68 (1.58, 4.55)

Continued

Appendix 17 continued

Complication	Nonclinical $CVDRS_{T2D}$ categories (~) (10-year probability of developing cardiovascular disease)		
	<679 (<5%)	679 to <751 (5 to <10%)	≥751 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	1.14 (0.63, 2.06)	1.34 (0.71, 2.53)
Neuropathy			
Cases / person-years	18 / 1,787.1	55 / 3,500.9	166 / 8,491.8
Crude model	1.00 (Ref.)	1.57 (0.92, 2.67)	2.31 (1.42, 3.76)
Age- and sex-adjusted model	1.00 (Ref.)	1.22 (0.70, 2.15)	1.38 (0.76, 2.51)
Retinopathy			
Cases / person-years	8 / 1,796.9	10 / 3,605.8	25 / 8,797.0
Crude model	1.00 (Ref.)	0.66 (0.25, 1.72)	0.78 (0.34, 1.75)
Age- and sex-adjusted model	1.00 (Ref.)	0.55 (0.20, 1.57)	0.54 (0.18, 1.60)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score

Appendix 18 HRs and 95% CIs for microvascular and macrovascular complications by categories of the nonclinical CVDRS calculated at EPIC-Potsdam recruitment, n=1226

Complication	Nonclinical $CVDRS_{REC}$ categories (~) (10-year probability of developing cardiovascular disease)		
	<679 (<5%)	679 to <751 (5 to <10%)	≥751 (≥10%)
Total complications			
Cases / person-years	76 / 5,023.4	136 / 6,239.5	242 / 8,744.9
Crude model	1.00 (Ref.)	1.58 (1.19, 2.08)	2.11 (1.63, 2.72)
Age- and sex-adjusted model	1.00 (Ref.)	1.38 (1.01, 1.90)	1.74 (1.23, 2.46)
Macrovascular complications			
Cases / person-years	15 / 5,180.9	25 / 6,537.2	62 / 9,279.0
Crude model	1.00 (Ref.)	1.38 (0.72, 2.65)	2.46 (1.40, 4.33)
Age- and sex-adjusted model	1.00 (Ref.)	0.96 (0.44, 2.09)	1.41 (0.60, 3.32)
Microvascular complications			
Cases / person-years	62 / 5,071.3	125 / 6,334.5	208 / 8,973.0
Crude model	1.00 (Ref.)	1.82 (1.34, 2.47)	2.23 (1.68, 2.97)
Age- and sex-adjusted model	1.00 (Ref.)	1.66 (1.18, 2.33)	1.95 (1.35, 2.82)
Kidney disease			
Cases / person-years	27 / 5,175.1	76 / 6,489.7	126 / 9,246.5
Crude model	1.00 (Ref.)	2.46 (1.59, 3.82)	2.99 (1.97, 4.52)

Continued

Appendix 18 continued

Complication	Nonclinical $CVDRS_{REC}$ categories (~) (10-year probability of developing cardiovascular disease)		
	<679 (<5%)	679 to <751 (5 to <10%)	≥751 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	2.03 (1.28, 3.23)	2.20 (1.35, 3.58)
Neuropathy			
Cases / person-years	35 / 5,136.6	78 / 6,503.0	125 / 9,254.9
Crude model	1.00 (Ref.)	1.92 (1.28, 2.86)	2.24 (1.54, 3.27)
Age- and sex-adjusted model	1.00 (Ref.)	1.78 (1.14, 2.79)	2.03 (1.23, 3.34)
Retinopathy			
Cases / person-years	11 / 5,198.6	10 / 6,626.3	22 / 9,490.0
Crude model	1.00 (Ref.)	0.80 (0.33, 1.93)	1.21 (0.58, 2.54)
Age- and sex-adjusted model	1.00 (Ref.)	0.70 (0.25, 1.99)	0.98 (0.34, 2.80)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score

Appendix 19 HRs and 95% CIs for microvascular and macrovascular complications by categories of the clinical CVDRS calculated at EPIC-Potsdam recruitment, n=669

Complication	Clinical CVDRS categories (~) (10-year probability of developing cardiovascular disease)		
	<855 (<5%)	855 to <927 (5 to <10%)	≥927 (≥10%)
Total complications			
Cases / person-years	49 / 2,866.1	88 / 4,057.5	124 / 3,862.4
Crude model	1.00 (Ref.)	1.31 (0.92, 1.86)	2.07 (1.48, 2.87)
Age- and sex-adjusted model	1.00 (Ref.)	1.09 (0.73, 1.63)	1.54 (0.99, 2.39)
Macrovascular complications			
Cases / person-years	10 / 2,980.4	15 / 4,259.9	32 / 4,134.7
Crude model	1.00 (Ref.)	1.11 (0.49, 2.54)	2.47 (1.19, 5.12)
Age- and sex-adjusted model	1.00 (Ref.)	0.86 (0.32, 2.34)	1.63 (0.58, 4.56)
Microvascular complications			
Cases / person-years	42 / 2,907,0	76 / 4,126.9	108 / 3,976.1
Crude model	1.00 (Ref.)	1.33 (0.91, 1.95)	2.10 (1.47, 3.00)
Age- and sex-adjusted model	1.00 (Ref.)	1.11 (0.73, 1.70)	1.56 (0.98, 2.47)
Kidney disease*			
Cases / person-years	22 / 2,976.5	44 / 4,245.8	71 / 4,104.1
Crude model	1.00 (Ref.)	1.42 (0.85, 2.36)	2.60 (1.62, 4.17)

Continued

Appendix 19 continued

Complication	Clinical CVDRS categories (~) (10-year probability of developing cardiovascular disease)		
	<855 (<5%)	855 to <927 (5 to <10%)	≥927 (≥10%)
Age- and sex-adjusted model	1.00 (Ref.)	1.02 (0.59, 1.75)	1.51 (0.86, 2.65)
Neuropathy			
Cases / person-years	23 / 2,960.8	47 / 4,227.2	62 / 4,130.1
Crude model	1.00 (Ref.)	1.47 (0.89, 2.43)	1.28 (1.14, 1.44)
Age- and sex-adjusted model	1.00 (Ref.)	1.23 (0.68, 2.20)	1.49 (0.76, 2.92)
Retinopathy			
Cases / person-years	8 / 3,001.1	12 / 4,302.3	12 / 4,253.9
Crude model	1.00 (Ref.)	1.19 (0.47, 3.00)	1.18 (0.47, 2.97)
Age- and sex-adjusted model	1.00 (Ref.)	1.10 (0.38, 3.20)	1.03 (0.36, 2.95)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score

Appendix 20 HRs and 95% CIs for microvascular and macrovascular complications per 50 units of the nonclinical and clinical CVDRS calculated at diabetes diagnosis and EPIC-Potsdam recruitment, complete case analysis

Complication	Nonclinical $CVDRS_{T2D}$ n=941	Nonclinical $CVDRS_{REC}$ n=941	Clinical CVDRS n=514
Total complications			
Cases / person-years	316 / 10,242.8	316 / 15,839.4	182 / 8589.0
Crude model	1.23 (1.15, 1.32)	1.18 (1.10, 1.26)	1.25 (1.13, 1.39)
Age- and sex-adjusted model	1.18 (1.06, 1.30)	1.16 (1.06, 1.27)	1.20 (1.05, 1.37)
Macrovascular complications			
Cases / person-years	60 / 10,951.5	60 / 16,548.1	35 / 9023.1
Crude model	1.39 (1.18, 1.63)	1.35 (1.14, 1.59)	1.29 (0.97, 1.72)
Age- and sex-adjusted model	1.36 (1.08, 1.70)	1.31 (1.06, 1.62)	1.27 (0.90, 1.79)
Microvascular complications			
Cases / person-years	279 / 10,494.7	279 / 16,091.3	159 / 8749.1
Crude model	1.21 (1.13, 1.30)	1.15 (1.07, 1.22)	1.26 (1.13, 1.40)
Age- and sex-adjusted model	1.13 (1.02, 1.25)	1.12 (1.02, 1.22)	1.17 (1.02, 1.34)
Kidney disease			
Cases / person-years	160 / 10,869.4	160 / 16,466.0	98 / 8967.9
Crude model	1.27 (1.16, 1.40)	1.18 (1.09, 1.29)	1.31 (1.15, 1.51)
Age- and sex-adjusted model	1.17 (1.03, 1.33)	1.12 (1.00, 1.25)	1.17 (0.99, 1.38)

Continued

Appendix 20 continued

Complication	Nonclinical $CVDRS_{T2D}$ n=941	Nonclinical $CVDRS_{REC}$ n=941	Clinical CVDRS n=514
Neuropathy			
Cases / person-years	177 / 10,854.0	177 / 16,450.6	96 / 8982.9
Crude model	1.22 (1.12, 1.34)	1.15 (1.06, 1.25)	1.25 (1.09, 1.43)
Age- and sex-adjusted model	1.14 (1.00, 1.31)	1.14 (1.02, 1.27)	1.18 (0.98, 1.41)
Retinopathy			
Cases / person-years	22 / 11,175.3	22 / 16,771.9	13 / 9179.5
Crude model	1.07 (0.82, 1.39)	1.17 (0.93, 1.46)	1.18 (0.81, 1.73)
Age- and sex-adjusted model	0.98 (0.66, 1.47)	1.17 (0.87, 1.56)	1.06 (0.68, 1.66)

Table presents combined rounded values from the ten imputation datasets

HRs, Hazard ratios; CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score

Appendix 21 C-indices and 95% CIs, complete case analysis

C-indices and 95% CIs of the nonclinical and clinical GDRS according to complication, complete case analysis

Complication	Nonclinical $GDRS_{T2D}$	Nonclinical $GDRS_{REC}$	Clinical GDRS
Total complications	0.61 (0.51, 0.71)	0.61 (0.52, 0.70)	0.63 (0.51, 0.75)
Macrovascular complications	0.61 (0.41, 0.80)	0.63 (0.43, 0.80)	0.61 (0.36, 0.85)
Microvascular complications	0.61 (0.50, 0.71)	0.61 (0.51, 0.70)	0.64 (0.50, 0.76)
Kidney disease	0.62 (0.48, 0.74)	0.61 (0.48, 0.73)	0.63 (0.46, 0.78)
Neuropathy	0.60 (0.47, 0.73)	0.60 (0.47, 0.72)	0.63 (0.46, 0.78)
Retinopathy	0.62 (0.24, 0.95)	0.65 (0.31, 0.93)	0.69 (0.26, 0.93)

Table presents combined rounded values from the ten imputation datasets

CIs, Confidence intervals; GDRS, German diabetes risk score

C-indices and 95% CIs of the nonclinical and clinical CVDRS according to complication, complete case analysis

Complication	Nonclinical $CVDRS_{T2D}$	Nonclinical $CVDRS_{REC}$	Clinical CVDRS
Total complications	0.62 (0.52, 0.71)	0.59 (0.50, 0.68)	0.59 (0.47, 0.71)
Macrovascular complications	0.63 (0.44, 0.81)	0.63 (0.44, 0.81)	0.60 (0.34, 0.83)
Microvascular complications	0.61 (0.50, 0.71)	0.58 (0.48, 0.67)	0.60 (0.46, 0.72)
Kidney disease	0.63 (0.49, 0.76)	0.59 (0.46, 0.71)	0.61 (0.44, 0.77)
Neuropathy	0.60 (0.47, 0.74)	0.57 (0.45, 0.70)	0.60 (0.42, 0.76)
Retinopathy	0.52 (0.16, 0.88)	0.60 (0.26, 0.90)	0.60 (0.17, 0.98)

Table presents combined rounded values from the ten imputation datasets

CIs, Confidence intervals; CVDRS, Cardiovascular disease risk score