Selected lifestyle factors and mortality risk in individuals with diabetes mellitus: Are the associations different from individuals without diabetes?

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"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

Sir Austin Bradford Hill, 1965

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Abbreviations

CHD	Coronary heart disease
CI	Confidence Interval
CVD	Cardiovascular disease
DAG	Directed acyclic graphs
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
HbA_{1c}	Glycated hemoglobin
HR	Hazard ratio
ICD-10	International Classification of Diseases, Injuries and Causes of Death, 10^{th} revision
MET	Metabolic equivalent
NHANES	National Health and Nutrition Examination Survey

Abstract

Introduction

Diabetes mellitus is one of the most common non-communicable diseases globally. It is a chronic disease that requires continuing medical care and patient self-management education to achieve glycemic control and to reduce the risk of cardiovascular diseases (CVD) and premature mortality. When a patient is diagnosed with diabetes, treatment measures which need to be taken by general practitioners are well-established: glycemic control is the main objective of diabetes management, generally achieved by medication and to less extent by lifestyle interventions. Because conclusive evidence on long-term benefits of tight glycemic control are lacking, diabetes management should be an overall intervention strategy including lifestyle modification and aimed at primary prevention of CVD and premature mortality. Due to a lack of epidemiological studies in persons with diabetes, diet and lifestyle advices in diabetes to prevent complications are appropriate for people with and without diabetes. Therefore, it was firstly aimed to provide proof for evidence-based diet and lifestyle recommendations to prevent premature mortality in diabetes. The second objective was to investigate whether the associations between lifestyle factors and mortality were different from individuals without diabetes.

Methods

Within the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort was formed of 6,384 persons with a confirmed diagnosis of diabetes at baseline. Subsequently, EPIC participants without a verified or self-reported diabetes diagnosis were randomly selected and matched 1:3 to the persons with diabetes by age, sex, and study center. Diet and lifestyle during the previous 12 months were assessed at baseline with questionnaires. Associations between the following factors and overall mortality risk were studied using multivariable Cox regression models: body mass index, waist circumference, waist/hip ratio, waist/height ratio, 26 food groups, alcohol consumption, total and leisure-time physical activity, and walking. Next, using a competing risk approach, joint Cox proportional hazard regression models of persons with and without diabetes were built for the selected lifestyle factors and overall mortality risk. Likelihood ratio tests for heterogeneity assessed statistical differences in associations.

Results

After a median follow-up of 9.5 years, 830 (13%) persons with diabetes and 1,338 (7%) persons without diabetes died. Diabetes conferred an independent increased mortality risk with a hazard ratio of 1.54 (95% confidence interval 1.41, 1.70). Measures of abdominal, but not general, adiposity were positively associated with mortality. A healthy diet including an alcohol consumption within the recommended limits, a high consumption of vegetables, nuts and seeds, pasta, rice, bread, and coffee, a moderate consumption of cheese, vegetable oil, and juices and a low consumption of butter and margarine and soft

drinks was associated with reduced mortality risks. Furthermore, higher levels of physical activity were related to reduced mortality. The favorable associations of leisure-time physical activity and coffee consumption and mortality were stronger in persons with diabetes compared with diabetes-free individuals. Diabetes status did not substantially influence the associations between the other studied lifestyle factors and mortality risk, including adiposity, other food groups, and alcohol consumption.

Discussion

Overall, although diabetes confers an independently increased mortality risk, no indications were found that diet and lifestyle recommendations should be different in persons with diabetes compared with persons without diabetes. A healthy lifestyle as recommended to the general population was also in persons with diabetes associated with lower mortality risk. Thus, in terms of primary prevention of CVD and premature mortality by diet and lifestyle, it is not necessary to know whether a person has been diagnosed with diabetes. Our study has shown that persons with and without diabetes, but also persons with pre-diabetes or undiagnosed diabetes should receive similar diet and lifestyle recommendations from their health care providers. A healthy diet and lifestyle allows people with and without diabetes to live healthier and longer; this should be advised and communicated to an even larger proportion than the general population.

Zusammenfassung

Einleitung

Diabetes mellitus ist weltweit eine der häufigsten nicht-übertragbaren Erkrankungen. Dabei handelt es sich um eine chronische Erkrankung, die eine kontinuierliche medizinische und Selbstbeobachtung erfordert, um eine Normalisierung des Blutzuckerspiegels zu erreichen und das Risiko für Herz-Kreislauferkrankungen und vorzeitige Mortalität zu senken. Die Diabetestherapie ist gut etabliert: das Hauptziel der Behandlung ist die Einstellung des Blutzuckerspiegels, was in erster Linie durch Medikamente, aber auch zum Teil durch die Änderung des Lebensstils erreicht werden soll. Jedoch ist die wissenschaftliche Evidenz der langfristigen positiven Effekte straffe Einstellung des Blutzuckerspiegels nicht endgültig gesichert. Aus diesem Grund sollte die Lebensstiländerung die Grundlage der Diabetesbehandlung und primäre Prävention von Komplikationen das Hauptziel bilden. Infolge des Mangels an wissenschaftlicher Evidenz sind die Ernährungs- und Lebensstilempfehlungen für Diabetiker jedoch ähnlich denen der Allgemeinbevölkerung. Somit war das erste Ziel dieser Arbeit, eine wissenschaftliche Grundlage evidenzbasierter Lebensstilempfehlungen für Diabetiker zu liefern. Das zweite Ziel war, zu untersuchen, ob sich die Beziehungen zwischen Lebensstilfaktoren und dem Mortalitätsrisiko bei Diabetikern zu denen von Nicht-Diabetikern unterscheiden, und damit, ob Diabetiker spezielle Empfehlungen erhalten sollten.

Methoden

Innerhalb der “European Prospective Investigation into Cancer and Nutrition (EPIC)-Studie” wurde eine Subkohorte von 6384 prävalenten Diabetikern, für die verifizierte Diagnosen vorlagen, gebildet. Anschließend wurden aus den Studienteilnehmern der restlichen Kohorte ohne Diabetes willkürlich 19152 Personen ausgewählt und den Diabetikern in einem Verhältnis von 1:3 zugeordnet, wobei für Alter, Geschlecht und Studienzentrum kontrolliert wurde. Ernährungs- und Lebensstilgewohnheiten der letzten 12 Monate wurden zu Studienbeginn mit Hilfe von Fragenbögen erfasst. Die Assoziationen der folgenden Faktoren mit dem Gesamtmortalitätsrisiko wurde mittels multivariater Cox Regression untersucht: Body-Mass-Index, Bauchumfang, Verhältnis Bauch-/Hüftumfang, Verhältnis Bauchumfang/ Körpergröße, 26 Lebensmittelgruppen, Alkoholkonsum, körperliche Aktivität - insgesamt und in der Freizeit - sowie Spazierengehen. Basierend auf der Idee des ‚Competing risk‘-Modells wurde ein kombiniertes Cox Regressionsmodell von Diabetikern und Nicht-Diabetikern gebildet. Mit diesem Modell wurde mittels Likelihood-Ratio-Test geprüft ob sich die Assoziationen statistisch unterschieden.

Ergebnisse

Während einer mittleren Nachbeobachtungszeit von 9,5 Jahren sind 830 (13%) Diabetiker und 1338 (7%) Nicht-Diabetiker verstorben. Diabetes war unabhängig mit einem 54% erhöhten Mortalitätsrisiko verbunden (Hazard Ratio: 1.54; 95%-Konfidenzintervall: 1.41-1.70). Abdominale Adipositas war positiv mit dem Mortalitätsrisiko assoziiert. Eine gesunde Ernährung - einschließlich eines moderaten Alkoholkonsums - ging mit einem gesenkten Mortalitätsrisiko einher. Das waren im Genaueren: ein erhöhter Gemüse-, Nüsse und Samen-, Nudeln-, Reis- und Brotverzehr sowie ein erhöhter Kaffeekonsum, ein moderater Konsum von Käse, Pflanzenöl und Säften sowie ein eingeschränkter Genuss von Butter, Margarine und Limonade. Weiterhin war körperliche Aktivität, insgesamt und in der Freizeit, mit einem niedrigeren Gesamtmortalitätsrisiko assoziiert. Im Vergleich zu den Nicht-Diabetikern, traten die beobachteten günstigen Beziehungen hinsichtlich körperlicher Aktivität in der Freizeit und Kaffeekonsum bei den Diabetikern besonders stark zutage. Diabetes hatte jedoch keinen substantiellen Einfluss auf die Beziehungen der anderen untersuchten Ernährungs- und Lebensstilfaktoren zum Mortalitätsrisiko.

Diskussion

Diabetes war unabhängig mit einem erhöhten Mortalitätsrisiko verbunden, aber insgesamt wurden keine Hinweise darauf gefunden, dass sich Ernährungs- und Lebensstilempfehlungen für Diabetikern von denen für Nicht-Diabetikern unterscheiden sollten. Ein gesunder Lebensstil, wie er für die Allgemeinbevölkerung empfohlen wird, war auch in Diabetiker mit einem niedrigeren Mortalitätsrisiko assoziiert. In Bezug auf die primäre Prävention von Herz-Kreislauferkrankungen und einer vorzeitige Mortalität ist es somit nicht notwendig zu wissen, ob eine Person an Diabetes erkrankt ist oder nicht. Schlussfolgernd hat diese Studie gezeigt, dass Diabetiker und Nicht-Diabetiker, aber auch Prä-Diabetiker und Personen mit einem noch unerkannten Diabetes, gleichartige Ernährungs- und Lebensstilempfehlungen erhalten sollten. Damit sind diese Empfehlungen für eine größere Fraktion als nur der Allgemeinbevölkerung gültig. Eine gesunde Ernährung und ein gesunder Lebensstil ermöglichen Personen mit oder ohne Diabetes länger und gesünder zu leben.

Samenvatting

Inleiding

Diabetes mellitus is wereldwijd één van de meest voorkomende niet-overdraagbare ziektes. Het is een chronische ziekte die een continue medische behandeling en zelfzorg van de patiënt noodzaakt om glucosewaarden te controleren en het risico op hart- en vaatziekten en sterfte te minimaliseren. Wanneer de diagnose diabetes wordt gesteld, is de behandeling duidelijk: het controleren van glucosewaarden door middel van medicijnen en in mindere mate leefstijladviezen. Niettemin is het wetenschappelijk bewijs over het langetermijneffect van deze therapie niet afdoende. Daarom is het belangrijk dat voedings- en leefstijladviezen de hoeksteen van de diabetesbehandeling vormen. Vanwege een gebrek aan sluitend wetenschappelijk bewijs zijn de huidige richtlijnen voor een gezonde voeding en leefstijl voor mensen met diabetes gelijk aan de adviezen voor de algemene bevolking. Het eerste doel van dit proefschrift was daarom om bewijs te leveren voor evidence-based voedings- en leefstijlrichtlijnen voor mensen met diabetes om het risico op sterfte te verlagen. Ten tweede is onderzocht of de associaties tussen verschillende leefstijlfactoren en sterfte verschillen met die van mensen zonder diabetes.

Methoden

Binnen de "European Prospective Investigation into Cancer and Nutrition" (EPIC) werd een cohort gecreëerd van 6384 personen met een geverifieerde diabetesdiagnose. Vervolgens zijn studiedeelnemers zonder diabetesdiagnose willekeurig geselecteerd en gekoppeld aan de personen met diabetes met een ratio van 1:3, waarbij is gecontroleerd voor leeftijd, geslacht en onderzoekscentrum. Voedings- en leefstijlgedrag in de afgelopen 12 maanden werd aan het begin van de studie gemeten met behulp van vragenlijsten. De associaties tussen de volgende factoren en het risico op sterfte werden berekend met multivariabele "Cox proportional hazard" regressiemodellen: body mass index, middelomtrek, middel/heup ratio, middel/lengte ratio, 26 voedingsmiddelengroepen, alcoholconsumptie, lichamelijke beweging in de vrije tijd en in totaal en wandelen. Daarna zijn gecombineerde Cox regressiemodellen geconstrueerd voor personen met en zonder diabetesdiagnose, gebaseerd op de ideeën van het "competing risk" model. Met een "Likelihood ratio" test voor heterogeniteit is vervolgens met dit gecombineerde model berekend of de associaties tussen de leefstijlfactoren en het risico op sterfte statistisch verschilden tussen mensen met en zonder diabetes.

Resultaten

Gedurende een follow-up tijd van 9,5 jaar, zijn 830 (13%) personen met diabetes en 1338 (7%) personen zonder diabetes gestorven. Diabetici hadden een onafhankelijk verhoogd sterfterisico vergeleken met personen zonder diabetes: hazard ratio was 1.54 (95% betrouwbaarheidsinterval 1.41, 1.70). Mensen met een hogere mate van abdominale obesitas hadden een verhoogd risico op sterfte; voor body mass index

werd geen verband gevonden. Ook een gezonde voeding bestaande uit een alcoholconsumptie binnen de aanbevolen grenzen, een hoge inname van groenten, noten en zaden, pasta, rijst, brood en koffie, een matige consumptie van kaas, plantaardige olie en vruchtensappen en een lage inname van roomboter, margarine en frisdranken was gerelateerd aan een lager sterfterisico. Vervolgens was een hogere lichamelijke beweging geassocieerd met een verminderd risico op totaalsterfte. De gevonden gunstige associaties voor koffieconsumptie en lichamelijke beweging in de vrije tijd waren sterker zichtbaar in mensen met diabetes vergeleken met personen zonder diabetes. Diabetes had geen substantiële invloed op de overige bestudeerde associaties tussen leefstijlfactoren en sterfte.

Discussie

Ondanks dat diabetici een onafhankelijk verhoogd risico op sterfte hebben, zijn er geen indicaties gevonden dat adviezen voor een gezonde voeding en leefstijl voor mensen met diabetes zouden moeten verschillen van de algemene bevolking. Een gezonde leefstijl zoals aanbevolen aan de algemene bevolking was ook gerelateerd aan een lager risico op sterfte in mensen met diabetes. Het dus niet noodzakelijk om te weten of een persoon ooit de diagnose diabetes heeft gehad als het gaat om de primaire preventie van hart- en vaatziekten en sterfte. Deze studie laat zien dat personen met en zonder diabetes, maar ook personen met prediabetes of niet-gediagnosticeerde diabetes, dezelfde voedings- en leefstijladviezen zouden moeten ontvangen. Een gezonde voeding en leefstijl maakt het mogelijk dat mensen met én zonder diabetes langer en gezonder kunnen leven: dit zou geadviseerd en gecommuniceerd moeten worden aan een grotere groep dan de algemene bevolking.

1. Introduction

1.1 Diabetes epidemiology

Diabetes mellitus is one of the most common non-communicable diseases globally. It is the fourth to fifth leading cause of death in most high-income countries. In 2011, the International Diabetes Federation estimated the comparative prevalence in Europe at 6.7%. This is expected to rise with 22% to a comparative prevalence of 6.9% in the year 2030. In addition, the prevalence of undiagnosed diabetes cases is estimated at 3%. The largest number of diabetes cases can be found in the age group of 40 till 59 years and this will probably shift to the ages of 60 till 79 years in 2030 [1].

According to the International Diabetes Federation, diabetes mellitus is "a group of heterogeneous disorders with the common elements of hyperglycemia and glucose intolerance, due to insulin deficiency, impaired effectiveness of insulin action or both" [1]. Based on the etiology and clinical manifestation, diabetes is classified into four types, of which type 1 and type 2 diabetes are the most prevalent. Type 1 diabetes is caused by destruction of the insulin-producing cells, the beta-cells, of the pancreas, mostly due to an auto-immune reaction. As a result, the beta-cells produce little or no insulin. Type 1 diabetes is one of the most frequent endocrine and metabolic conditions in childhood, but can affect people of any age. Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency. It is generally diagnosed after the age of 40, but may also occur earlier. Type 2 diabetes can remain undetected for many years and the diagnosis is often made from associated complications. Because the clinical manifestation and disease progression may vary considerably in both types, some patients cannot be clearly classified as type 1 or type 2 [2].

An identified, unique biological marker that separates persons with impaired fasting glucose, impaired glucose tolerance, or diabetes from persons with a normal glucose metabolism is lacking [3]. Therefore, the clinical diagnosis of diabetes is defined by the level of hyperglycemia giving rise to risk of retinopathy, a diabetes-related microvascular complication. Thus, the diagnosis is defined by a pre-specified cut-off point on a continuous scale of decreasing glycemic control. The diagnostic criteria of the American Diabetes Association are listed in **Box 1.1**. For several decades, the fasting plasma glucose test was preferred to diagnose diabetes in children and non-pregnant adults. Glycated hemoglobin (HbA_{1c}) is the measure of average blood glucose levels over the preceding two to three months. HbA_{1c} is considered the best measurement of long-term glycemic control and was added to the diagnostic criteria in 2011 [1, 2].

Diabetes is a chronic disease that requires continuing medical care and patient self-management education to achieve glycemic control and to reduce the risk of long-term complications [2]. The natural history of diabetes mellitus is displayed in **Figure 1.1**. Diabetes is a progressive disease and glycemic control worsens as it advances [4]. Risk of diabetes complications increases with longer disease duration [5] and with poorer glycemic control [6].

Box 1.1: Diagnostic Criteria Of Diabetes Mellitus Of The American Diabetes Association [2].

Diagnostic criteria of diabetes mellitus
1. $HbA_{1c} \geq 6.5\%$
2. Fasting plasma glucose ≥ 7.0 mmol/l. Fasting is defined as no caloric intake for at least eight hours.
3. Two-hour plasma glucose ≥ 11.1 mmol/l during an oral glucose tolerance test.
4. Classic symptoms of hyperglycemia and a causal plasma glucose ≥ 11.1 mmol/l. Causal is defined as any time of day without regard to time since last meal. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

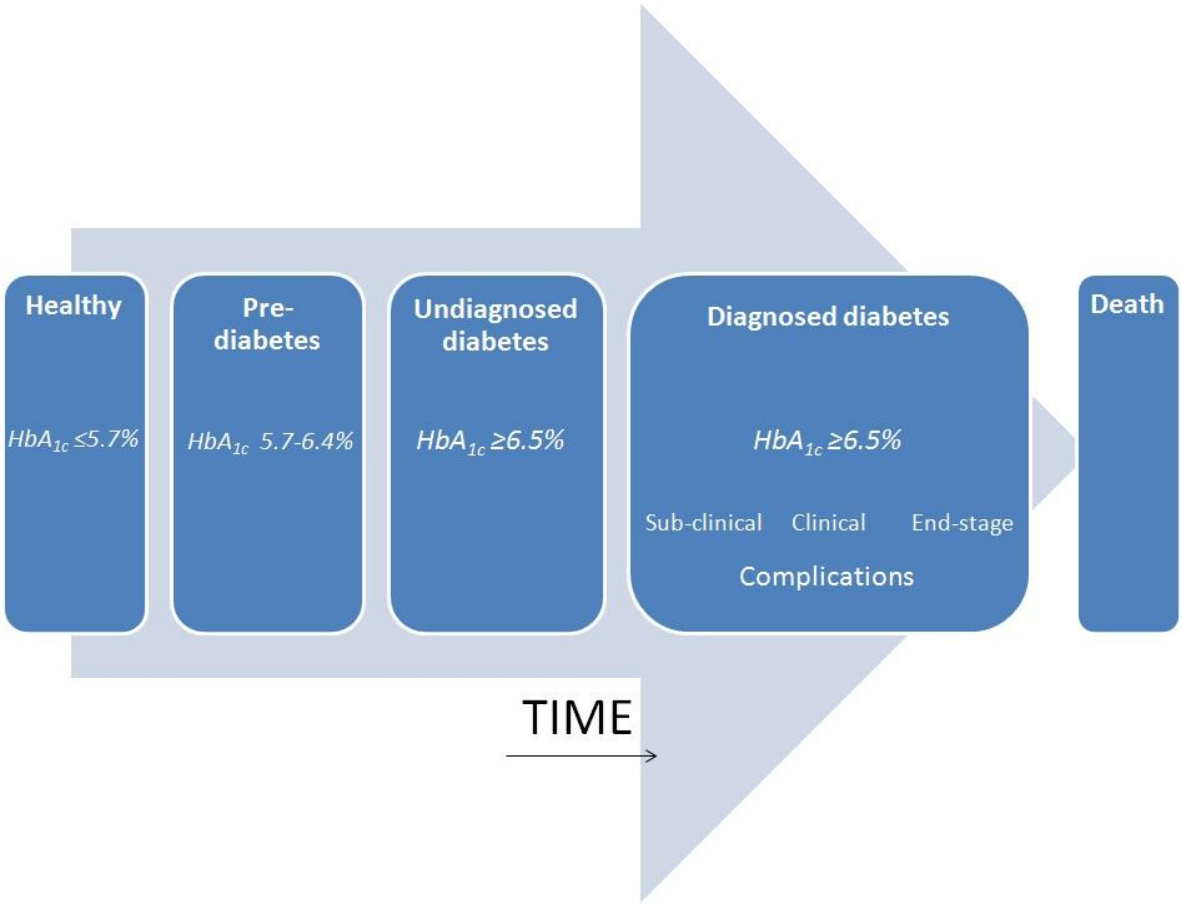

Figure 1.1: Natural History Of Diabetes Mellitus [2].

1.2 Diabetes complications

The costs associated with diabetes are mostly driven by the complications caused by the disease [3]. Major diabetes complications include nephropathy, neuropathy, retinopathy, and cardiovascular disease (CVD). Moreover, individuals with diabetes are at increased risk of premature death in general [7]. Although the prevalence of nephropathy, neuropathy, and retinopathy is higher, macrovascular complications have a larger impact on quality of life and life expectancy [8]. Across all diabetes complications, hyperglycemia, hypertension, and hypercholesterolemia are the main risk factors [5].

CVD is the leading cause of death in persons with diabetes and accounts for 65% of all deaths [5, 8]. Diabetes confers about a twofold excess risk for a wide range of CVD, independently from other conventional risk factors [9]. Long-term CVD risk in persons with diabetes is estimated to be similar to those without diabetes, but who have had a prior myocardial infarction [10, 11].

Moreover, risk of all-cause mortality is almost twice as much among people with diabetes compared to those without. In the Emerging Risk Factors Collaboration Study, which included 820,900 people from 97 prospective studies, the total mortality risk of having diabetes was estimated at 1.80 (95% confidence interval (CI) 1.71, 1.90) [12]. Cause-specific risks were 1.25 (95% CI 1.19, 1.31) for cancer mortality, 2.32 (95% CI 2.11, 2.56) for CVD mortality, and 1.73 (95% CI 1.62, 1.85) for death from other causes. People with diabetes were found to have a higher risk of developing cancer of the liver, pancreas, ovary, colon and rectum, lung, bladder, and breast. Moreover, they were at increased risk of dying from renal disease, liver disease, pneumonia, other infectious diseases, mental disorders, non-hepatic digestive disorders, and lung diseases [12].

In addition, although diabetes is independently associated with higher mortality, about 85% of the persons with diabetes additionally have the metabolic syndrome; a combination of obesity, high triglycerides, low HDL-cholesterol, hypertension, and insulin resistance and are all independent CVD risk factors [10]. Risk factors for CVD in individuals with diabetes are similar to those for people without diabetes, including hypertension, hyperlipidemia, smoking, obesity, diet, and physical activity [5]. Moreover, poor glycemic control is also associated with CVD incidence in diabetes [13].

1.3 Diabetes therapy

When a patient is diagnosed with diabetes, treatment measures which need to be taken by general practitioners are well-established. Glycemic control is the main objective of diabetes management, generally achieved by medication and to less extent by lifestyle interventions. Furthermore, diabetes care usually requires many issues beyond glycemic control, such as treatment of hypertension and hyperlipidemia. Since diabetes mellitus has become a chronic, but manageable condition, primary prevention of complications should be considered the most important treatment goal.

1.3.1 Diabetes medication

Diabetes medications including insulin and oral hypoglycemic agents are for most individuals with diabetes the main therapeutic option for glycemic control [2]. Glycemic regulation is often easy to achieve in the first few months after diagnosis, but becomes more difficult as the disease progresses [4]. Therefore, combinations of several blood glucose lowering medications are often required to achieve glycemic control as patients progress through the natural history of the disease [14]. Both the American Diabetes Association and International Diabetes Federation recommend oral hypoglycemic agents when lifestyle interventions are unable to maintain glycemic control in type 2 diabetes patients. Metformin is the drug of first choice, but when insufficient, therapy should be augmented with additional agents from different classes, and finally insulin therapy. In type 1 diabetes patients, insulin therapy is the only treatment option [2, 15]. Thus, different classes of medication appear to be effective at different stages of the disease [14] and type of medication used will reflect the disease stage.

Diabetes therapy has been predominantly aimed at controlling hyperglycemia by medication strategies, although long-term benefits are lacking [16, 17]. Moreover, the incidence of macrovascular complications increases with increasing hyperglycemia, already starting at glucose levels below the diabetic threshold [18]. Several randomized controlled trials investigated the effect of tight glycemic control (HbA_{1c} target ranging from 6.0-6.5%) over standard therapy (HbA_{1c} target 7.0-7.9%). Overall, intensive treatment was associated with reduced CVD incidence, in particular non-fatal myocardial infarction, but not with total and CVD mortality [19-22]. The United Kingdom Prospective Diabetes Study Group has shown that intensive blood-glucose control reduced microvascular complications [23]. Moreover, improved glycemic control was associated with a reduced risk of diabetes complications across all ranges of achieved HbA_{1c} values [13]. A meta-analysis of five randomized controlled trials showed that intensive glycemic control reduced coronary events but was not associated with overall mortality compared with standard control [22]. Furthermore, several observational studies showed that elevations in HbA_{1c} were associated with ischemic heart disease mortality [24], CVD [25-27], and total mortality [25, 27]. Other studies, however, have suggested that the association between HbA_{1c} and mortality might be U-shaped: Currie *et al.* reported a higher mortality risk in diabetics with observed HbA_{1c} lower than 7.5% [28] and the Action to Control Cardiovascular Risk in Diabetes Study Group suggest that intensive glycemic control for 3.7 years to target a HbA_{1c} below 6% increases 5-year mortality from any cause in a group of individuals with type 2 diabetes [29].

1.3.2 Lifestyle recommendations in diabetes

Because conclusive evidence on long-term benefits of tight glycemic control are lacking, it has been suggested that clinicians should prioritize the well-being and healthy lifestyle of persons with diabetes over complex treatment programs [16]. Diabetes management should be an overall intervention strategy including lifestyle modification [10, 16]. Lifestyle factors such as diet, physical activity and obesity can

have major influence on the development and progression of diabetes complications. Therefore, lifestyle modification is an important strategy for diabetes management and to reduce complications such as CVD, and premature mortality. Lifestyle modification is one of the cornerstones of diabetes self-management. Unlike many other diseases persons with diabetes can actively reduce their risk of complications by improving their lifestyle.

A scientific statement from the American Heart Association and American Diabetes Association lists a set of lifestyle recommendations for persons with diabetes to improve glycemic control and control other major CVD risk factors [30]. In addition, the American Diabetes Association published a separate position statement on nutrition recommendations and interventions for diabetes [31]. Moreover, the International Diabetes Federation published their own lifestyle advices [15]. These three sets of recommendations are summarized in **Box 1.2**. Due to lack of epidemiological studies in persons with diabetes, these lifestyle recommendations in diabetes are appropriate for people with and without diabetes [30].

Lifestyle plays an important role in diabetes management and diabetes patients will receive lifestyle counseling as part of their therapy. Despite wide dissemination of evidence-based guidelines and the availability of new therapeutic agents, there has been little improvement in other modifiable CVD risk factors, such as blood pressure control, diet, exercise, and treatment adherence. Meeting the dietary and physical activity guidelines were the most frequently reported barriers of diabetes management according to a survey among >2,000 adults with diabetes [32].

One would assume that a diabetes diagnosis would increase awareness of the importance of primary prevention of complications and increase the willingness to improve lifestyle. However, studies show that this is not reflected in the actual lifestyles of diabetic persons. It was shown that individuals with diabetes from the National Health and Nutrition Examination Survey (NHANES) did not adhere to a healthy lifestyle more frequently than people without [33]. Next, more findings from NHANES reported that of 1,480 adults with self-reported diagnosis of type 2 diabetes, a large majority was overweight, did not engage in regular physical activity, and did not follow dietary guidelines for fruit and vegetable consumption. In addition, their diet was high in saturated fat [34]. When looking at diet in particular, Greek diabetic adults reported to consume much less sugar and confectionary, soft drinks, juices, and alcohol than non-diabetic adults [35]. Moreover, they consumed less legumes, potatoes, fruits, and nuts. Furthermore, a cross-sectional analysis among individuals with and without diabetes from different countries and ethnic groups, but with similar age, sex, and body mass index, showed that persons with diabetes consumed more soft drinks and less sweets, juice, wine and beer compared with persons without diabetes. Vegetable, fish, and meat consumption was slightly higher in individuals with diabetes, but the observed differences were smaller than 10% [36].

In conclusion, lifestyle modification is an important strategy for diabetes management and the primary prevention of complications. Because persons with diabetes are at higher risk of CVD and premature mortality, it is important to determine whether lifestyle factors can produce similar beneficial effects in this high-risk population. Studies on lifestyle and mortality in persons with diabetes are needed to

establish evidence-based lifestyle recommendations for diabetic individuals and to investigate whether these should be different from the general population.

Box 1.2: Summary Of Diet And Lifestyle Recommendations For Persons With Diabetes Mellitus By The American Heart Association, American Diabetes Association, And International Diabetes Federation [15, 30, 31].

Diet and lifestyle recommendations for persons with diabetes
1. Weight loss is recommended for all overweight and obese individuals with diabetes.
2. Individuals with diabetes should receive individualized medical nutrition therapy.
3. A dietary pattern that includes a variety of fiber-containing foods and carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged for good health.
4. Monitoring carbohydrate intake remains a key strategy in achieving glycemic control. The use of the glycemic index and glycemic load may provide a modest additional benefit for glycemic control over that observed when carbohydrate is considered alone.
5. Sucrose-containing foods can be substituted for other carbohydrates or covered with insulin or other glucose-lowering medications. Care should be taken to avoid excess energy intake.
6. Saturated fat intake should be <7% of total calories. Intake of *trans* fat should be minimized. Lower dietary cholesterol to <200 mg/d.
7. Sugar alcohols and nonnutritive sweeteners are safe when consumed within the daily intake levels established by the Food and Drug Authority.
8. Two or more servings of fish per week (with the exception of commercially fried fish filets) provide n-3 polyunsaturated fatty acids and are recommended.
9. Individualized meal planning should include optimization of food choices to meet recommended dietary allowance or dietary reference intakes for all micronutrients.
10. Diets high in fruits, vegetables, whole grains, and nuts may reduce the risk of microvascular and macrovascular complications.
11. If adults with diabetes choose to consume alcohol, daily consumption should be limited to a moderate amount: one drink per day or less for adult women and two drinks per day or less for adult men.
12. People with diabetes should be advised to perform at least 150 minutes per week or up to 30 to 45 minutes on 3 to 5 days per week of moderate-intensity aerobic physical activity (50-70% of the maximum heart rate).
13. All patients are advised not to smoke.

1.4 Studies on lifestyle and mortality risk in diabetes

The association between lifestyle factors and risk of mortality in persons with diabetes has been investigated in several studies. **Table 1.2** contains a comprehensive literature overview of prospective studies into lifestyle factors and mortality in persons with diabetes mellitus. It was seen that having two or more favorable lifestyle factors including smoking, body mass index, physical activity, and diet, were associated with lower mortality risk in 1,263 German men and women with diabetes [37]. Also among Chinese diabetes patients, persons who reported to smoke, consume alcohol and not to engage in physical exercise had an increased risk of overall mortality and mortality due to diabetes and CVD. Of all lifestyle factors, exercise showed the strongest associations [38].

1.4.1 General and abdominal adiposity

Weight loss is recommended for the overweight and obese [15, 30]. In the general population, general and abdominal obesity have been associated with increased risk of mortality [39, 40]. Studies on adiposity and mortality in individuals with diabetes, however, have yielded inconsistent results. Three cohort studies demonstrated that a high body mass index was related to increased mortality [41, 42] and coronary heart disease [43]. Other investigations reported an inverse association body mass index and mortality [44-47]. In two further studies, body mass index was not associated with risk of death when the level of exercise capacity was taken into account [48, 49] and two others found a U- or J-shaped relationship between body mass index and mortality [50, 51]. Measures of abdominal adiposity have received much less attention. In the EURODIAB Prospective Complications Study, waist/hip ratio was negatively associated with overall, cardiovascular, and non-cardiovascular mortality, whereas no association was observed for body mass index [52]. Moreover, waist circumference was not associated with CVD incidence in a study among Japanese diabetes patients [53]. In conclusion, the association between body mass index and mortality in persons with diabetes remains unclear and measures of abdominal adiposity have hardly been investigated as a risk factor for diabetes complications and premature mortality.

1.4.2 Diet

There is currently no universal approach to the optimal dietary strategy for diabetes; it is unlikely that the optimal combination of nutrients to prevent CVD exists. The diabetes patient should seek individualized medical nutrition therapy and recommendations with respect to diet are general: a dietary pattern high in fruits, vegetables, whole grains, legumes, low-fat milk, nuts, and fish is recommended [15, 30, 31]. A Cochrane review was published in 2005 with the objectives to assess the effects of dietary advice to adults with diabetes on morbidity, quality of life, mortality, weight and measures of diabetic control using data from randomized clinical trials. They concluded that no high quality data were found on the efficacy of dietary treatment in type 2 diabetes. However, the data indicated that dietary advice showed favorable effects on glycemic control. These diets commonly advised for glycemic control are low-fat and high in unrefined carbohydrates [54]. Furthermore, several prospective studies have investigated the associations of selected food group and nutrients on mortality risk in persons with diabetes and found that a higher consumption of eggs, saturated lipids, and a lower polyunsaturated fat to saturated fat ratio was associated with a higher risk of coronary heart disease (CHD) and overall mortality [35, 55]. Furthermore, for consumption of coffee [56], nuts and seeds [57], fish and long chain n-3 fatty acids [58], wholegrain and bran [59], and vegetables, fruits, and legumes [60] protective associations for CVD and total mortality were found. In conclusion, current evidence from cohort studies suggest that in line with the recommendations, a diet high in vegetables, fatty fish, nuts, and whole-grain and low in saturated fat is associated with lower risk of macrovascular complications and mortality in persons with diabetes. However, more studies are needed to confirm these results and investigate the associations for other food groups.

Table 1.2: Prospective Studies On Lifestyle Factors And Mortality Risk In Individuals With Diabetes Mellitus.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Lifestyle								
Lin, 2012 [38] Taichung Diabetes Study, Taiwan	M/F	>30	5,686	Clinically confirmed based on criteria of the ADA	4.0 y	- Smoking - Alcohol drinking - Physical activity - Carbohydrate intake (Interview-administered questionnaire and 24h-dietary recall)	429 total mortality; 105 diabetes mortality; 83 CVD mortality; 122 cancer mortality	Smoking, alcohol consumption, and exercise were associated with increased total mortality risk. Exercise was also associated with diabetes and CVD mortality. The combined lifestyle score was associated with higher total mortality and due to diabetes, CVD and cancer.
Nöthlings, 2010 [37] EPIC-Potsdam, Germany	M/F	35-65	1,263	Self-report confirmed with use of diabetes medication, consistent self-report in follow-up, or additional contact with the participant	7.7 y	- BMI (Measured) - Smoking status - Physical Activity - Alcohol consumption (Questionnaire) - Fruit, vegetable, wholegrain, and red meat intake (FFQ)	130 total mortality; 48 CVD mortality; 47 cancer mortality; 34 mortality due to other causes.	Having 2 or more favorable lifestyle factors (no smoking, BMI <30 kg/m^2, ≥3.5 h/wk physical activity, higher intake of fruit, vegetable, wholegrain and lower intake of red meat) was associated with lower mortality risk.
Trichopoulou, 2006 [35] EPIC-Greece, Greece	M/F	>35	1,013	Self-reported diagnosis and use of diabetes medication	4.5 y	- Waist/height ratio - Hip circumference (Measured) - Total physical activity (Questionnaire) - Dietary intake: 16 inclusive food groups, nutrients, beverages (FFQ)	80 total mortality	Consumption of eggs and saturated lipids was significantly associated with mortality. Waist/height ratio was positively, whereas hip circumference was inversely associated with mortality. Physical activity was inversely associated with mortality.
Adiposity								
Chaturvedi, 1995 [44] World Health Organization Multinational Study of Vascular Diseases in Diabetes	M/F	35-54	1,220	Insulin-dependent diabetes mellitus: someone who was receiving insulin within 1 year of diagnosis	9.0 y	- Body mass index (Measured)	247 total mortality	Men and women with a BMI <20 had increased mortality compared with a BMI of 22-24 kg/m^2. Higher BMI levels were not associated with mortality.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Chaturvedi, 1995 [41] World Health Organization Multinational Study of Vascular Diseases in Diabetes	M/F	35-55	2,960	Non-insulin dependent diabetes mellitus: those who were not confirmed as insulin-dependent	9.0 y	- Body mass index (Measured)	544 total mortality	No clear relationship between BMI and mortality could be detected; probably due to its positive associations with age, blood pressure, cholesterol.
Church, 2004 [48] Aerobics Center Longitudinal Study, US	M	23-79	2,196	Self-reported insulin use, physician-diagnosed history of diabetes, or fasting plasma ≥7.0 mmol/l	14.6 y	- Body mass index (Measured)	275 total mortality;	Compared with a BMI <25, men with a BMI ≥30 had increased mortality risk, but this was not independent of physical fitness.
Eeg-Olofsson, 2008 [42] Swedish National Diabetes Register, Sweden	M/F	30-74	13,087	Type 2 diabetes confirmed by treatment with diabetes-related medication (incl. diet)	5.6 y	- Body mass index (Measured)	664 total mortality	Risk of total mortality increases with 27% with a 5 unit increase in BMI at baseline.
Khalangot, 2009 [50] System of Diabetes Mellitus Care in Ukraine, Ukraine	M/F	Adults	89,443	Type 2 diabetes patients from population-based diabetes register confirmed with official criteria	2.7 y	- Body mass index (Measured)	7,804 total mortality; 3,320 CVD mortality	Risks of total and CVD mortality were increased in diabetic men and women with extreme obesity (≥35 kg/m^2) and low-normal weight (<23 kg/m^2).
McAuley, 2007 [49] Veterans Exercise Study, US	M	23-88	831	Type 2 diabetes: physician-diagnosed, treatment with OHA, or a fasting plasma glucose ≥7.0 mmol/l	4.8 y	- Body mass index (Measured)	112 total mortality	BMI (continuously) was neither protective nor predictive of mortality; physical fitness was strongly related to mortality independent of BMI.
McEwen, 2007 [45] Translating Research Into Action for Diabetes Study, US	M/F	≥18	8,733	Patients served by health care plans and provider groups	3.7 y	- Body mass index (Measured)	791 total mortality	Having a BMI <26 kg/m^2 was most strongly associated with increased mortality risk compared with a BMI of 26-30 kg/m^2. A BMI >30 kg/m^2 was not associated with mortality.
Ross, 1997 [51] Rancho Bernardo Study, US	M/F	40-79	373	Diabetes defined by history of diagnosis or a fasting plasma glucose >7.76 mmol/l	14 y	- Body mass index (Measured)	Total mortality	Lowest mortality was observed in those with average weight. Those who were classified as thin, overweight, or obese had poorer survival rates.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Soedamah-Muthu, 2008 [52] EURODIAB Prospective Complications Study, Europe	M/F	15-60	2,787	Type 1 diabetes: diabetes diagnosed before 36 y with a continuous need for insulin within 1 year of diagnosis	7 y	- Body mass index - Waist/hip ratio (Measured)	102 total mortality; 24 CHD mortality; 5 other CVD mortality; 38 non-CVD mortality; 35 mortality due to unknown causes	A higher waist/hip ratio was related to mortality due to CVD, non-CVD, and all causes. A higher BMI was not associated with mortality.
Weiss, 2009 [46] Acute geriatric ward at Rabin Medical Center, Israel	M/F	>60	470	Medical history, use of insulin or OHA, recorded fasting plasma glucose >7.0 mmol/l	3.7 y	- Body mass index (Measured)	67 total mortality; 30 CVD mortality	BMI was independently inversely associated with both total and CVD mortality.
Zoppini, 2003 [47] Verona Diabetes Study, Italy	M/F	<65 y and ≥65 y	3,398	Type 2 diabetes patients identified by diabetes clinics, family physicians, and drug consumption database	10 y	- Body mass index (Measured)	1,212 total mortality	Under the age of 65, obesity was a negative prognostic factor, whereas in older age overweight and obesity were associated with increased risk of dying.
Diet								
Bidel, 2006 [56] Six independent population surveys (1972-1997), Finland	M/F	25-74	3,837	Type 2 diabetes confirmed by WHO criteria	18.7 y	- Coffee consumption (Questionnaire)	1,471 total mortality; 909 CVD mortality; 598 CHD mortality; 210 stroke mortality	An inverse association between coffee consumption and the risk of total, CVD, and CHD mortality was found.
He, 2010 [59] Nurses' Health Study, US	F	30-55	7,822	Self-report confirmed with elevated glucose and classical symptoms, elevated glucose on 2 occasions, or treatment with insulin or OHA	26 y	- Whole grain, cereal fiber, bran, and germ intake (Semi-quantitative FFQ at baseline and repeated during follow-up)	852 total mortality; 295 CVD mortality	Wholegrain and bran intakes were related to reduced total and cardiovascular mortality rates; however, only the association for bran intake was independent of other lifestyle and dietary factors.
Hu, 2003 [58] Nurses' Health Study, US	F	30-55	5,103	Self-report confirmed with elevated glucose and classical symptoms, elevated glucose on 2 occasions, or treatment with insulin or OHA	9.0 y	- Fish intake (Semi-quantitative FFQ at baseline and repeated during follow-up)	468 total mortality; 161 CVD mortality; 172 cancer mortality; 135 mortality due to other causes	Higher consumption of fish and omega-3 fatty acids was associated with lower incidence of total mortality, even after adjustment for established CVD risk factors including other dietary factors.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Li, 2009 [57] Nurses' Health Study, US	F	30-55	6,309	Self-report confirmed with elevated glucose and classical symptoms, elevated glucose on 2 occasions, or treatment with insulin or OHA	8.7 y	- Nut and peanut butter consumption (Semi-quantitative FFQ at baseline and repeated during follow-up)	452 CVD mortality	Frequent nut and peanut butter consumption (5 or more servings per week) was associated with a significantly lower risk of fatal and non-fatal CVD.
Nöthlings, 2008 [60] EPIC, Europe	M/F	35-70	10,449	Self-report	9 y	- Vegetable, fruit, and legume consumption (FFQ validated with a computerized 24-h dietary recall in a subsample)	1,346 total mortality; 517 CVD mortality; 319 cancer mortality; 323 mortality due to other causes.	Inverse associations were observed for total intake of vegetables, legumes, and fruits and overall, CVD and non-CVD/non-cancer mortality. Strongest associations were observed for vegetables.
Soinio, 2003 [55] Turku and Kuopio University Hospital District, Finland	M/F	45-64	661	Type 2 diabetes patients identified with national drug reimbursement register	7 y	- P/S ratio (53-item FFQ)	65 CHD mortality	A low P/S ratio was associated with an increased rate of CHD death.
Zhang, 2009 [61] Nurses' Health Study, US	F	30-55	7,170	Self-report confirmed with elevated glucose and classical symptoms, elevated glucose on 2 occasions, or treatment with insulin or OHA	8.7 y	- Coffee consumption (Semi-quantitative FFQ at baseline and repeated during follow-up)	734 total mortality; 282 CHD or stroke mortality ; 182 cancer mortality; 270 mortality due to other causes	Higher coffee consumption was not associated with a higher risk of all-cause mortality or mortality due to specific causes.
Zhang, 2009 [62] Health Professionals Follow-up Study, US	M	40-75	3,497	Self-report	6.9 y	- Coffee consumption (Semi-quantitative FFQ sent at baseline and repeatedly during follow-up)	538 total mortality; 215 CHD mortality; 145 cancer mortality; 178 mortality due to other causes	Higher coffee consumption was not associated with a higher risk of CVD or all-cause mortality.
Alcohol consumption								
Ajani, 2000 [63] Physicians' Health Study, US	M	40-84	2,790	Self-reported history of diabetes or use of insulin or other anti-diabetic medication	5.5 y	- Alcohol consumption: rarely/never, monthly, weekly, daily	850 CHD mortality	Compared with those who consumed rarely or never alcohol, daily consumption was associated with lower risk of CHD mortality.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
De Vegt, 2002 [64] Hoorn Study, the Netherlands	M/F	50-75	659	Fasting plasma ≥7.0 mmol/l or postload glucose ≥11.1 mmol/l or diabetes treatment by a general practitioner or clinician	6 y	- Alcohol consumption: yes/no alcohol consumption and no. of glasses per week (Semi-quantitative FFQ)	268 total mortality	Moderate alcohol consumption up to 10 gram per day was associated with the lowest risk of mortality. Compared with a moderate consumption, no association was observed for 0 or >10 grams/day.
Diem, 2003 [65] Swiss cohort of WHO Multinational Study of Vascular Disease in Diabetes, Switzerland	M/F	35-41	287	Diagnosis >1 year earlier and receiving diabetes treatment from a physician.	12.6 y	- Alcohol consumption: weekly consumption of beer, wine, and spirits (Questionnaire)	70 total mortality; 21 CHD mortality; 49 mortality due to other causes	Compared with those who did not report alcohol consumption at baseline, daily intake of 16-30 grams was associated with reduced risk of total and CHD mortality.
Nakamura, 2009 [66] National Survey on Circulatory Disorders 1980, Japan	M	>30	209	Casual blood glucose ≥200 mg/dL, or fasting blood glucose ≥126 mg/dL, or self-reported history of diabetes	19 y	- Alcohol consumption: almost never / daily / occasionally/ stopped, but used to drink (Questionnaire)	990 total mortality; 328 CVD mortality; 337 cancer mortality; 325 non-CVD/non-cancer mortality	Compared with never drinking, daily drinking was associated with lower risk of CVD mortality. No relationships with other causes of death were observed.
Solomon, 2000 [67] Nurses' Health Study, US	F	30-55	5,103	Self-report confirmed with 2 or more glucose levels diagnostic of diabetes or by medical record review	14 y	- Alcohol consumption: beer, wine, and spirits. (Semi-quantitative FFQ sent at baseline and repeatedly during follow-up)	101 CHD mortality	Compared with no reported alcohol consumption, a usual consumption of more than 0 g/d was associated with reduced risk of CHD mortality.
Tanasescu, 2001 [68] Health Professionals Follow-up Study, US	M	40-75	2,419	Self-reported diagnosis >30 confirmed with raised fasting, random plasma concentration, at least 2 raised plasma glucose concentrations on separate occasions in the absence of symptoms, or use of diabetes medication	10 y	- Average daily consumption of beer, wine and spirits (Semi-quantitative FFQ at baseline and repeatedly during follow-up)	69 CHD mortality	Compared with abstainers at baseline, daily intake of >2 alcoholic drinks was associated with lower risk of total MI, but not significantly with fatal CHD.
Valmadrid, 1999 [69] Wisconsin Epidemiologic Study of Diabetic Retinopathy , US	M/F	>30	983	Diagnosis of older-onset diabetes identified through primary care physicians	12.3 y	- Alcohol consumption: never, former, <2 g/d, 2-3 g/d, ≥14 g/d (Questionnaire)	198 CHD mortality	Compared with never drinkers (excluding former drinkers), alcohol consumption of <2 to ≥14 g/d was associated with a reduced risk of CHD mortality.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Physical Activity								
Batty, 2002 [70] Whitehall II Study, United Kingdom	M	40-64	352	Type 2 diabetes/ IGT: Oral Glucose Tolerance Test	25 y	- Walking pace - Leisure-time activity (Questionnaire)	215 total mortality; 79 CHD mortality; 39 other CVD mortality	Walking pace and leisure-time physical activity were inversely related to all-cause, CHD, and other CVD mortality in men with diabetes and impaired glucose tolerance.
Ford, 1991 [71] National Health and Nutrition Examination Survey I: Epidemiologic Follow-Up Study 1982-1984, US	M/F	40-77	602	Self-reported diabetes	10 y	Leisure-time physical activity (Questionnaire)	233 total mortality; 92 CHD mortality	Non-leisure time physical inactivity, but not leisure-time inactivity, was significantly associated with total and CHD mortality.
Gaziano, 2002 [72] Physicians' Health Study enrolment cohort, US	M	40-84	2,838	Self-reported diabetes	5.2 y	Vigorous exercise (Questionnaire)	356 total mortality	Compared to those who rarely or never exercised, those who exercised once or more times per week had lower risk of overall mortality.
Gregg, 2003 [73] National Health Interview Survey, US	M/F	>18	2,896	Self-reported diabetes	8.0 y	- Walking - Total physical activity (Questionnaire)	671 total mortality; 316 CVD mortality	Compared with inactive persons, those who walked or were physically active for at least 2 hours per week had lower all-cause and CVD mortality risk.
Hu, 2004 [74] Six independent population surveys (1972-1997), Finland	M/F	25-74	3,316	Type 2 diabetes confirmed by WHO criteria	18.4 y	Occupational, commuting, and leisure-time physical activity (Questionnaire)	1,410 total mortality; 903 CVD mortality	Moderate to high levels of physical activity were associated with reduced total and CVD mortality; this was seen for leisure-time, occupational, and commuting physical activities.
Hu, 2005 [75] Six independent population surveys (1972-1997), Finland	M/F	25-74	3,708	Type 2 diabetes confirmed by WHO criteria	18.7 y	Total physical activity (Questionnaire)	1,423 total mortality; 906 CVD mortality	Moderate or high levels of total physical activity were associated with lower CVD and total mortality, independent of BMI, blood pressure, total cholesterol, and smoking status.

FIRST AUTHOR [REF], STUDY, COUNTRY	SEX	AGE (Y)	N	DIABETES VERIFICATION	F-UP	EXPOSURE (ASSESSMENT)	OUTCOME, NO. OF CASES	RESULTS
Jonker, 2006 [76] Framingham Heart Study, US	M/F	28-62	292	Random blood glucose ≥200 mg/dl or treatment with hypoglycemic agent	3x12 y	Total physical activity (Interview)	292 total mortality	Risk for a transition from prevalent diabetes to death was lower in those with a high level of physical activity compared with those with a low activity level.
Smith, 2007 [77] Rancho Bernardo Study, US	M/F	50-90	347	Type 2 diabetes confirmed by WHO criteria	10.0 y	Walking (Interview)	538 total mortality; 143 CHD mortality; 138 other CVD mortality	Adults who walked ≥1 mile per day were half as likely to die from all-causes and less than one fifth as likely to die from non-CHD CVD compared with inactive persons.
Tanasescu, 2003 [78] Health Professionals' Follow-up Study (1986-1998), US	M	40-75	2,803	Self-reported diagnosis at >30 y confirmed with 1 or more classic symptoms plus raised plasma glucose or OHA use	14.0 y	- Walking - Total physical activity (Questionnaire)	355 total mortality; 96 CVD mortality	Higher levels of total activity and walking were associated with lower risk of total mortality, but not with CVD morbidity and mortality.
Wei, 2000 [79] Aerobics Center Longitudinal Study, US	M	50	1,188	Type 2 diabetes defined according to criteria of ADA	11.7 y	Leisure-time physical activity (Questionnaire)	180 total mortality	Physical inactivity was associated with increased risk of mortality, independent of age, co-morbidities, and other lifestyle factors.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; F-up, follow-up; M, male; MI, myocardial infarction; IGT, impaired glucose tolerance; OHA, oral hypoglycemic agents; P/S, Ratio of polyunsaturated to saturated fatty acids; US, United States; WHO, World Health Organization.

1.4.3 Alcohol consumption

If adults with diabetes choose to consume alcohol, a moderate consumption – limited to one glass per day for women and two glasses per day for men – is advised [15, 30]. This recommended upper limit also holds for the general population [80]. Within the general population, moderate alcohol consumption has been associated with lower cardiovascular mortality [81] as well as total mortality [82] compared with non-consumption. The same associations have been reported for persons with diabetes: a meta-analysis of six studies showed that moderate alcohol consumption was related to a reduced CVD risk [66, 83]. However, a well-known difficulty in such comparisons is the use of non-consumers as a reference group, which might include both lifelong abstainers and former drinkers. This group has shown to be very heterogeneous and as a consequence appears to be less healthy than moderate consumers [84, 85]. Thus, non-consumers may not be an ideal reference group. In addition, as persons who have experienced CVD, persons with diabetes may have modified their drinking habits after diagnosis [86]. However, to our knowledge, alcohol consumption in the past has not been investigated in relation to mortality in persons with diabetes [83, 87]. It has been reported in the general population that the relationship between alcohol and mortality attenuated when taking alcohol consumption in the past into account [82, 88, 89]. In conclusion, several studies have suggested that moderate alcohol consumption is beneficial in persons with diabetes, but history of alcohol consumption has hardly been taken into account.

1.4.4 Physical activity

Physical activity has been defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”[90]. To improve glycemic control, assist with weight loss or maintenance, and reduce the risk of CVD, the American Diabetes Association and the American College of Sports Medicine jointly recommend persons with diabetes to engage at least 150 min/week in moderate-intensity aerobic physical activity (corresponding approximately to 40-60% of maximal aerobic capacity) or at least 90 minutes in vigorous aerobic exercise per week [91, 92]. Walking, the most common form of physical activity, has been defined as “an act or instance of going on foot especially for exercise or pleasure” [93]. Because walking requires no specific facilities, it can be easily implemented in the daily routine, and is relatively safe, it has been of particular interest in the treatment of diabetes [94]. Observational studies as well as randomized clinical trials have shown the overall benefits of physical activity in persons with diabetes. A meta-analysis of 14 controlled trials showed exercise programs improved glycemic control [95]. Moreover, several observational studies have related higher levels of physical activity to a reduced CVD and total mortality risk [35, 70-79]. Protective associations were observed for total physical activity, leisure-time physical activity as well as walking. However, these studies had relatively small sample sizes and some adjusted for intermediate factors such as body mass index, blood pressure, and cholesterol. These factors are potential intermediate factors in the pathway between physical activity and outcome, adjustment may not be appropriate. Previous studies may therefore have underestimated the true association between physical activity and mortality.

1.5 Objectives

The objectives of this thesis are twofold. Because there is a lack of evidence on lifestyle and prevention of CVD and mortality in persons with diabetes, lifestyle recommendations for diabetic individuals are similar to those for the general population. Therefore, it is firstly aimed to provide proof for evidence-based lifestyle recommendations in persons with diabetes by investigating the associations between the following selected lifestyle factors and overall mortality risk:

a. General and abdominal adiposity, as measured by body mass index, waist circumference, waist/hip ratio and waist/height ratio;

b. Food group consumption: potatoes, vegetables, legumes, fruits, nuts and seeds, milk and milk products, cheese, yogurt, pasta, rice, bread, breakfast cereals, red meat, processed meat, fish and shellfish, eggs, vegetable oil, butter and margarine, sugar and confectionary, cakes and cookies, soft drinks, juices, tea, and coffee.

c. Alcohol consumption, taking into account alcohol consumption in the past;

d. Physical activity: total physical activity, leisure-time activity, and walking.

Secondly, several epidemiological studies and clinical trials have investigated the associations between lifestyle factors and mortality in individuals with diabetes; moreover, many other studies on lifestyle and mortality risk have systematically excluded persons with diabetes to simplify analysis of the results, making it unclear how to apply these results to persons with diabetes. It remains unknown whether the associations between lifestyle factors and mortality risk are different from individuals without diabetes. To our knowledge, no other studies have attempted to quantify the differences in associations between persons with and without diabetes. It has been hypothesized that diabetes only enhances mortality risk [96] and as a result persons with diabetes should benefit more from a healthy lifestyle [30], but from the existing literature, no indications were found that associations are different for persons with diabetes. Therefore, this thesis' second aim is to investigate whether these associations are different from individuals without diabetes.

1.6 Structure of the thesis

This first chapter has provided the rationale and objectives of the thesis. In chapter 2, the study design, study population and the methodology used to investigate the objectives are described. Chapter 3 provides the results of the associations of the selected lifestyle factors in persons with diabetes. For every studied lifestyle factor, first the associations within persons with diabetes are shown, second the differences in associations between persons with and without diabetes will be given. Next, in chapter 4 the results will be interpreted, put into context with the current literature, and the methodology will be discussed. Finally, in chapter 5, the overall conclusion and implications of this thesis will be described.

2. Subjects and Methods

2.1 Study design

2.1.1 The European Prospective Investigation into Cancer and Nutrition

The analyses were embedded into the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC is an ongoing multi-center prospective cohort study, designed to investigate the relationship between nutrition and cancer, with the potential for studying other diseases as well. The study currently includes 519,978 participants who were recruited from 1992 to 2000 in 23 centers located in ten European countries. The countries and study centers participating in the EPIC study are displayed in **Figure 2.1**. Study approval was obtained from the ethical review boards of the International Agency for Research on Cancer and from review boards at the local centers where participants were recruited. Participants were aged 35 to 70 years and were recruited predominantly from the general population residing in a given geographic area (town or province). There were, however, some exceptions to this recruitment scheme: the French cohort was based on members of the health insurance for teachers, components of the Italian and Spanish cohorts included members of local blood donor associations, the cohorts in Utrecht (the Netherlands) and Florence (Italy) included women invited for a local population-based breast cancer screening program. Furthermore, in Oxford (United Kingdom) half of the cohort was recruited among subjects who did not eat meat. In France, Norway, Utrecht (the Netherlands), and Naples (Italy) only women were recruited. Participants were invited either by mail or in person. Those who signed informed consent forms were mailed a diet questionnaire and a lifestyle questionnaire. Most participants completed these questionnaires at home and were then invited to a study center for an examination. This included collection of the two questionnaires, venipuncture, anthropometry, and blood pressure measurement [97].

2.1.2 Establishment of the Prevalent Diabetes Cohort in EPIC

Within EPIC, fifteen study centers from six countries provided additional data on diabetes diagnosis and medication. These study centers comprised Aarhus and Copenhagen (Denmark), Heidelberg and Potsdam (Germany), Florence, Milan, Naples, Ragusa, and Turin (Italy), Bilthoven and Utrecht (the Netherlands), Pamplona and San Sebastian (Spain), and Malmö and Umeå (Sweden). Self-reports of diabetes diagnosis obtained at baseline were confirmed by additional information sources. **Table 2.1** shows the number of participants by study center with a confirmed diagnosis of diabetes mellitus at study entry.

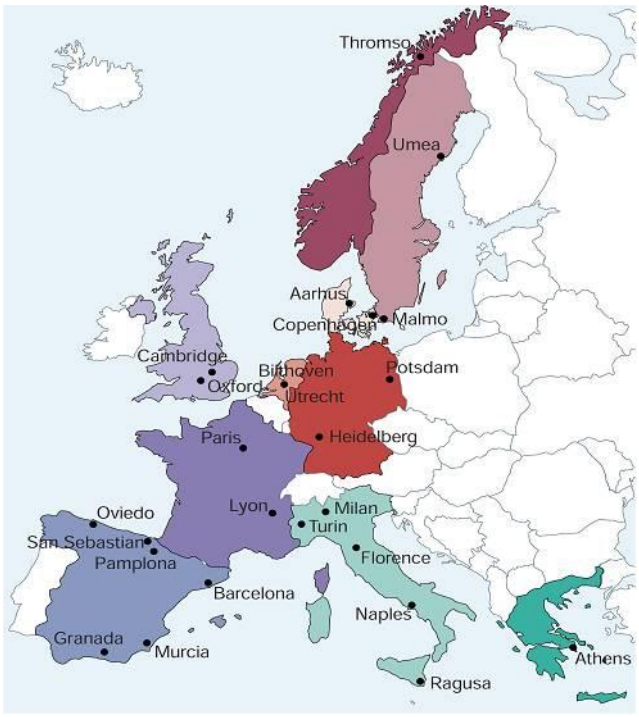

Figure 2.1: Countries Participating In The European Prospective Investigation into Cancer and Nutrition.

Of the initial 7,048 self-reports in the participating EPIC centers, 5,542 participants were confirmed to have had diabetes at baseline. Subsequently, 870 additional cases were included because they turned out to have been prevalent diabetes cases. This led to a cohort comprising 6,412 individuals with confirmed diabetes at study entry. The additional information sources used for verification varied by study center and include the following: contact to a medical practitioner, self-reported use of diabetes-related medication (e.g. use of insulin or oral hypoglycemic agents), repeated self-report during follow-up, linkage to diabetes registries, or a baseline HbA_{1c} above 6% (measured in Malmö only). **Table 2.2** gives an overview of the verification methods by study center.

2.2 Study population

The cohort comprised 6,412 individuals with confirmed diabetes at study entry. After exclusion of participants without follow-up information on vital status (n = 27), the analytical sample included 6,385 individuals with diabetes. Subsequently, EPIC participants without a verified or a self-reported diabetes diagnosis at baseline were randomly selected and matched 1:3 by age in 5-year categories, sex, and study center to the persons with diabetes. One person with diabetes was excluded, since only two matched controls were available. Thus, the analytical sample of this cohort study matched for potential confounding factors included 6,384 individuals with and 19,152 individuals without diabetes.

Table 2.1: Participants With Confirmed Diagnoses Of Diabetes Mellitus At Study Entry In The European Prospective Investigation Into Cancer And Nutrition.

Country	Center	Self-report of diabetes at baseline				False – self-report	Confirmed
		n	Verified as prevalent diabetes [a] (true + self-report)	Verified as not prevalent diabetes [b] (false + self-report)	Not verified [c]		
Italy	Florence	316	223	15	78	17	240
	Varese	273	142	0	131	0	142
	Ragusa	148	95	17	36	15	110
	Turin	139	132	0	7	60	192
	Naples	133	131	0	0	1	132
Spain	Navarra	223	191	0	32	22	213
	San Sebastian	473	298	0	175	28	326
Netherlands	Bilthoven	286	180	21	85	35	215
	Utrecht	492	311	0	181	48	359
Germany	Heidelberg	879	756	4	119	77	833
	Potsdam	1,310	1,106	76	128	226	1,332
Sweden	Malmö	855	629	0	226	54	683
	Umeå	317	195	18	104	110	305
Denmark	Aarhus	292	287	0	5	46	333
	Copenhagen	912	866	0	46	131	997
Total		7,048	5,542	153	1,355	870	6,412

[a] Diabetes mellitus was verified by contact to medical practitioner, confirmation of diagnosis based on use of diabetes related medication, or confirmation of diagnosis based on repeated self-report during follow-up, via repeated contact with the participant, HbA_{1c}, or by use of registries.
[b] No diagnosis of diabetes mellitus, incident diabetes mellitus, or a different disease related to carbohydrate - metabolism. It was not systematically looked for false positives
[c] Diabetes mellitus is not verified or verification was not possible.

2.3 Exposure and covariate assessment

2.3.1 Anthropometric data

Weight and height were measured with participants not wearing shoes. Waist circumference was measured either at the narrowest circumference of the torso (in Italy, Utrecht, Heidelberg, Denmark, and Spain) or at the midpoint between the lower ribs and iliac crest (in Bilthoven, Potsdam, and Malmö). Hip circumference was measured either horizontally at the widest circumference of the hips (in Italy, Spain, Bilthoven, and Malmö) or over the buttocks (in Utrecht, Germany, and Denmark). Since the amount of clothing worn during the measurement differed among study centers, each participant's body weight and waist and hip circumference were corrected in order to reduce heterogeneity due to these protocol differences. For participants who were normally dressed and without shoes 1.5 kg for weight and 2.0 cm for circumferences were subtracted from the original measurement (Utrecht and Turin), while for participants in light clothing without shoes 1 kg was subtracted from weight (Bilthoven and Malmö).

Table 2.2: Overview Verification Sources For Confirmed Cases Of Prevalent Diabetes.

Study Center	Verification						
	Verified by contact to a medical practitioner	Use of diabetes-related medication	Repeated self-report during follow-up or repeated contact to the participant	HbA_{1c} ≥ 6.0%	Contact with the general practitioner and use of diabetes-related medication	Patients in regional diabetes register but not the drug prescription database	Total
Florence	0	98	142	0	0	0	240
Naples	0	0	132	0	0	0	132
Ragusa	0	0	110	0	0	0	110
Turin	0	133	0	0	0	59	192
Varese	0	0	142	0	0	0	142
Navarra	194	2	17	0	0	0	213
San Sebastian	42	2	271	0	11	0	326
Bilthoven	179	36	0	0	0	0	215
Utrecht	337	22	0	0	0	0	359
Heidelberg	194	455	184	0	0	0	833
Potsdam	207	733	392	0	0	0	1,332
Malmö	0	0	223	460	0	0	683
Umeå	305	0	0	0	0	0	305
Aarhus	301	0	32	0	0	0	333
Copenhagen	900	0	97	0	0	0	997
Total	2,659	1,481	1,742	460	11	59	6,412

No corrections were made for the other study centers where participants were light underwear only [39]. Body mass index, waist/hip ratio, and waist/height ratio were calculated.

2.3.2 Dietary intake

Dietary intake during the previous 12 months was assessed at baseline by means of country-specific instruments that had been developed and validated in a series of studies within the various source populations. Extensive quantitative dietary questionnaires with up to 300 to 500 food items were used in Italy, the Netherlands, Germany, and Spain. Semi-quantitative questionnaires were used in Naples and combined dietary methods of food records and questionnaires were used in Malmö [97]. In addition, a highly standardized reference dietary measurement was taken from an 8% age-stratified random sample of the cohort (n = 36,994) using a computerized 24-hour dietary recall. Foods were organized into 39 food groups and food group intake was analyzed as predicted by regression calibration [98]. Analyses were performed on 26 meaningful food groups: potatoes, vegetables, fruit, legumes, nuts and seeds, milk and milk products, yogurt, cheese, pasta, rice, bread, breakfast cereals, red meat, processed meat, offals, poultry, fish and shellfish, eggs, vegetable oil, butter and margarine, sugar and confectionary, cakes and cookies, soft drinks, juices, tea, and coffee.

2.3.3 Alcohol consumption

2.3.3.1 Alcohol consumption at recruitment

Information on alcohol consumption at recruitment was obtained from a food frequency questionnaire applied during baseline examination, which asked about consumption of alcoholic beverages (cider, beer, wine, and spirits) during the previous 12 months. Detailed information obtained from the 24-hour dietary recall in the 8% sample of EPIC study participants was used to estimate the average alcohol content (grams/day) contained in "standard" glasses in the EPIC countries, as they provide information on the type of glass, glass volume, and levels of filling. The average alcohol content values were estimated at the country level, separately for men and women, and by weighting for weekday versus weekend day, and seasonality. In addition, the 24-hour dietary recall data were used to compute country-specific average volumes (ml) of alcohol into average intake (grams), according to the particular alcohol subtypes consumed in the different countries. The average alcohol content per glass was set at 12 grams and cut-points were used of >0-6 (0-0.5 glass, light consumption), >6-12 (0.5-1 glass), >12-24 (1-2 glasses), and in women >24 (≥2 glasses), and in men >24-60 (2-5 glasses), and >60 grams/day (≥5 glasses) [97, 99].

2.3.3.2 Lifetime alcohol consumption

Weekly consumption of wine, beer or cider, fortified wine, and liquor (spirits) was assessed retrospectively at the ages of 20, 30, 40, and 50 years in the lifestyle questionnaire. The study centers of Bilthoven, Naples, and Sweden did not include this question. To estimate alcohol consumption at different ages and recruitment, an algorithm was used that combined the information available on the length of time alcohol was consumed and the amount of alcohol consumed at these different ages for a given period. Rather than estimating the average lifetime consumption as a simple mean of alcohol intake at ages 20, 30, 40, etc. which would not capture information on different time lengths between ages where information is available, it was decided to incorporate calculated time lengths of alcohol consumption. Prior alcohol consumption was defined as none, always moderate, and sometimes heavy consumption. Heavy consumption was defined as consuming 2.5 times the upper recommended limit at certain ages, i.e. >30 grams/day in women and >60 grams/day in men. The amount of alcoholic beverages consumed in history by comparable age cohorts at certain ages was validated by comparison of self-reported data with the respective per capita measures from 1950 to 1995. Ethanol intake estimates were on average around 72% compared with the per capita consumption data; only small differences in reproducibility between the various techniques existed and ranking individuals according to intake was acceptable [100].

2.3.4 Physical activity

At baseline, participants received a lifestyle questionnaire by mail, which they completed at home. This questionnaire asked about occupational activity, and duration and frequency of walking, cycling, gardening (average values of summer and winter), household work, do-it-yourself activities, and sports during the previous 12 months.

2.3.4.1 Total physical activity

Total physical activity was investigated with the Cambridge Physical Activity Index [101], which combines self-reported occupational activity with time participating in cycling and sports. Occupational activity was categorized as sedentary, standing, manual, or heavy manual occupation. The sum of hours per week spent on cycling and sports were categorized in four levels. Based on a four-by-four matrix, participants were divided into four categories, i.e. inactive (sedentary job and no recreational activity), moderately inactive, moderately active, and active (sedentary job with >1 h recreational activity per day, standing or physical job with some recreational activity, or a heavy manual job). The index has been shown to have an acceptable repeatability (weighted kappa = 0.60) and it was positively associated with objective measures of the ratio of daytime expenditure to resting metabolic rate (*P*-trend = 0.003) and cardiorespiratory fitness (*P*-trend = 0.001) [101].

2.3.4.2 Leisure-time physical activity

Leisure-time physical activity included walking, cycling, gardening, sports, household work, and do-it-yourself activities. Duration and frequency were directly assessed and intensity, i.e. energy expenditure, was estimated by assigning metabolic equivalents (MET), ranging from 3 for walking and household activities to 6 for sports [26]. MET is defined as the ratio of work metabolic rate to a standard metabolic rate of 1.0 kcal (4.184 kJ)*kg-1*h-1. One MET is the energy expended by a person while sitting quietly. The Compendium of Physical Activities has assigned intensity codes to a wide range of activities from sleeping (0.9 METs) to running at high speed (18 METs). Using MET-hours per week makes it possible to compare and equally treat activities with different intensities in the analyses [102].

2.3.4.3 Walking

Hours per week spent in walking was assessed in the questionnaire separately for summer and winter. Subsequently, the intensity was assigned with the MET conversion method as outlined above. A mean variable of walking in summer and winter expressed in MET-hours/week was used in the analyses.

2.3.5 Diabetes medication

Information on insulin therapy or use of oral hypoglycemic agents was either self-reported at the visit to the study center or obtained during medical verification. Medication use was classified according to the Anatomical Therapeutic Chemical classification of the World Health Organization in the following categories: no medication use, insulin therapy and of oral hypoglycemic agents, insulin therapy, or of oral hypoglycemic agents use. In addition, the lifestyle questionnaire included a question on insulin therapy. Medication use classified according to the Anatomical Therapeutic Chemical classification was not available for Spain and Denmark and medication use was set to missing for participants from these countries. For the other study centers, when a participant did not report the use of diabetes medication during the visit to the study center or report insulin therapy in the questionnaire, we assumed the participant did not take any diabetes medication.

2.3.6 Disease duration

Duration since diabetes diagnosis was calculated by subtracting the self-reported year of diagnosis or, when available, the exact date of diagnosis supplied by the medical practitioner from the age at baseline examination. For participants who reported an older age at diabetes diagnosis than their respective age at recruitment, the disease duration was set to missing.

2.3.7 HbA_{1c} measurement

HbA_{1c} was measured in July 2010 in erythrocytes of blood which was drawn at baseline between 1991 and 1998 in 4,345 participants from the study centers of Germany, Italy, the Netherlands, Spain, and Sweden. Blood samples were stored at -80°C and a part of blood samples from the Netherlands and Italy was stored at -196°C. For all centers except Potsdam, both HbA_{1c} and hemoglobin were measured on an auto-analyzer (LX20-Pro, Beckman-Coulter). In Potsdam, HbA_{1c} was measured with the automatic ADVIA 1650 analyzer (Siemens Medical Solutions, Erlangen, Germany) in November 2008.

2.3.8 Blood pressure measurement

Systolic and diastolic blood pressure was measured in millimeters of mercury by trained personnel at baseline. Two readings were performed on the right arm in a sitting position (spaced by 1–5 minutes) after an initial resting time of at least 5 minutes by use of a standard mercury manometer or oscillometric device. Exceptions were the Swedish centers where one single measurement was taken in the supine position.

2.3.9 Other lifestyle and health-related variables

Further lifestyle and health-related variables were collected using questionnaires, with close to identical questions translated for the different countries. These questionnaires included questions on smoking history (i.e. smoking status, duration, and intensity), educational attainment, and medical history including prevalent heart disease, stroke, and cancer.

2.4 Outcome ascertainment

Causes and dates of deaths were ascertained using record linkages with local, regional, or central cancer registries, boards of health, or death indexes (Denmark, Italy, the Netherlands, Spain, and Sweden). Germany identified deceased participants with follow-up mailings through participants and their next of kin and subsequent inquiries to municipality registries, regional health departments, physicians, or hospitals. Mortality data were coded according to the International Classification of Diseases, Injuries and Causes of Death, Tenth Revision (ICD-10). For the cause-specific analyses, deaths due to circulatory diseases (ICD-10 I00-I99), cancer (ICD-10 C00-D48), and all other known causes were grouped accordingly. Deaths where the specific cause was unavailable were not included in the cause-specific analysis (n = 237 excluded).

2.5 Statistical analyses

2.5.1 Cox proportional hazard regression

Statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC). Hazard ratios (HR) and 95% CI of CVD and total mortality were calculated with Cox proportional hazard regression (PROC PHREG). This method is preferred over the logistic model when survival time information is available and censoring is present because the occurrence of the event and the time to the event are taken into account. Effect estimates are given as hazard ratios, the ratio of the instantaneous risk of death at a certain time, given that the individual has survived up to that time, for exposed compared with unexposed individuals [103]. In the analyses within persons with diabetes, center and age at recruitment in 1-y categories were entered as stratum variables to control for differences in questionnaire design, follow-up procedures, and other non-measured center effects, and to be more robust against violation of the proportionality assumption. Age was used as the primary time variable with entry time defined as the subject's age in years at recruitment and exit time defined as the subject's age in years at death or censoring (lost to follow-up or the end of follow-up period). Age has been recommended to be used in Cox regression as the underlying time scale because using time-on-study may lead to biased relative risk estimates [104]. Median values within categories were modeled as continuous variables in Cox regression to test for trend.

Body mass index, waist circumference, waist/hip ratio, and waist/height ratio were analyzed in sex-specific quintiles, using the first as reference. Selected food group intake was energy adjusted with the residual method [105]. Food groups were analyzed in quartiles, using the first as reference. Sex-specific categories of baseline alcohol consumption were defined as outlined earlier, using light alcohol consumption as a reference category. In addition, hazard ratios were calculated using non-consumers as a reference category. Total physical activity was analyzed in four categories ranging from inactive to active; using inactive as reference. Leisure-time physical activity and walking were divided into quartiles of MET-hours per week, using the first quartile as reference.

2.5.2 Confounder selection

Putative confounding factors were selected using directed acyclic graphs (DAG) which is a combination of graphical probability theory with causal path diagrams which helps understanding confounding and selection bias and selecting covariates for adjustment subsequently [106]. **Figure 2.2 – 2.5** display the DAGs of the separate study questions, composed with DAGitty program [107]. A minimal sufficient adjustment set of covariates was selected using the DAG program v0.20 [108]. These minimal sufficient adjustment sets included the following covariates, listed per lifestyle variable:

- Adiposity: age, gender, severity of the disease, co-morbidities, diet, physical activity, alcohol consumption, and smoking behavior;
- Diet: age, gender, severity of the disease, co-morbidities, socio-economic status (SES), physical activity, alcohol consumption, and smoking behavior;
- Alcohol consumption: age, gender, severity of the disease, co-morbidities, socio-economic status, diet, physical activity, and smoking behavior;
- Physical activity: age, gender, severity of the disease, co-morbidities, socio-economic status, diet, alcohol consumption, and smoking behavior;

Competing DAGs were drawn and analyzed, but did not lead to a different minimal sufficient adjustment set of covariates.

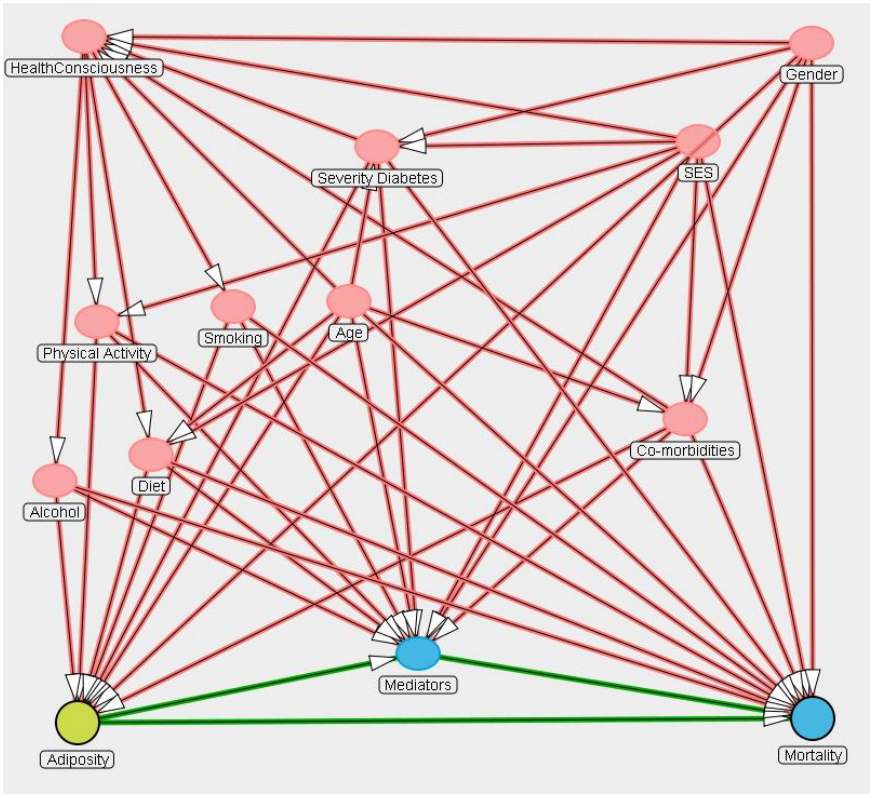

Figure 2.2: Directed Acyclic Graph For The Association Between Adiposity And Mortality.

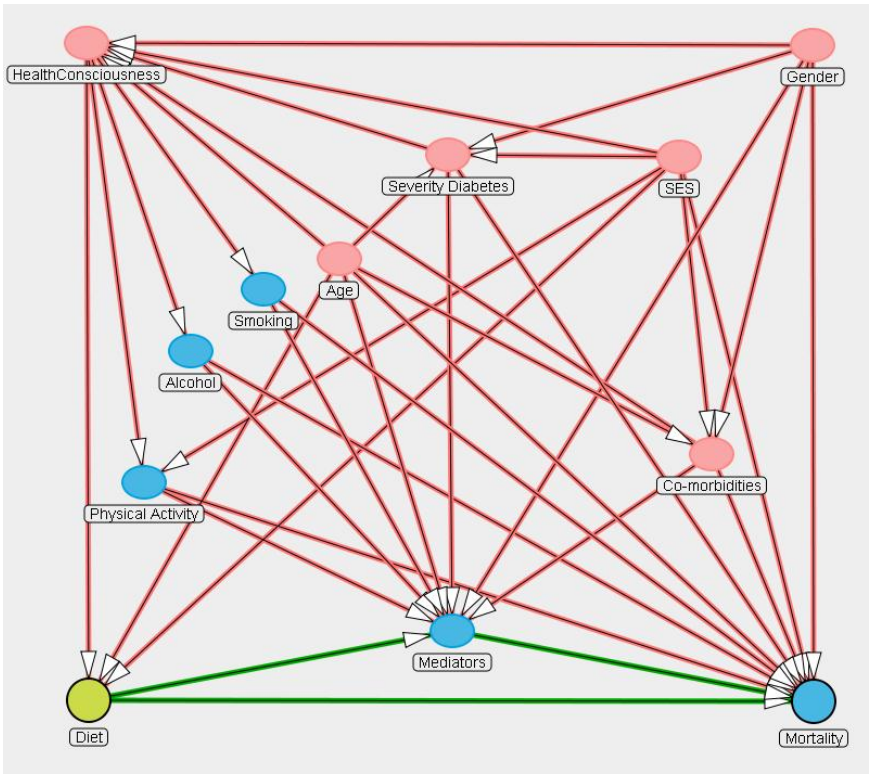

Figure 2.3: Directed Acyclic Graph For The Association Between Diet And Mortality.

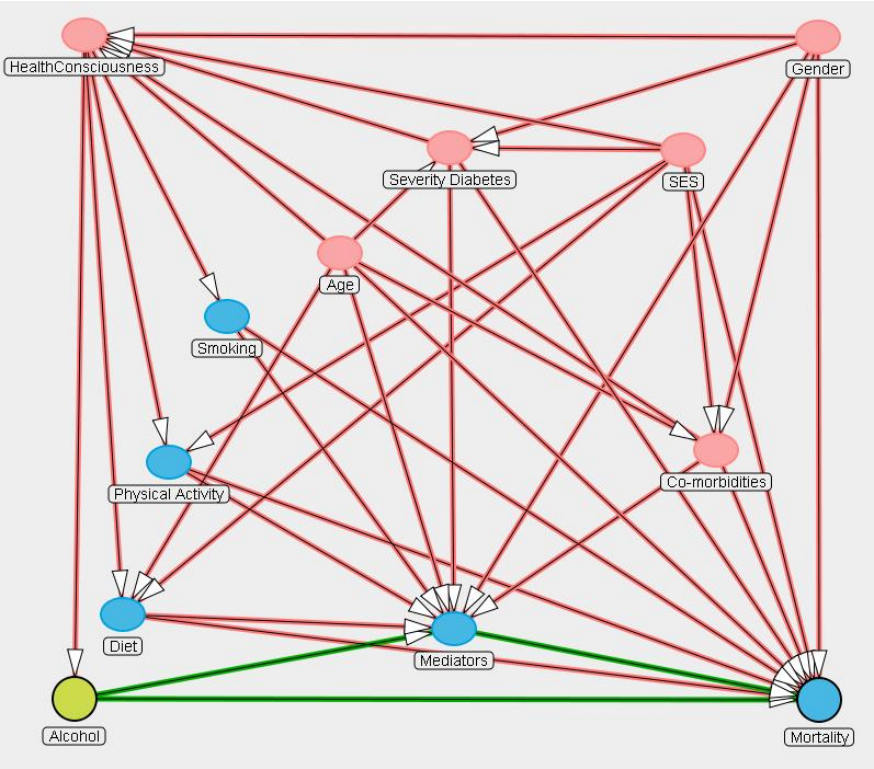

Figure 2.4: Directed Acyclic Graph For The Association Between Alcohol Consumption And Mortality.

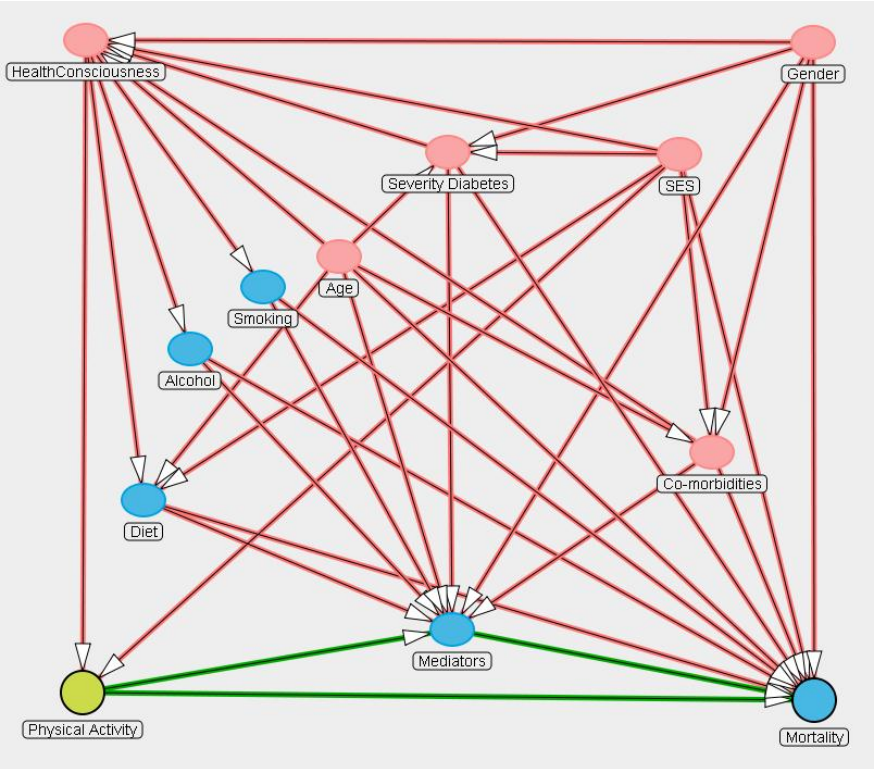

Figure 2.5: Directed Acyclic Graph For The Association Between Physical Activity And Mortality.

2.5.3 Confounder adjustment

Categorical covariates were included in the model as joint indicator variables. Severity of the disease was operationalized in disease duration (years), medication use (categories of none, use of oral hypoglycemic agents, use of both insulin and oral hypoglycemic agents, and insulin use), and HbA_{1c}. Although HbA_{1c} can be considered as a mediating factor, it can also be seen as an objective measurement of glycemic control. Because disease duration and medication use were self-reported, we decided to include adjustment for HbA_{1c} for all lifestyle factors as an additional indication of the severity of the disease. Co-morbidities were modeled as self-reported heart disease, stroke, or cancer at baseline (yes/no). As an indicator of socio-economic status, it was adjusted for educational attainment in the categories none, primary school, secondary school, technical or professional school, and higher (including university degree). Alcohol consumption was modeled in grams/day and physical activity in four categories ranging from inactive to active. Smoking behavior was adjusted for as never, former (quit ≤ 10 y ago, 11-20 y ago, >20 y ago), or current (smoking duration ≤ 10 y, 11-20 y, 21-30 y, 31-40 y, and >41 y, <15, 15-24 or >25 cigarettes smoked daily). To adjust for diet, principal component analysis using PROC FACTOR was performed on 27 food groups. The individual scores for the first three derived factors (dietary patterns) were used for adjustment. The factor scores and loadings for the first three dietary patterns are shown in **Table 2.3**. The associations between food group consumption and mortality were also adjusted for study center to take into account differences in food group consumption between countries.

In an extra model, the associations for body mass index were additionally adjusted for quintiles of waist/height ratio, and measures of abdominal adiposity were additionally adjusted for quintiles of body mass index. Associations between food group consumption and mortality were additionally adjusted for body mass index and waist/height ratio as well as for other food groups. These food groups were selected using stepwise regression and the presence of collinearity among independent variables was tested measuring the variance inflation factor in linear regression analysis. Furthermore, the mortality risks associated with alcohol consumption were additionally adjusted for past alcohol consumption, categorized as none, always moderate, and sometimes heavy.

2.5.4 Missing values

Proportions of missing data were similar between persons with and without diabetes and were <1% for BMI, 6% for waist/height ratio, 2% for diet, <1% for alcohol consumption, 6% for physical activity, <1% for smoking status, <1% for education, 1% for prevalent heart disease, 6% for prevalent stroke, and 10% for prevalent cancer. Among persons with diabetes, 32% had no measured HbA_{1c}, 29% had missing data on medication and 9% on disease duration. Missing values for the exposure variables or any of the covariates were imputed using the multiple imputation method, which aims to take into account the uncertainty about missing data by creating several different plausible imputed datasets and appropriately

Table 2.3: Eigenvalues And Factor Loadings Of The First Three Patterns Derived With Factor Analysis On 27 Food Groups In 6,384 Persons With Diabetes.

	Factor 1	Factor 2	Factor 3
Eigenvalue	3.94	3.74	2.89
Food group	*Scores*	*Scores*	*Scores*
Potatoes	-0.44699	0.10956	0.52090
Vegetables	0.55490	0.34522	-0.06286
Legumes	0.42380	0.66665	-0.16225
Fruits	0.54986	0.26566	-0.23472
Nuts and seeds	0.23745	-0.24993	0.11100
Dairy			
- Milk and milk products	-0.16408	0.33100	0.06368
- Yogurt	-0.23217	-0.02837	0.06905
- Cheese	0.18637	-0.43041	0.46175
Cereal products			
- Pasta	0.73523	-0.33765	-0.10915
- Rice	0.56689	-0.08785	0.04937
- Bread	0.15623	0.10642	0.72177
- Breakfast cereals	-0.32376	0.12468	0.13811
Meat			
- Red meat	0.28768	0.55953	0.44692
- Processed meat	-0.12998	-0.06876	0.62748
- Poultry	0.70225	0.38316	0.03437
- Offals	0.46599	0.12322	0.07117
Fish and shellfish	0.17069	0.83357	0.04975
Eggs	0.05629	0.75892	0.18431
Fats and oils			
- Vegetable oils	0.65260	0.60695	-0.28500
- Butter	0.01225	-0.31799	0.23918
- Margarine	-0.51533	-0.07530	0.47431
Sugar and confectionary	-0.20694	-0.16696	0.46303
Cakes and cookies	-0.07140	-0.46916	0.20683
Non-alcoholic beverages			
- Juices	-0.02742	-0.29244	0.19950
- Soft drinks	-0.07313	0.03427	0.42464
- Coffee	-0.44553	-0.09407	0.46842
- Tea	-0.04251	-0.14081	0.21336

combining results obtained from each of them. All variables (exposure, outcome, and covariates) included in the full Cox proportional hazard models were also included in the procedure. Although some of these variables did not have missing values, they could be predictive of the missingness or influence the process causing the missing data. Twenty duplicate datasets were produced and after statistical inference on the duplicate datasets, a pooled hazard ratio was calculated with PROC MIANALYZE [109].

2.5.5 Comparison with persons without diabetes

A survival curve was drawn stratified by diabetes status and a log-rank test was used to test for differences between persons with and without diabetes. Hazard ratios and 95% confidence intervals of all-cause mortality were calculated with Cox proportional hazard regression [103] where the matching factors sex, study center and age at recruitment in 5-y categories were entered as stratum variables.

Based upon the ideas and methodology of the competing risk model [110] and a statistical test for the equality of differently adjusted incidence rate ratios [111] was used to quantify differences in associations between lifestyle and mortality risk between individuals with and without diabetes. The competing risk model is an extension of the Cox proportional hazards model, built to fit a single model for mortality, assuming different associations of each risk factor with each specific cause of mortality. In this case, a joint model was built where different associations were assumed of persons with and without diabetes with lifestyle factors and overall mortality. Multiplication of the covariates with a variable for diabetes status resulted in exclusion of the covariates for persons with diabetes in the model for the persons without diabetes and vice versa although they were all included in the joint model. Robust sandwich estimates for the covariance matrix were not calculated, since the observations were not dependent. Diabetes status was entered as stratum variable to allow the baseline hazard functions to have no constant ratio. Subsequently, Likelihood ratio tests for heterogeneity were used to quantify differences in associations between lifestyle and mortality risk between individuals with and without diabetes. The hypothesis for this test reads that the two hazard ratios for persons with and without diabetes are equal. The SAS Syntax written and used for this procedure is shown in **Box 2.1**.

Lifestyle factors were divided into diabetes-unspecific quantiles. Hazard ratios from age-, sex- and center-stratified Cox models were adjusted for sex, self-reported heart disease, stroke, or cancer, educational attainment, alcohol consumption, total physical activity, smoking status, duration and number of cigarettes smoked daily, and diet, when these were no exposure variables. In persons with diabetes, hazard ratios were additionally adjusted for disease duration and use of diabetes-related medication.

2.5.6 Sensitivity analyses

To investigate the robustness of the results for the selected lifestyle factors and mortality risk in persons with diabetes, sensitivity analyses were performed. Because co-morbidities can confound the association between adiposity, diet, alcohol consumption, and physical activity, participants were excluded who reported prevalent heart disease, stroke, or cancer at baseline as well as those with a follow-up time shorter than two years (n = 874 excluded). Moreover, results were compared with results from analyses without multiple imputation to see whether missing observations influenced the effect estimates. For these analyses, subjects with missing data in continuous variables were excluded and missing values for categorical variables were modeled as a separate indicator variable. It was chosen not to adjust for HbA_{1c} to prevent a large power reduction by exclusion of too many subjects.

Box 2.1 SAS Syntax To Test For Differences In Associations Between Lifestyle Factors And Mortality Risk In Persons With And Without Diabetes.

SAS Syntax

```
DATA b;
        SET a;
        Exposure_D = Exposure*ccid;
        Exposure_N = Exposure*(1-ccid);
        Confounder_D = Confounder*ccid;
        Confounder_N = Confounder*(1-ccid);
        *ccid is the coding variable for diabetes: 1=yes, 0=no;
RUN;
```

```
PROC PHREG DATA=b NOSUMMARY OUTEST=c COVOUT NOPRINT;
        STRATA ccid age_categories center sex;
        MODEL (age_recruitment, age_exit)*mortality(0) = Exposure_D Exposure_N
        Confounder_D Confounder_N / RL;
        BY _imputation_;
RUN;
```

```
PROC MIANALYZE DATA=c EDF=510719;
        MODELEFFECTS Exposure_D Exposure_N;
        TEST: TEST Exposure_D = Exposure_N;
RUN;
```

Next, for the comparison of the associations between persons with and without diabetes, those with co-morbidities at baseline were excluded (n = 874 diabetics and n = 5,520 non-diabetics excluded). Moreover, it was checked whether excluding energy misreporting (those who were in the top and bottom 1% of the ratio of energy intake to energy requirement) influenced the results on the difference in associations on food groups (n = 177 diabetics and n = 352 non-diabetics excluded).

3. Results

3.1 General characteristics

3.1.1 Prevalent Diabetes Cohort

The Prevalent Diabetes Cohort consisted of 6,384 individuals with diabetes (**Table 3.1**). A small majority (54%) was male and the mean age was 57.4 years. Median disease duration was 4.9 years and the majority of the cohort was diagnosed after they reached the age of 50. Most participants (43%) reported to use oral hypoglycemic agents, 17% used insulin, and 33% reported to not use any diabetes medication. The participants reported a median daily consumption of 85 grams potatoes, 157 grams vegetables, 137 grams milk and milk products, 128 grams bread, 50 grams red meat, and 487 ml of coffee. Mean body mass index was 28.9 kg/m^2, most participants were moderately inactive (31%) and never smoker (39%), and had a median alcohol consumption of 5.5 grams/day.

Compared with men, women had a slightly higher HbA_{1c}, were more likely to be diagnosed with diabetes longer ago and to use insulin than oral hypoglycemic agents. Moreover, women had a higher body mass index, but lower measures of abdominal adiposity than men. Men had a higher intake of all food groups except for tea, had higher alcohol consumption, and were more likely to be a current or former smoker and to have a history of heart disease. However, they were also more likely to be physically active and to be higher educated than women.

After a median follow-up of 9.5 years [Inter-Quartile Range 8.1–10.7 years], 830 (13%) participants died. Twenty-eight percent (n = 233) of the deaths was due to CVD, 20% (n = 170) was due to cancer, 23% (n = 190) due to other and external causes, and for 29% (n = 237) the cause of death was not yet verified or the cause was unknown. Deceased participants were older, had a higher HbA_{1c}, longer disease duration, and were more likely to use diabetes medication. Moreover, they had higher measures of abdominal, but not general, adiposity compared to the surviving participants. Furthermore, they were more likely to have co-morbidities and a higher blood pressure than their surviving counterparts and had more unfavorable lifestyle factors, including a lower intake of fruit, vegetables, higher alcohol consumption and being more likely to be inactive and a current smoker.

Table 3.1: General Characteristics Of 6,384 Individuals With Diabetes Mellitus.

	All	Men	Women	Alive	Deceased
N (% male)	6,384 (54)	3,453	2,931	5,554 (52)	830 (67)
Age, y	57.4 (6.7)	57.2 (6.4)	57.7 (6.9)	56.9 (6.7)	60.6 (5.7)
HbA_{1c}, %	8.1 (1.7)	8.0 (1.7)	8.1 (1.7)	8.0 (1.7)	8.5 (1.7)
Age at diagnosis, y	51 [45-57]	51 [45-56]	51 [45-57]	51 [45-56]	53 [48-58]
Disease duration, y	4.9 [2.1-10.0]	4.6 [2.1-9.7]	5.2 [2-10]	4.8 [2.1-9.9]	5.3 [2.5-10.5]
Medication use, n (%)					
- No	33	34	31	34	34
- OHA	43	45	41	42	42
- OHA and insulin	6	5	8	6	6
- Insulin	17	15	19	17	17
Body Mass Index, kg/m^2	28.9 (4.9)	28.5 (4.3)	29.4 (5.6)	28.9 (4.9)	28.7 (5.1)
Waist circumference, cm	96.5 (13.1)	100.3 (11.5)	92.1 (13.4)	96.2 (13.0)	99.0 (13.3)
Waist/hip ratio	0.92 (0.09)	0.98 (0.07)	0.86 (0.07)	0.92 (0.09)	0.95 (0.09)
Waist/height ratio	0.58 (0.08)	0.58 (0.07)	0.57 (0.09)	0.58 (0.08)	0.58 (0.08)
Blood pressure, mmHg					
- Systolic	144.7 (20.9)	145.1 (20.4)	144.2 (21.4)	143.8 (20.5)	150.5 (22.1)
- Diastolic	85.4 (11.0)	86.5 (11.2)	84.1 (10.7)	85.4 (11.0)	85.7 (11.3)
Food group intake, g/d					
Potatoes	85 [60-116]	102 [70-134]	74 [49-91]	83 [57-112]	99 [77-133]
Vegetables	157 [129-192]	158 [130-194]	157 [129-191]	159 [132-195]	142 [114-171]
Legumes	3 [0-7]	3 [0-7]	3 [0-6]	3 [0-7]	1 [0-5]
Fruit	193 [133-281]	175 [116-274]	209 [153-284]	198 [137-287]	158 [111-221]
Nuts and seeds	1 [0-2]	1 [0-2]	1 [0-3]	1 [0-3]	0 [0-1]
Dairy					
- Milk and milk products	137 [64-238]	132 [62-245]	142 [70-224]	135 [64-233]	153 [66-267]
- Yogurt	32 [3-71]	25 [0-66]	41 [12-75]	32 [4-71]	30 [0-74]
- Cheese	31 [24-39]	34 [26-43]	27 [22-36]	31 [24-40]	31 [23-39]
Grains					
- Pasta	16 [8-34]	17 [7-38]	15 [22-36]	17 [9-37]	11 [0-21]
- Rice	10 [6-17]	11 [5-17]	10 [6-15]	11 [6-17]	8 [0-13]
- Bread	128 [100-164]	151 [122-184]	104 [86-130]	128 [100-164]	127 [100-164]
- Breakfast cereals	0 [0-6]	0 [0-8]	0 [0-5]	0 [0-5]	0 [0-16]
Meat					
- Red meat	50 [38-66]	61 [49-77]	39 [31-49]	50 [37-66]	54 [40-69]
- Processed meat	49 [34-70]	66 [51-82]	36 [24-45]	48 [33-70]	56 [40-72]
- Poultry	16 [11-23]	17 [13-25]	14 [10-20]	16 [11-24]	14 [10-19]
- Offals	1 [0-2]	1 [0-3]	1 [0-2]	1 [0-2]	0 [0-2]
Fish and shellfish	27 [18-41]	32 [21-48]	24 [16-34]	27 [18-41]	33 [21-45]
Eggs	13 [10-18]	14 [11-20]	12 [9-16]	13 [10-18]	14 [11-20]
Fats and oils					
- Vegetable oil	2 [1-5]	3 [1-5]	2 [1-5]	3 [1-6]	2 [0-3]
- Butter	1 [0-7]	1 [0-9]	1 [0-5]	1 [0-7]	0 [0-7]
- Margarine	16 [2-31]	23 [3-39]	11 [2-23]	15 [2-29]	25 [11-37]
Sweets and confectionary	27 [19-36]	29 [19-39]	25 [19-31]	26 [19-36]	30 [21-38]
Cakes and cookies	42 [33-53]	43 [33-55]	42 [35-51]	43 [34-53]	41 [30-53]
Non-alcoholic beverages					
- Soft drinks	9 [0-104]	15 [0-124]	3 [0-85]	4 [0-99]	44 [0-149]
- Juices	34 [0-97]	39 [2-103]	28 [0-86]	34 [0-98]	28 [0-91]
- Tea	25 [0-151]	18 [0-120]	34 [0-183]	28 [0-154]	3 [0-135]
- Coffee	487 [211-664]	542 [290-754]	454 [166-605]	481 [181-654]	548 [370-771]
Alcohol, g/d	5.5 [0.5-20.2]	12.5 [3.2-33.1]	1.4 [0-6.9]	5.4 [0.5-19.9]	6.2 [0.5-23.2]

	All	Men	Women	Alive	Deceased
Total physical activity, n (%)					
- Inactive	29	25	34	28	39
- Moderately inactive	31	30	33	32	29
- Moderately active	21	23	18	21	16
- Active	19	21	16	19	17
Leisure-time physical activity, n (%)					
- Low	26	36	15	25	35
- Medium	23	27	18	22	25
- High	25	21	29	25	23
- Very high	26	16	37	27	16
Walking, MET-hours/week	15 [6-29]	15 [6-30]	14 [6-27]	15 [6-30]	12 [5-27]
Smoking status, n (%)					
- Never	39	25	56	41	25
- Former	36	45	25	35	40
- Current	25	30	19	24	35
Educational attainment, n (%)					
- None	4	4	4	4	2
- Primary school	42	39	46	41	48
- Secondary school	27	26	28	27	26
- Techn./prof. school	11	9	13	12	8
- Longer (incl. University)	16	23	9	16	16
Co-morbidities, n (%)					
- Hypertension	55	54	58	55	61
- Heart disease	7	9	4	5	17
- Stroke	4	4	3	3	10
- Cancer	4	3	5	4	6

Continuous variables are shown as mean (standard deviation) when normally distributed and median [Inter-Quartile Range] when not normally distributed. Categorical variables are shown as percentages.

3.1.2 Persons with and without diabetes

After a median follow-up of 9.5 years [Inter-Quartile Range 8.1–10.7 years], 830 (13%) persons with diabetes died and 1,338 (7%) persons without diabetes. Compared with persons without diabetes, the persons with diabetes had a higher body mass index and waist/height ratio (**Table 3.2**). Persons with diabetes had a lower alcohol consumption, were more likely to be physically inactive, to be lower educated, and to be a former smoker compared with their non-diabetic counterparts. In addition, prevalence of hypertension and heart disease was higher among persons with diabetes.

Table 3.2: General Characteristics Of 6,384 Persons With Diabetes And 19,152 Comparable Persons Without Diabetes From The European Prospective Investigation Into Cancer And Nutrition.

	Diabetics	Non-diabetics
n	6,384	19,152
Age, y	57.4 (6.7)	57.0 (6.9)
Male, %	54	54
Body Mass Index, kg/m²	28.9 (4.9)	26.5 (3.9)
Waist/height ratio	0.58 (0.08)	0.53 (0.07)
Food group intake, g/d		
Potatoes	85 [60-116]	84 [59-117]
Vegetables	157 [129-192]	151 [124-181]
Fruit	193 [133-281]	193 [131-281]
Legumes	3 [0-7]	4 [0-7]
Nuts and seeds	1 [0-2]	1 [0-3]
Dairy		
- Milk and milk products	137 [64-238]	131 [67-232]
- Cheese	31 [24-39]	31 [24-39]
- Yogurt	32 [3-71]	33 [8-70]
Grains		
- Pasta	16 [8-34]	17 [10-35]
- Rice	10 [6-17]	11 [6-17]
- Bread	128 [100-164]	127 [100-162]
- Breakfast cereals	0 [0-6]	0 [0-9]
Meat		
- Red meat	50 [38-66]	48 [35-63]
- Processed meat	49 [34-70]	46 [32-67]
- Poultry	16 [11-23]	15 [11-22]
- Offals	1 [0-2]	1 [0-2]
Fish and shellfish	27 [18-41]	27 [18-40]
Eggs	13 [10-18]	13 [10-18]
Fats and oils		
- Vegetable oil	2 [1-5]	2 [1-4]
- Butter and margarine	22 [7-37]	23 [8-38]
Sugar and confectionary	27 [19-36]	35 [26-44]
Cake and cookies	42 [34-53]	49 [39-63]
Non-alcoholic beverages		
- Soft drinks	9 [0-104]	14 [0-88]
- Juices	33 [0-96]	47 [12-111]
- Tea	26 [0-151]	35 [0-160]
- Coffee	487 [211-664]	491 [234-657]
Alcohol consumption, g/d	5 [1-20]	10 [2-24]
Physical activity, %		
- Inactive	29	20
- Moderately inactive	31	32
- Moderately active	19	21
- Active	16	21
Smoking status, %		
- Never	39	42
- Former	28	19
- Current	25	25

	Diabetics	Non-diabetics
Blood pressure, mmHg		
- Systolic	145 (21)	136 (20)
- Diastolic	85 (11)	84 (10)
Educational attainment, %		
- None	4	3
- Primary school	42	34
- Secondary school	27	27
- Technical/prof. school	11	14
- Higher (incl. University)	16	22
Co-morbidities, %		
- Hypertension	55	35
- Heart disease	7	2
- Stroke	4	1
- Cancer	4	4

Continuous variables are shown as mean (standard deviation) when normally distributed and median [Inter-Quartile Range] when not normally distributed. Categorical variables are shown as percentages.

3.1.3 All-cause and cause-specific mortality risk when having diabetes

Persons with diabetes had a higher mortality risk compared with persons without diabetes (**Figure 3.1** and **Table 3.3**). Unadjusted all-cause mortality risk among persons with diabetes was HR 1.94 (95% CI 1.78, 2.11). Exclusive adjustment for lifestyle factors reduced the hazard ratio from 1.75 (95% CI 1.60, 1.92) in model 2 to 1.54 (95% CI 1.41, 1.70) in model 3, suggesting that lifestyle explained 23% of the mortality risk in diabetes. Risk of mortality due to CVD and other causes, but not cancer, was increased. After adjustment for lifestyle factors, mortality risk was slightly higher in men compared with women.

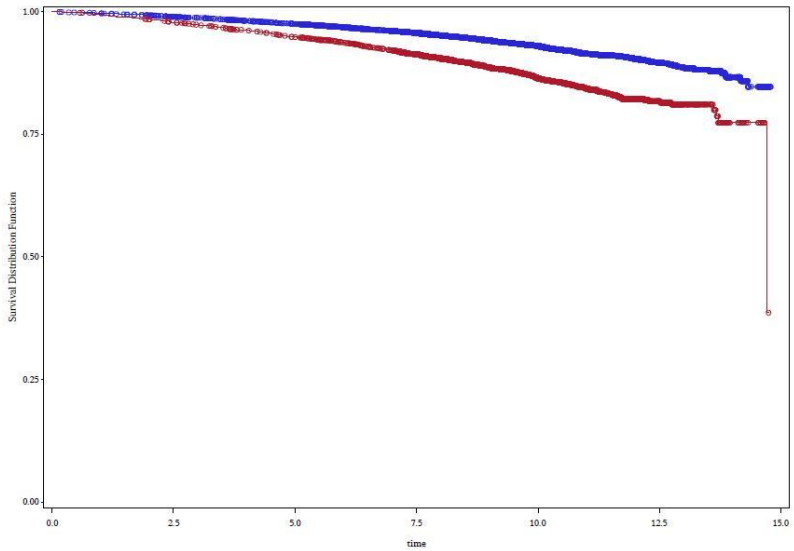

Figure 3.1 Survival Curves Of 6,384 Persons With Diabetes (red) Versus 19,152 Persons Without Diabetes (blue). P-Value Of Log-rank Test <.0001.

Table 3.3: All-Cause And Cause-Specific Mortality Risk Of Diabetes Mellitus Among 6,384 Persons With Diabetes And 19,152 Persons Without Diabetes.

	Total mortality	Cause-specific mortality			P for differences		
		CVD	*Cancer*	*Other causes*	*CVD vs. cancer*	*CVD vs. other*	*Cancer vs. other*
All							
HR (95% CI)[a]	1.94 (1.78, 2.11)	2.47 (2.08, 2.93)	1.06 (0.89, 1.26)	3.14 (2.57, 3.84)	<.0001	0.08	<.0001
HR (95% CI)[b]	1.75 (1.60, 1.92)	2.07 (1.74, 2.47)	1.03 (0.86, 1.22)	2.81 (2.29, 3.46)	<.0001	0.03	<.0001
HR (95% CI)[c]	1.54 (1.41, 1.70)	1.72 (1.43, 2.08)	0.96 (0.80, 1.15)	2.50 (2.00, 3.13)	<.0001	0.01	<.0001
Men							
HR (95% CI)[a]	1.93 (1.74, 2.15)	2.41 (1.97, 2.95)	1.09 (0.87, 1.36)	2.87 (2.25, 3.66)	<.0001	0.28	<.0001
HR (95% CI)[b]	1.74 (1.56, 1.94)	2.02 (1.64, 2.48)	1.04 (0.83, 1.31)	2.60 (2.02, 3.34)	<.0001	0.13	<.0001
HR (95% CI)[c]	1.58 (1.44, 1.77)	1.73 (1.38, 2.15)	1.00 (0.80, 1.26)	2.36 (1.81, 3.08)	0.001	0.08	<.0001
Women							
HR (95% CI)[a]	1.95 (1.67, 2.27)	2.63 (1.91, 3.63)	1.02 (0.77, 1.35)	3.81 (2.66, 5.45)	<.0001	0.13	<.0001
HR (95% CI)[b]	1.78 (1.53, 2.09)	2.15 (1.54, 3.00)	1.00 (0.75, 1.33)	3.35 (2.31, 4.88)	0.001	0.08	<.0001
HR (95% CI)[c]	1.50 (1.26, 1.79)	1.83 (1.27, 2.62)	0.88 (0.64, 1.21)	3.07 (1.99, 4.72)	0.003	0.07	<.0001

[a] Model 1: Stratified for age in 5-year categories, sex, and study center;
[b] Model 2: Model 1 adjusted for self-reported prevalence of heart disease, stroke, or cancer, and educational attainment;
[c] Model 3: Model 2 additionally adjusted for body mass index, waist/height ratio, diet, alcohol consumption, physical activity, and smoking behavior.

3.2 General and abdominal adiposity

3.2.1 Associations within persons with diabetes

In men, body mass index was slightly positive but not significantly associated with mortality. The hazard ratio in the 5th quintile was 1.07 (95% CI 0.80, 1.44) (**Table 3.4**). Indicators of abdominal adiposity were positively associated with mortality in men. The strongest association was observed for waist/height ratio: the hazard ratio in the highest quintile was 1.52 (95% CI: 1.12, 2.05). Mutual adjustment for other anthropometric measurements was performed to investigate abdominal and general adiposity independent of each other. After adjustment for waist/height ratio, an inverse relationship between body mass index and mortality was observed (HR in 5th quintile: 0.41 [95% CI 0.24, 0.70]). The adjustment for body mass index in models of waist circumference, waist/hip ratio and waist/height ratio led to stronger associations.

Among women, the pattern observed was similar to the one seen for men. There was a trend suggesting that body mass index was associated with mortality; however, hazard ratios were not significant (**Table 3.5**). The strongest associations were observed for waist/hip ratio and waist/height ratio: the hazard ratios between the extreme quintiles were respectively 1.85 (95% CI: 1.16, 2.95) and 1.81 (95% CI 1.14, 2.87) when adjusted for the minimal sufficient adjustment set. As in men, the adjustment for waist/height ratio in models of body mass index and mortality inversed the relationship. Furthermore, when the measurements of abdominal adiposity were adjusted for body mass index the associations were strengthened.

Hazard ratios for cause-specific mortality risks per quintile increase in the respective anthropometric measurement are shown in **Table 3.6**. Increased mortality risks associated with measures of adiposity were not associated with a specific cause of death.

Table 3.4: Hazard Ratios (95% CI) Of The Associations Between Measures Of General And Abdominal Adiposity And Mortality In 3,453 Men With Diabetes.

	Quintiles of anthropometric measurement					P-trend
	Body mass index, kg/m²					
Median	23.4	26.1	28.0	30.3	34.0	
Cases / PY	124/6,348	110/6,317	104/6,311	108/6,398	109/6,112	
HR (95% CI)[a]	1 (ref)	0.92 (0.70, 1.20)	0.83 (0.63, 1.09)	0.93 (0.71, 1.23)	1.12 (0.85, 1.47)	0.41
HR (95% CI)[b]	1 (ref)	0.90 (0.68, 1.18)	0.82 (0.62, 1.09)	0.92 (0.69, 1.22)	1.10 (0.83, 1.46)	0.47
HR (95% CI)[c]	1 (ref)	0.90 (0.68, 1.18)	0.81 (0.61, 1.08)	0.92 (0.69, 1.23)	1.07 (0.80, 1.44)	0.57
HR (95% CI)[d]	1 (ref)	0.68 (0.48, 0.95)	0.33 (0.33, 0.73)	0.44 (0.28, 0.70)	0.41 (0.24, 0.70)	0.001
	Waist circumference, cm					
Median	86.0	94.4	100.0	105.7	115.0	
Cases / PY	110/6,373	109/6,895	88/5,927	119/6,276	129/6,015	
HR (95% CI)[a]	1 (ref)	0.94 (0.70, 1.25)	0.93 (0.69, 1.25)	1.14 (0.87, 1.51)	1.27 (0.97, 1.67)	0.03
HR (95% CI)[b]	1 (ref)	0.91 (0.68, 1.22)	0.89 (0.66, 1.20)	1.12 (0.84, 1.48)	1.22 (0.92, 1.62)	0.06
HR (95% CI)[c]	1 (ref)	0.88 (0.65, 1.19)	0.86 (0.63, 1.17)	1.05 (0.79, 1.41)	1.15 (0.86, 1.54)	0.16
HR (95% CI)[d]	1 (ref)	0.99 (0.71, 1.38)	1.07 (0.73, 1.58)	1.43 (0.92, 2.23)	1.54 (0.93, 2.53)	0.08
	Waist/hip ratio					
Median	0.90	0.95	0.98	1.01	1.06	
Cases / PY	108/6,697	89/7,580	109/6,331	128/6,071	122/4,807	
HR (95% CI)[a]	1 (ref)	0.76 (0.56, 1.02)	1.14 (0.86, 1.50)	1.39 (1.05, 1.83)	1.56 (1.18, 2.06)	<.0001
HR (95% CI)[b]	1 (ref)	0.79 (0.59, 1.07)	1.18 (0.89, 1.57)	1.43 (1.08, 1.90)	1.51 (1.13, 2.02)	<.0001
HR (95% CI)[c]	1 (ref)	0.77 (0.57, 1.04)	1.10 (0.82, 1.48)	1.33 (0.99, 1.78)	1.36 (1.02, 1.83)	0.001
HR (95% CI)[d]	1 (ref)	0.83 (0.61, 1.14)	1.25 (0.91, 1.70)	1.54 (1.12, 2.13)	1.60 (1.13, 2.25)	0.0003
	Waist/height ratio					
Median	0.49	0.54	0.57	0.61	0.67	
Cases / PY	102/6,420	106/6,323	109/6,319	111/6,298	128/6,127	
HR (95% CI)[a]	1 (ref)	1.13 (0.85, 1.50)	1.24 (0.93, 1.65)	1.29 (0.97, 1.72)	1.67 (1.26, 2.22)	0.0002
HR (95% CI)[b]	1 (ref)	1.11 (0.83, 1.49)	1.18 (0.89, 1.59)	1.30 (0.97, 1.73)	1.64 (1.22, 2.20)	0.001
HR (95% CI)[c]	1 (ref)	1.08 (0.80, 1.45)	1.15 (0.85, 1.55)	1.22 (0.91, 1.65)	1.52 (1.12, 2.05)	0.004
HR (95% CI)[d]	1 (ref)	1.44 (1.02, 2.04)	1.95 (1.29, 2.96)	2.45 (1.52, 3.93)	3.25 (1.90, 5.58)	<.0001

Abbreviations: PY, person-years.

[a] Model 1: Age- and center-stratified;

[b] Model 2: Model 1 additionally adjusted for HbA_{1c}, diabetes duration, medication use, and self-reported heart disease, cancer, or stroke;

[c] Model 3: Model 2 additionally adjusted for alcohol consumption, smoking behavior, diet, and physical activity;

[d] Model 4: Model 3 additionally adjusted for quintiles of waist/height ratio (when analyzing body mass index) or quintiles of body mass index (when analyzing waist circumference, waist/hip ratio, and waist/height ratio).

Table 3.5: Hazard Ratios (95% CI) Of The Associations Between Measures Of General And Abdominal Adiposity And Mortality In 2,931 Women With Diabetes.

	Quintiles of anthropometric measurement					P-trend
	Body mass index, kg/m²					
Median	22.7	26.2	28.9	31.8	36.7	
Cases / PY	53/5,485	53/5,457	46/5,533	70/5,298	52/5,401	
HR (95% CI)[a]	1 (ref)	0.93 (0.62, 1.41)	0.92 (0.60, 1.40)	1.36 (0.93, 2.00)	1.17 (0.78, 1.76)	0.13
HR (95% CI)[b]	1 (ref)	0.97 (0.64, 1.47)	1.00 (0.65, 1.53)	1.28 (0.86, 1.91)	1.13 (0.74, 1.72)	0.30
HR (95% CI)[c]	1 (ref)	0.87 (0.57, 1.35)	0.96 (0.61, 1.52)	1.26 (0.82, 1.94)	1.07 (0.67, 1.69)	0.38
HR (95% CI)[d]	1 (ref)	0.79 (0.47, 1.33)	0.71 (0.37, 1.36)	0.67 (0.33, 1.36)	0.38 (0.17, 0.85)	0.01
	Waist circumference, cm					
Median	75.0	85.0	92.0	99.0	110.0	
Cases / PY	52/5,589	36/5,479	54/5,580	59/5,251	74/5,281	
HR (95% CI)[a]	1 (ref)	0.72 (0.45, 1.15)	0.98 (0.65, 1.49)	1.24 (0.82, 1.88)	1.66 (1.12, 2.44)	0.001
HR (95% CI)[b]	1 (ref)	0.73 (0.45, 1.19)	1.01 (0.66, 1.54)	1.22 (0.79, 1.88)	1.55 (1.03, 2.34)	0.004
HR (95% CI)[c]	1 (ref)	0.69 (0.42, 1.13)	0.93 (0.59, 1.46)	1.24 (0.79, 1.95)	1.30 (0.83, 2.05)	0.04
HR (95% CI)[d]	1 (ref)	0.77 (0.44, 1.35)	1.17 (0.62, 2.21)	1.73 (0.85, 3.52)	2.20 (0.99, 4.87)	0.02
	Waist/hip ratio					
Median	0.77	0.83	0.87	0.90	0.95	
Cases / PY	42/5,649	61/6,747	42/4,769	54/5,111	74/4,904	
HR (95% CI)[a]	1 (ref)	1.23 (0.80, 1.88)	1.31 (0.83, 2.08)	1.60 (1.03, 2.49)	2.28 (1.50, 3.47)	<.0001
HR (95% CI)[b]	1 (ref)	1.22 (0.79, 1.89)	1.34 (0.84, 2.15)	1.62 (1.03, 2.56)	2.23 (1.44, 3.47)	0.0001
HR (95% CI)[c]	1 (ref)	1.13 (0.72, 1.77)	1.20 (0.73, 1.95)	1.43 (0.89, 2.30)	1.85 (1.16, 2.95)	0.01
HR (95% CI)[d]	1 (ref)	1.13 (0.72, 1.79)	1.25 (0.76, 2.08)	1.45 (0.88, 2.41)	1.89 (1.14, 3.11)	0.01
	Waist/height ratio					
Median	0.47	0.53	0.57	0.62	0.68	
Cases / PY	53/5,666	41/5,394	47/5,403	57/5,453	76/5,265	
HR (95% CI)[a]	1 (ref)	0.92 (0.59, 1.44)	0.99 (0.64, 1.52)	1.20 (0.79, 1.80)	2.08 (1.42, 3.07)	<.0001
HR (95% CI)[b]	1 (ref)	0.95 (0.60, 1.50)	1.03 (0.66, 1.61)	1.15 (0.74, 1.77)	1.98 (1.31, 2.98)	0.001
HR (95% CI)[c]	1 (ref)	0.95 (0.59, 1.52)	1.03 (0.65, 1.64)	1.17 (0.74, 1.83)	1.81 (1.14, 2.87)	0.01
HR (95% CI)[d]	1 (ref)	1.13 (0.65, 1.99)	1.36 (0.71, 2.61)	1.82 (0.88, 3.76)	3.74 (1.66, 8.47)	0.001

Abbreviations: PY, person-years.

[a] Model 1: Age- and center-stratified;

[b] Model 2: Model 1 additionally adjusted for HbA_{1c}, diabetes duration, medication use, and self-reported heart disease, cancer, or stroke;

[c] Model 3: Model 2 additionally adjusted for alcohol consumption, smoking behavior, diet, and physical activity;

[d] Model 4: Model 3 additionally adjusted for quintiles of waist/height ratio (when analyzing body mass index) or quintiles of body mass index (when analyzing waist circumference, waist/hip ratio, and waist/height ratio).

Table 3.6: Hazard Ratios[a] (95% CI) Of Associations Between Measures Of General And Abdominal Adiposity (Per Quintile Increase) And Cause-Specific Mortality In 3,453 Men And 2,931 Women With Diabetes.

	CVD	Cancer	Other causes
Men			
Body mass index	1.03 (0.90, 1.17)	1.03 (0.88, 1.22)	0.99 (0.86, 1.15)
Waist circumference	1.03 (0.91, 1.17)	1.14 (0.97, 1.34)	1.03 (0.89, 1.18)
Waist/hip ratio	1.06 (0.93, 1.21)	1.23 (1.04, 1.46)	1.10 (0.96, 1.27)
Waist/height ratio	1.10 (0.96, 1.25)	1.09 (0.92, 1.29)	1.12 (0.97, 1.29)
Women			
Body mass index	0.89 (0.70, 1.14)	1.03 (0.82, 1.29)	1.08 (0.87, 1.34)
Waist circumference	0.99 (0.77, 1.27)	1.11 (0.88, 1.39)	1.07 (0.86, 1.33)
Waist/hip ratio	1.21 (0.96, 1.51)	1.14 (0.92, 1.43)	1.04 (0.83, 1.30)
Waist/height ratio	1.03 (0.80, 1.33)	1.08 (0.86, 1.36)	1.10 (0.89, 1.38)

[a] Age- and center-stratified and adjusted for HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, alcohol consumption, smoking behavior, diet, and physical activity;

3.2.2 Associations between persons with and without diabetes

Associations of adiposity measures and mortality were not significantly different between persons with and without diabetes (**Table 3.7** and **Table 3.8**). A higher body mass index as well as waist/height ratio were related to increased mortality in diabetes-free individuals. These associations tended to be weaker in persons with diabetes although not significant. In non-diabetic women, the association between body mass index and mortality was of similar strength as measures of abdominal adiposity.

Table 3.7: Hazard Ratios (95% CI) Of Associations Between Measures Of Adiposity And Mortality In 3,453 Men With Diabetes And 10,359 Men Without Diabetes And The Ratio Between These Associations.

	Adiposity measures				
	Body Mass Index, kg/m^2				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.81 (0.60, 1.10)	0.82 (0.61, 1.11)	0.69 (0.51, 0.93)	0.92 (0.71, 1.21)
Non-diabetics [a]	1 (ref)	0.74 (0.60, 0.91)	0.85 (0.69, 1.04)	0.93 (0.76, 1.15)	1.07 (0.86, 1.32)
Ratio	1 (ref)	1.10 (0.76, 1.58)	0.97 (0.68, 1.40)	0.74 (0.52, 1.07)	0.86 (0.61, 1.22)
P for difference		0.63	0.88	0.11	0.40
	Waist circumference, cm				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.64 (0.46, 0.90)	0.82 (0.60, 1.12)	0.88 (0.65, 1.19)	0.95 (0.71, 1.26)
Non-diabetics [a]	1 (ref)	0.84 (0.68, 1.03)	0.90 (0.73, 1.12)	0.96 (0.77, 1.19)	1.20 (0.97, 1.49)
Ratio	1 (ref)	0.77 (0.51, 1.14)	0.91 (0.62, 1.33)	0.92 (0.63, 1.33)	0.79 (0.55, 1.12)
P for difference		0.19	0.62	0.65	0.18
	Waist/hip ratio				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.58 (0.41, 0.83)	0.84 (0.61, 1.16)	1.02 (0.75, 1.38)	1.07 (0.79, 1.44)
Non-diabetics [a]	1 (ref)	0.87 (0.70, 1.09)	0.97 (0.78, 1.21)	1.11 (0.90, 1.38)	1.36 (1.09, 1.70)
Ratio	1 (ref)	0.67 (0.44, 1.02)	0.86 (0.58, 1.28)	0.92 (0.63, 1.34)	0.78 (0.54, 1.14)
P for difference		0.06	0.46	0.66	0.20
	Waist/height ratio				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.68 (0.48, 0.98)	0.91 (0.66, 1.24)	0.85 (0.63, 1.18)	1.12 (0.84, 1.50)
Non-diabetics [a]	1 (ref)	0.92 (0.74, 1.15)	0.86 (0.69, 1.07)	1.07 (0.86, 1.33)	1.32 (1.06, 1.64)
Ratio	1 (ref)	0.74 (0.49, 1.13)	1.06 (0.72, 1.56)	0.81 (0.55, 1.19)	0.85 (0.59, 1.23)
P for difference		0.16	0.78	0.28	0.39

[a] Age-, sex- and center-stratified and adjusted for prevalence of heart disease, cancer, or stroke, alcohol consumption, smoking behavior, educational attainment, physical activity, diet, and disease duration and diabetes medication use (in diabetics only);

Table 3.8: Hazard Ratios (95% CI) Of Associations Between Measures Of Adiposity And Mortality In 2,931 Women With Diabetes And 8,793 Women Without Diabetes And The Ratio Between These Associations.

	Adiposity measures				
	Body Mass Index, kg/m^2				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.84 (0.49, 1.44)	0.87 (0.52, 1.45)	0.90 (0.56, 1.44)	1.18 (0.75, 1.83)
Non-diabetics [a]	1 (ref)	1.07 (0.79, 1.45)	1.32 (0.98, 1.78)	1.28 (0.93, 1.76)	1.52 (1.09, 2.13)
Ratio	1 (ref)	0.79 (0.43, 1.45)	0.66 (0.36, 1.19)	0.70 (0.40, 1.24)	0.77 (0.44, 1.35)
P for difference		0.44	0.17	0.22	0.36
	Waist circumference, cm				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	1.39 (0.78, 2.50)	0.67 (0.35, 1.27)	1.18 (0.68, 2.04)	1.57 (0.94, 2.65)
Non-diabetics [a]	1 (ref)	1.36 (1.00, 1.84)	1.30 (0.95, 1.78)	1.41 (1.03, 1.94)	1.54 (1.09, 2.19)
Ratio	1 (ref)	1.02 (0.53, 1.98)	0.51 (0.25, 1.05)	0.84 (0.44, 1.57)	1.02 (0.54, 1.91)
P for difference		0.95	0.07	0.58	0.95
	Waist/hip ratio				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.98 (0.50, 1.92)	0.93 (0.49, 1.75)	1.23 (0.70, 2.16)	1.77 (1.01, 3.07)
Non-diabetics [a]	1 (ref)	1.12 (0.83, 1.50)	1.24 (0.91, 1.69)	1.13 (0.82, 1.55)	1.55 (1.11, 2.17)
Ratio	1 (ref)	0.88 (0.42, 1.83)	0.74 (0.37, 1.51)	1.09 (0.57, 2.08)	1.14 (0.60, 2.17)
P for difference		0.73	0.42	0.20	0.70
	Waist/height ratio				
	Q1	Q2	Q3	Q4	Q5
Diabetics [a]	1 (ref)	0.92 (0.51, 1.66)	0.65 (0.36, 1.19)	0.92 (0.54, 1.57)	1.29 (0.78, 2.14)
Non-diabetics [a]	1 (ref)	0.95 (0.70, 1.30)	1.11 (0.82, 1.51)	1.37 (1.01, 1.87)	1.45 (1.02, 2.05)
Ratio	1 (ref)	0.97 (0.50, 1.87)	0.59 (0.30, 1.15)	0.67 (0.36, 1.24)	0.89 (0.48, 1.65)
P for difference		0.92	0.12	0.28	0.71

[a] Age-, sex- and center-stratified and adjusted for prevalence of heart disease, cancer, or stroke, alcohol consumption, smoking behavior, educational attainment, physical activity, diet, and disease duration and diabetes medication use (in diabetics only).

3.3 Food group consumption

3.3.1. Associations within persons with diabetes

Table 3.9 shows associations of consumption of 26 food groups and mortality risk in 6,384 persons with diabetes. Higher consumption of vegetables, nuts and seeds, pasta, rice, bread, cakes and cookies and coffee was associated with a lower mortality risk compared with low consumption. Strongest risk reduction was observed for coffee intake: hazard ratio in the highest quartile was 0.58 (95% CI 0.44, 0.76) after adjustment for diabetes-related variables, co-morbidities, and lifestyle factors. Of the grain products, bread consumption showed the lowest mortality risk: hazard ratio in the highest versus lowest quartile was 0.70 (95% CI 0.55, 0.90). Additional adjustment for body mass index and waist/height ratio as well as adjustment for other food groups did not alter the associations for these food groups. A high intake of butter and margarine as well as soft drinks was associated with a higher mortality risk. Mortality risk of persons in the highest tertile of butter and margarine consumption was HR 1.44 (95% CI 1.09, 1.91) after adjustment for diabetes-related variables, co-morbidities, and lifestyle factors. Mortality risk of persons with the highest soft drink consumption was HR 1.31 (95% CI 1.04, 1.65). Additional adjustment for anthropometric measurements and other food groups slightly attenuated this association. Moreover, persons with a moderate consumption of cheese, vegetable oil, sugar and confectionary, and juices had a lower mortality risk compared with those who reported the lowest intakes. For cheese, additional adjustment for body mass index and waist/height ratio or other food groups attenuated the relationship. Fruit consumption tended to be related to a lower mortality risk, but associations were non-significant after adjustment for body mass index and waist/height ratio or other food groups. No significant associations were observed for consumption of potatoes, legumes, milk and yogurt, breakfast cereals, meat, fish, eggs, and tea.

Table 3.10 displays associations between food group consumption and cause-specific mortality and shows that associations found between certain food groups and mortality risk were not due to a specific cause of mortality.

Associations were by and large similar for men and women. Among women, the relationship between nuts and seed consumption and mortality was slightly stronger: hazard ratio in the highest category was 0.46 (95% CI 0.28, 0.78) compared with a HR of 0.86 (95% CI 0.66, 1.12) in the highest category of consumption in men. Furthermore, in men an association between offals and mortality could be detected, whereas this was not significant in women. Hazard ratio in the highest category was 1.35 (95% CI 1.05, 1.73) in men and 1.08 (95% CI 0.73, 1.60) in women. However, the relationship for butter and margarine consumption and mortality risk was more present in women: hazard ratio was 1.82 (95% CI 1.05, 3.17) in women who reported the highest consumption of butter and margarine and 1.24 (95% CI 0.89, 1.72) in men with the highest consumption. Finally, coffee consumption was more strongly related to mortality risk in men than in women. Hazard ratio in the highest quartile was 0.48 (95% CI 0.35, 0.66) in men compared with a hazard ratio in the highest quartile of 0.65 (95% CI 0.39, 1.07) in women.

Table 3.9: Hazard Ratios (95% CI) Of The Associations Between Consumption Of 26 Food Groups And Mortality Risk In 6,384 Individuals With Diabetes Mellitus.

	Quartiles of food group intake				P-Trend
	Potatoes				
Median (g/d)	43	73	95	138	
Cases / PY	105/14,742	173/14,658	237/14,568	315/14,699	
HR (95% CI)[a]	1 (ref)	1.03 (0.77, 1.37)	1.12 (0.84, 1.51)	1.05 (0.79, 1.41)	0.76
HR (95% CI)[b]	1 (ref)	1.00 (0.75, 1.34)	1.10 (0.82, 1.47)	1.04 (0.77, 1.39)	0.79
HR (95% CI)[c]	1 (ref)	1.01 (0.76, 1.36)	1.09 (0.81, 1.47)	1.04 (0.78, 1.40)	0.79
	Vegetables				
Median (g/d)	109	144	172	227	
Cases / PY	329/15,111	217/14,285	162/14,163	122/15,108	
HR (95% CI)[a]	1 (ref)	0.86 (0.70, 1.05)	0.80 (0.63, 1.00)	0.74 (0.56, 0.96)	0.02
HR (95% CI)[b]	1 (ref)	0.88 (0.72, 1.07)	0.81 (0.65, 1.02)	0.76 (0.58, 0.99)	0.03
HR (95% CI)[c]	1 (ref)	0.88 (0.71, 1.07)	0.82 (0.65, 1.04)	0.76 (0.58, 1.01)	0.05
	Fruits				
Median (g/d)	100	162	231	347	
Cases / PY	303/15,144	237/14,556	182/14,022	108/14,945	
HR (95% CI)[a]	1 (ref)	0.85 (0.70, 1.04)	0.86 (0.68, 1.08)	0.76 (0.57, 1.02)	0.07
HR (95% CI)[b]	1 (ref)	0.88 (0.72, 1.06)	0.88 (0.70, 1.11)	0.78 (0.58, 1.04)	0.10
HR (95% CI)[c]	1 (ref)	0.88 (0.72, 1.07)	0.90 (0.71, 1.14)	0.82 (0.61, 1.11)	0.22
	Legumes				
Median (g/d)	0	3	10		
Cases / PY	378/19,859	277/19,130	175/19,678		
HR (95% CI)[a]	1 (ref)	0.95 (0.77, 1.17)	0.95 (0.71, 1.27)		0.74
HR (95% CI)[b]	1 (ref)	0.94 (0.76, 1.15)	0.93 (0.70, 1.25)		0.65
HR (95% CI)[c]	1 (ref)	0.94 (0.76, 1.17)	0.93 (0.69, 1.27)		0.73
	Nuts and Seeds				
Median (g/d)	0	1	3		
Cases / PY	404/19,933	269/19,629	157/19,104		
HR (95% CI)[a]	1 (ref)	0.81 (0.68, 0.97)	0.73 (0.57, 0.92)		0.02
HR (95% CI)[b]	1 (ref)	0.80 (0.67, 0.96)	0.74 (0.58, 0.94)		0.03
HR (95% CI)[c]	1 (ref)	0.81 (0.67, 0.97)	0.74 (0.58, 0.94)		0.03
	Milk and milk products				
Median (g/d)	50	91	180	341	
Cases / PY	211/14,026	178/14,111	184/14,958	256/15,571	
HR (95% CI)[a]	1 (ref)	0.83 (0.67, 1.03)	0.92 (0.73, 1.14)	1.04 (0.83, 1.29)	0.29
HR (95% CI)[b]	1 (ref)	0.84 (0.68, 1.05)	0.92 (0.74, 1.16)	1.05 (0.85, 1.31)	0.26
HR (95% CI)[c]	1 (ref)	0.84 (0.67, 1.05)	0.93 (0.74, 1.17)	1.05 (0.84, 1.31)	0.26
	Yogurt				
Median (g/d)	18	27	34	48	
Cases / PY	233/15,221	200/14,353	202/14,510	196/14,582	
HR (95% CI)[a]	1 (ref)	0.89 (0.72, 1.12)	0.85 (0.68, 1.06)	0.86 (0.70, 1.07)	0.24
HR (95% CI)[b]	1 (ref)	0.89 (0.71, 1.11)	0.87 (0.70, 1.09)	0.87 (0.70, 1.07)	0.29
HR (95% CI)[c]	1 (ref)	0.93 (0.74, 1.16)	0.91 (0.72, 1.13)	0.92 (0.74, 1.13)	0.51
	Cheese				
Median (g/d)	0	18	51	105	
Cases / PY	232/15,177	189/13,957	182/14,388	227/15,144	
HR (95% CI)[a]	1 (ref)	0.79 (0.63, 0.98)	0.84 (0.66, 1.05)	0.86 (0.68, 1.08)	0.16
HR (95% CI)[b]	1 (ref)	0.80 (0.64, 1.00)	0.86 (0.68, 1.08)	0.88 (0.70, 1.11)	0.26
HR (95% CI)[c]	1 (ref)	0.82 (0.66, 1.03)	0.90 (0.71, 1.13)	0.96 (0.75, 1.21)	0.53

	Quartiles of food group intake				P-Trend
	Pasta				
Median (g/d)	0	13	21	71	
Cases / PY	351/14,989	195/15,104	177/14,659	108/13,915	
HR (95% CI)[a]	1 (ref)	0.78 (0.64, 0.95)	0.78 (0.63, 0.97)	0.77 (0.55, 1.07)	0.12
HR (95% CI)[b]	1 (ref)	0.78 (0.64, 0.95)	0.78 (0.62, 0.97)	0.77 (0.55, 1.04)	0.12
HR (95% CI)[c]	1 (ref)	0.79 (0.64, 0.96)	0.80 (0.64, 1.00)	0.81 (0.57, 1.13)	0.22
	Rice				
Median (g/d)	0	8	13	22	
Cases / PY	317/14,352	240/14,438	149/14,813	123/15,064	
HR (95% CI)[a]	1 (ref)	0.90 (0.73, 1.10)	0.66 (0.52, 0.82)	0.76 (0.59, 0.98)	0.01
HR (95% CI)[b]	1 (ref)	0.91 (0.75, 1.12)	0.67 (0.53, 0.84)	0.79 (0.61, 1.02)	0.01
HR (95% CI)[c]	1 (ref)	0.91 (0.74, 1.12)	0.67 (0.53, 0.85)	0.78 (0.60, 1.01)	0.01
	Bread				
Median (g/d)	101	106	136	186	
Cases / PY	240/15,370	211/14,601	193/14,038	187/14,657	
HR (95% CI)[a]	1 (ref)	0.94 (0.76, 1.15)	0.86 (0.69, 1.07)	0.70 (0.55, 0.90)	0.004
HR (95% CI)[b]	1 (ref)	0.93 (0.76, 1.15)	0.86 (0.69, 1.07)	0.71 (0.55, 0.91)	0.01
HR (95% CI)[c]	1 (ref)	0.90 (0.73, 1.12)	0.83 (0.66, 1.04)	0.67 (0.51, 0.86)	0.002
	Breakfast cereals				
Median (g/d)	0	0	18		
Cases / PY	280/19,257	216/19,129	335/20,281		
HR (95% CI)[a]	1 (ref)	0.98 (0.79, 1.23)	0.92 (0.75, 1.13)		0.38
HR (95% CI)[b]	1 (ref)	0.99 (0.79, 1.24)	0.93 (0.76, 1.14)		0.43
HR (95% CI)[c]	1 (ref)	0.96 (0.77, 1.22)	0.92 (0.75, 1.14)		0.44
	Red Meat				
Median (g/d)	37	43	53	76	
Cases / PY	177/14,022	202/14,482	219/14,772	232/15.390	
HR (95% CI)[a]	1 (ref)	0.95 (0.77, 1.19)	0.92 (0.73, 1.16)	1.01 (0.80, 1.28)	0.82
HR (95% CI)[b]	1 (ref)	0.93 (0.75, 1.16)	0.88 (0.70, 1.12)	0.96 (0.75, 1.22)	0.83
HR (95% CI)[c]	1 (ref)	0.91 (0.73, 1.13)	0.84 (0.66, 1.07)	0.91 (0.71, 1.16)	0.53
	Processed Meat				
Median (g/d)	27	40	52	83	
Cases / PY	152/15,199	193/15,121	242/14,682	242/13,664	
HR (95% CI)[a]	1 (ref)	1.04 (0.81, 1.32)	1.16 (0.88, 1.52)	1.10 (0.83, 1.47)	0.52
HR (95% CI)[b]	1 (ref)	1.03 (0.81, 1.32)	1.13 (0.86, 1.48)	1.06 (0.79, 1.41)	0.75
HR (95% CI)[c]	1 (ref)	0.97 (0.76, 1.25)	1.06 (0.80, 1.41)	0.98 (0.72, 1.33)	0.90
	Poultry				
Median (g/d)	9	13	17	32	
Cases / PY	287/15,063	260/14,131	178/14,239	105/15,234	
HR (95% CI)[a]	1 (ref)	0.94 (0.78, 1.13)	0.80 (0.65, 1.00)	0.99 (0.73, 1.36)	0.52
HR (95% CI)[b]	1 (ref)	0.94 (0.78, 1.14)	0.80 (0.65, 1.00)	0.99 (0.73, 1.36)	0.52
HR (95% CI)[c]	1 (ref)	0.93 (0.76, 1.13)	0.78 (0.62, 0.97)	1.01 (0.73, 1.41)	0.57
	Offals				
Median (g/d)	0	1	3		
Cases / PY	324/19,990	267/19,602	239/19.074		
HR (95% CI)[a]	1 (ref)	1.03 (0.85, 1.24)	1.15 (0.94, 1.41)		0.15
HR (95% CI)[b]	1 (ref)	0.99 (0.82, 1.20)	1.11 (0.91, 1.36)		0.27
HR (95% CI)[c]	1 (ref)	0.98 (0.80, 1.19)	1.12 (0.92, 1.38)		0.22

	Quartiles of food group intake				P-Trend
	Fish and shellfish				
Median (g/d)	16	21	31	58	
Cases / PY	171/13,628	180/14,006	221/15,052	258/15,980	
HR (95% CI)[a]	1 (ref)	1.04 (0.81, 1.33)	1.01 (0.76, 1.34)	1.05 (0.78, 1.41)	0.78
HR (95% CI)[b]	1 (ref)	1.04 (0.82, 1.34)	1.01 (0.77, 1.34)	1.05 (0.78, 1.41)	0.78
HR (95% CI)[c]	1 (ref)	1.02 (0.79, 1.31)	1.00 (0.75, 1.34)	1.04 (0.76, 1.43)	0.77
	Eggs				
Median (g/d)	10	11	14	26	
Cases / PY	191/13,740	188/14,016	209/14,992	241/15,918	
HR (95% CI)[a]	1 (ref)	0.99 (0.80, 1.23)	1.12 (0.88, 1.42)	1.07 (0.85, 1.35)	0.54
HR (95% CI)[b]	1 (ref)	0.98 (0.79, 1.22)	1.08 (0.85, 1.37)	1.04 (0.82, 1.32)	0.72
HR (95% CI)[c]	1 (ref)	0.95 (0.77, 1.19)	1.07 (0.84, 1.37)	1.00 (0.79, 1.27)	0.93
	Vegetable oil				
Median (g/d)	1	2	18		
Cases / PY	416/19,633	273/19,211	142/19,822		
HR (95% CI)[a]	1 (ref)	0.81 (0.67, 0.97)	0.89 (0.65, 1.21)		0.87
HR (95% CI)[b]	1 (ref)	0.79 (0.66, 0.95)	0.83 (0.61, 1.15)		0.63
HR (95% CI)[c]	1 (ref)	0.79 (0.64, 0.97)	0.88 (0.62, 1.24)		0.94
	Butter and margarine				
Median (g/d)	2	22	45		
Cases / PY	142/20,349	325/19,290	364/19,028		
HR (95% CI)[a]	1 (ref)	1.46 (1.13, 1.88)	1.44 (1.09, 1.91)		0.03
HR (95% CI)[b]	1 (ref)	1.43 (1.11, 1.85)	1.46 (1.10, 1.94)		0.02
HR (95% CI)[c]	1 (ref)	1.46 (1.13, 1.89)	1.52 (1.13, 2.04)		0.01
	Sugar and confectionary				
Median (g/d)	15	23	30	41	
Cases / PY	178/14,233	154/14,178	230/14,981	267/15,273	
HR (95% CI)[a]	1 (ref)	0.69 (0.53, 0.89)	0.77 (0.59, 1.01)	0.79 (0.60, 1.04)	0.23
HR (95% CI)[b]	1 (ref)	0.70 (0.54, 0.90)	0.81 (0.61, 1.07)	0.81 (0.61, 1.08)	0.32
HR (95% CI)[c]	1 (ref)	0.70 (0.54, 0.90)	0.78 (0.59, 1.04)	0.81 (0.61, 1.08)	0.31
	Cakes and cookies				
Median (g/d)	23	38	47	63	
Cases / PY	262/15,429	185/14,426	189/14,157	194/14,655	
HR (95% CI)[a]	1 (ref)	0.74 (0.59, 0.93)	0.85 (0.67, 1.09)	0.78 (0.61, 0.99)	0.08
HR (95% CI)[b]	1 (ref)	0.77 (0.61, 0.97)	0.90 (0.70, 1.16)	0.82 (0.64, 1.05)	0.18
HR (95% CI)[c]	1 (ref)	0.72 (0.57, 0.91)	0.84 (0.66, 1.08)	0.74 (0.57, 0.96)	0.04
	Soft drinks				
Median (g/d)	0	0	44	198	
Cases / PY	189/14,490	195/14,270	167/14,927	279/14,978	
HR (95% CI)[a]	1 (ref)	1.04 (0.83, 1.31)	0.92 (0.72, 1.19)	1.31 (1.04, 1.65)	0.004
HR (95% CI)[b]	1 (ref)	1.05 (0.83, 1.31)	0.92 (0.72, 1.18)	1.26 (1.00, 1.60)	0.01
HR (95% CI)[c]	1 (ref)	1.04 (0.82, 1.30)	0.89 (0.69, 1.15)	1.28 (1.01, 1.61)	0.01
	Juices				
Median (g/d)	0	8	59	152	
Cases / PY	278/15,493	169/15,565	182/14,247	200/13,361	
HR (95% CI)[a]	1 (ref)	0.77 (0.61, 0.97)	0.81 (0.65, 1.03)	1.09 (0.85, 1.40)	0.14
HR (95% CI)[b]	1 (ref)	0.75 (0.59, 0.94)	0.82 (0.65, 1.03)	1.08 (0.84, 1.38)	0.15
HR (95% CI)	1 (ref)	0.76 (0.60, 0.96)	0.82 (0.65, 1.04)	1.08 (0.83, 1.39)	0.16

	Quartiles of food group intake				P-Trend
	Tea				
Median (g/d)	0	14	66	354	
Cases / PY	413/26,488	53/3,432	174/14,039	190/14,653	
HR (95% CI)[a]	1 (ref)	1.01 (0.72, 1.40)	1.03 (0.82, 1.29)	0.88 (0.70, 1.11)	0.18
HR (95% CI)[b]	1 (ref)	0.99 (0.71, 1.37)	1.03 (0.82, 1.30)	0.89 (0.70, 1.12)	0.22
HR (95% CI)[c]	1 (ref)	1.05 (0.75, 1.46)	1.08 (0.86, 1.35)	0.94 (0.74, 1.19)	0.39
	Coffee				
Median (g/d)	102	406	575	935	
Cases / PY	126/15,179	215/14,059	238/14,339	250/15,089	
HR (95% CI)[a]	1 (ref)	0.72 (0.54, 0.96)	0.67 (0.51, 0.90)	0.58 (0.44, 0.76)	0.0003
HR (95% CI)[b]	1 (ref)	0.73 (0.55, 0.98)	0.71 (0.53, 0.94)	0.61 (0.46, 0.82)	0.002
HR (95% CI)[c]	1 (ref)	0.72 (0.54, 0.96)	0.68 (0.51, 0.91)	0.61 (0.46, 0.81)	0.002

Abbreviations: PY, person-years.
[a] Model 1: Age- and center-stratified and adjusted for gender, HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment, alcohol consumption, smoking behavior, and physical activity;
[b] Model 2: Model 1 additionally adjusted for body mass index and waist/height ratio;
[c] Model 3: Model 1 additionally adjusted for intake of potatoes, vegetables, fruit, nuts and seeds, milk and milk products, bread, breakfast cereals, red meat, fish and shellfish, vegetable oil, butter, margarine, sugar and confectionary, cakes and cookies, and soft drinks.

3.3.2. Associations between persons with and without diabetes

Table 3.11 shows the associations for food group consumption in people with and without diabetes. For food group consumption, only few statistically significant differences were found. Coffee consumption was significantly associated with a lower mortality risk in people with diabetes; hazard ratio in the 4th quartile was 0.58 (95% CI 0.45, 0.77) for persons with and 0.93 (95% CI 0.72, 1.21) for persons without diabetes. This difference in hazard ratios was significant (*P*-value 0.02).

Furthermore, results suggested that a moderate to high consumption of vegetables, nuts and seeds, pasta, rice, and bread were related to a lower mortality risk in persons with diabetes. These associations tended to be stronger than in persons without diabetes, but not statistically significant. Moreover, a higher consumption of butter and margarine, sugar and confectionary, cakes and cookies, and soft drinks appeared to be more strongly related to a higher mortality risk in persons with diabetes. These associations also appeared to be stronger in persons with diabetes compared with diabetes-free individuals, but not significant.

For the consumption of potatoes, fruit, legumes, dairy, breakfast cereals, meat, fish, eggs, juices, and tea no associations with mortality or differences between individuals with and without diabetes were apparent.

Table 3.10: Hazard Ratios [a] (95% CI) Of Associations Between Food Group Consumption (Per Quartile Increase) And Cause-Specific Mortality In 6,147 Persons With Diabetes.

Food groups (g/d)	CVD	Cancer	Other causes
Potatoes	1.02 (0.85, 1.22)	1.01 (0.83, 1.24)	0.91 (0.76, 1.10)
Vegetables	0.91 (0.77, 1.08)	0.97 (0.80, 1.18)	0.83 (0.69, 0.98)
Fruit	0.88 (0.73, 1.04)	1.01 (0.81, 1.25)	0.89 (0.74, 1.08)
Legumes	1.03 (0.80, 1.33)	1.13 (0.84, 1.53)	0.76 (0.56, 1.04)
Nuts and seeds	0.95 (0.77, 1.18)	0.82 (0.64, 1.05)	0.82 (0.64, 1.04)
Milk and milk products	1.05 (0.91, 1.21)	1.00 (0.84, 1.18)	1.10 (0.94, 1.28)
Yogurt	1.00 (0.88, 1.14)	0.88 (0.74, 1.04)	1.12 (0.97, 1.30)
Cheese	0.88 (0.77, 1.01)	0.98 (0.84, 1.15)	0.99 (0.86, 1.14)
Pasta	0.98 (0.82, 1.17)	1.09 (0.87, 1.35)	0.80 (0.66, 0.98)
Rice	0.88 (0.76, 1.03)	0.87 (0.72, 1.04)	0.91 (0.77, 1.08)
Bread	0.88 (0.75, 1.03)	0.79 (0.66, 0.95)	0.91 (0.77, 1.07)
Breakfast cereals	0.98 (0.80, 1.20)	0.97 (0.76, 1.25)	0.97 (0.78, 1.21)
Red meat	0.94 (0.81, 1.08)	1.14 (0.96, 1.35)	0.88 (0.75, 1.02)
Processed meat	0.98 (0.81, 1.18)	1.17 (0.93, 1.46)	0.97 (0.80, 1.18)
Poultry	0.89 (0.74, 1.06)	0.92 (0.75, 1.13)	0.97 (0.80, 1.17)
Offals	1.07 (0.88, 1.31)	0.93 (0.74, 1.16)	1.14 (0.92, 1.41)
Fish and shellfish	1.04 (0.86, 1.26)	1.19 (0.94, 1.52)	0.93 (0.76, 1.15)
Eggs	1.01 (0.88, 1.17)	1.06 (0.87, 1.28)	1.01 (0.86, 1.18)
Vegetable oil	1.03 (0.78, 1.37)	1.03 (0.75, 1.41)	0.75 (0.55, 1.03)
Butter and margarine	1.08 (0.82, 1.42)	1.15 (0.84, 1.58)	1.12 (0.86, 1.46)
Sugar and confectionary	0.92 (0.78, 1.08)	1.05 (0.87, 1.28)	1.02 (0.85, 1.23)
Cakes and cookies	0.90 (0.77, 1.05)	1.38 (0.85, 1.25)	0.90 (0.76, 1.07)
Soft drinks	1.10 (0.95, 1.27)	1.13 (0.94, 1.35)	0.95 (0.81, 1.12)
Juices	1.08 (0.92, 1.27)	1.05 (0.87, 1.28)	1.15 (0.97, 1.36)
Tea	1.03 (0.88, 1.20)	1.01 (0.85, 1.20)	1.08 (0.93, 1.26)
Coffee	0.93 (0.79, 1.10)	0.91 (0.74, 1.12)	0.75 (0.63, 0.88)

[a] Age- and center-stratified and adjusted for gender, HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment, alcohol consumption, smoking behavior, and physical activity.

Table 3.11: Hazard Ratios (95% CI) Of Associations Between Consumption Of 26 Food Groups And Mortality In 6,384 Persons With Diabetes And 19,152 Persons Without Diabetes And The Ratio Between These Associations.

	Food group consumption				
	Potatoes				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	1.01 (0.76, 1.34)	1.00 (0.74, 1.34)	0.97 (0.73, 1.30)	0.89 (0.71, 1.10)
Non-diabetics [a]	1 (ref)	0.97 (0.79, 1.19)	0.96 (0.77, 1.20)	0.88 (0.70, 1.10)	0.90 (0.76, 1.07)
Ratio	1 (ref)	1.04 (0.74, 1.49)	1.03 (0.72, 1.50)	1.11 (0.77, 1.60)	0.98 (0.75, 1.29)
P for difference		0.81	0.86	0.59	0.90
	Vegetables				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	0.87 (0.71, 1.06)	0.80 (0.64, 1.00)	0.73 (0.57, 0.94)	0.82 (0.69, 0.98)
Non-diabetics [a]	1 (ref)	0.97 (0.84, 1.13)	1.01 (0.84, 1.20)	0.97 (0.78, 1.21)	0.97 (0.82, 1.14)
Ratio	1 (ref)	0.89 (0.69, 1.49)	0.80 (0.60, 1.06)	0.75 (0.54, 1.05)	0.85 (0.67, 1.07)
P for difference		0.37	0.11	0.10	0.17
	Fruit				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	0.90 (0.74, 1.11)	0.88 (0.70, 1.10)	0.80 (0.60, 1.05)	0.92 (0.84, 1.01)
Non-diabetics [a]	1 (ref)	0.93 (0.79, 1.08)	0.98 (0.82, 1.17)	0.85 (0.68, 1.06)	0.96 (0.90, 1.02)
Ratio	1 (ref)	0.97 (0.76, 1.24)	0.89 (0.67, 1.19)	0.94 (0.65, 1.34)	0.97 (0.86, 1.08)
P for difference		0.80	0.44	0.73	0.54
	Legumes				
	Q1	Q2	Q3		Per 10 g
Diabetics [a]	1 (ref)	0.89 (0.72, 1.11)	0.95 (0.71, 1.26)		0.98 (0.86, 1.13)
Non-diabetics [a]	1 (ref)	0.90 (0.76, 1.07)	1.05 (0.85, 1.31)		1.07 (1.01, 1.15)
Ratio	1 (ref)	0.99 (0.75, 1.30)	0.90 (0.62, 1.30)		0.92 (0.79, 1.07)
P for difference		0.94	0.57		0.26
	Nuts and Seeds				
	Q1	Q2	Q3		Per g
Diabetics [a]	1 (ref)	0.83 (0.69, 0.99)	0.80 (0.62, 1.03)		0.95 (0.91, 0.99)
Non-diabetics [a]	1 (ref)	1.14 (0.88, 1.16)	0.94 (0.79, 1.12)		0.99 (0.96, 1.01)
Ratio	1 (ref)	0.82 (0.65, 1.02)	0.85 (0.62, 1.17)		0.96 (0.92, 1.01)
P for difference		0.08	0.32		0.15
	Milk and milk products				
	Q1	Q2	Q3	Q4	Per 50 g
Diabetics [a]	1 (ref)	0.89 (0.71, 1.11)	0.94 (0.76, 1.18)	1.03 (0.83, 1.27)	1.01 (0.99, 1.03)
Non-diabetics [a]	1 (ref)	1.04 (0.88, 1.23)	0.95 (0.80, 1.14)	1.10 (0.93, 1.31)	1.02 (1.00, 1.04)
Ratio	1 (ref)	0.85 (0.64, 1.13)	0.99 (0.75, 1.31)	0.93 (0.71, 1.22)	0.99 (0.96, 1.02)
P for difference		0.26	0.94	0.60	0.53
	Cheese				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.84 (0.68, 1.04)	0.83 (0.66, 1.04)	0.89 (0.72, 1.11)	0.98 (0.92, 1.04)
Non-diabetics [a]	1 (ref)	0.91 (0.78, 1.07)	0.94 (0.79, 1.12)	0.91 (0.76, 1.09)	0.96 (0.91, 1.01)
Ratio	1 (ref)	0.92 (0.70, 1.21)	0.88 (0.66, 1.17)	0.98 (0.74, 1.29)	1.02 (0.94, 1.10)
P for difference		0.55	0.37	0.89	0.42
	Yogurt				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.92 (0.74, 1.15)	0.83 (0.67, 1.03)	0.86 (0.71, 1.05)	1.00 (0.99, 1.01)
Non-diabetics [a]	1 (ref)	1.00 (0.84, 1.18)	1.07 (0.90, 1.25)	0.98 (0.84, 1.16)	0.99 (0.98, 1.01)
Ratio	1 (ref)	0.92 (0.69, 1.22)	0.78 (0.60, 1.02)	0.88 (0.68, 1.13)	1.01 (0.99, 1.02)
P for difference		0.55	0.07	0.31	0.63

	Food group consumption				
	Pasta				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.78 (0.64, 0.95)	0.79 (0.63, 0.99)	0.72 (0.52, 0.99)	0.95 (0.90, 1.01)
Non-diabetics [a]	1 (ref)	0.90 (0.78, 1.05)	0.85 (0.70, 1.02)	0.93 (0.71, 1.21)	0.96 (0.93, 1.00)
Ratio	1 (ref)	0.87 (0.67, 1.11)	0.93 (0.69, 1.25)	0.77 (0.51, 1.18)	0.99 (0.93, 1.06)
P for difference		0.26	0.56	0.23	0.77
	Rice				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.88 (0.72, 1.08)	0.64 (0.50, 0.81)	0.73 (0.57, 0.94)	0.98 (0.91, 1.06)
Non-diabetics [a]	1 (ref)	0.91 (0.77, 1.07)	0.92 (0.77, 1.10)	0.87 (0.70, 1.06)	0.93 (0.86, 1.01)
Ratio	1 (ref)	0.97 (0.75, 1.26)	0.69 (0.52, 0.93)	0.85 (0.61, 1.18)	1.06 (0.94, 1.18)
P for difference		0.83	0.02	0.32	0.34
	Bread				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	0.86 (0.70, 1.07)	0.88 (0.70, 1.10)	0.70 (0.55, 0.89)	0.70 (0.55, 0.90)
Non-diabetics [a]	1 (ref)	0.98 (0.84, 1.14)	0.92 (0.78, 1.09)	0.88 (0.73, 1.06)	0.86 (0.71, 1.05)
Ratio	1 (ref)	0.88 (0.68, 1.15)	0.96 (0.72, 1.27)	0.80 (0.58, 1.08)	0.81 (0.59, 1.12)
P for difference		0.34	0.77	0.15	0.20
	Breakfast cereals				
	Q1	Q2	Q3		Per 10 g
Diabetics [a]	1 (ref)	1.09 (0.86, 1.36)	0.91 (0.74, 1.12)		0.98 (0.96, 1.01)
Non-diabetics [a]	1 (ref)	0.98 (0.82, 1.18)	0.86 (0.74, 1.01)		0.97 (0.95, 1.00)
Ratio	1 (ref)	1.10 (0.82, 1.48)	1.05 (0.81, 1.37)		1.01 (0.97, 1.05)
P for difference		0.50	0.69		0.56
	Red meat				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.09 (0.85, 1.40)	1.11 (0.87, 1.43)	1.07 (0.83, 1.38)	1.02 (0.97, 1.07)
Non-diabetics [a]	1 (ref)	1.23 (1.04, 1.46)	1.00 (0.83, 1.20)	1.22 (1.01, 1.47)	1.02 (0.98, 1.05)
Ratio	1 (ref)	0.88 (0.66, 1.19)	1.11 (0.82, 1.51)	0.88 (0.64, 1.21)	1.00 (0.95, 1.06)
P for difference		0.41	0.49	0.43	0.96
	Processed meat				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.94 (0.73, 1.21)	1.08 (0.82, 1.42)	1.03 (0.77, 1.37)	1.01 (0.97, 1.07)
Non-diabetics [a]	1 (ref)	1.14 (0.96, 1.36)	1.16 (0.95, 1.43)	1.19 (0.94, 1.49)	1.03 (0.99, 1.06)
Ratio	1 (ref)	0.82 (0.60, 1.12)	0.93 (0.66, 1.31)	0.87 (0.60, 1.25)	0.99 (0.93, 1.04)
P for difference		0.21	0.67	0.45	0.67
	Poultry				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.02 (0.84, 1.24)	0.88 (0.71, 1.08)	0.88 (0.65, 1.18)	0.99 (0.90, 1.10)
Non-diabetics [a]	1 (ref)	0.99 (0.85, 1.15)	1.07 (0.90, 1.27)	1.01 (0.79, 1.30)	0.97 (0.89, 1.06)
Ratio	1 (ref)	1.03 (0.80, 1.32)	0.82 (0.62, 1.07)	0.87 (0.59, 1.29)	1.02 (0.90, 1.16)
P for difference		0.95	0.15	0.49	0.71
	Offals				
	Q1	Q2	Q3		Per g
Diabetics [a]	1 (ref)	1.08 (0.88, 1.32)	1.19 (0.98, 1.45)		1.02 (0.99, 1.05)
Non-diabetics [a]	1 (ref)	1.02 (0.88, 1.19)	1.09 (0.93, 1.26)		1.01 (0.99, 1.03)
Ratio	1 (ref)	1.05 (0.82, 1.35)	1.10 (0.86, 1.41)		1.01 (0.98, 1.05)
P for difference		0.69	0.46		0.40

	Food group consumption				
	Fish and shellfish				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.05 (0.81, 1.36)	1.13 (0.85, 1.50)	1.01 (0.75, 1.36)	1.00 (0.95, 1.05)
Non-diabetics [a]	1 (ref)	0.90 (0.74, 1.09)	0.76 (0.61, 0.94)	0.80 (0.63, 1.01)	0.98 (0.94, 1.02)
Ratio	1 (ref)	1.17 (0.85, 1.61)	1.49 (1.04, 2.13)	1.27 (0.87, 1.87)	1.02 (0.96, 1.08)
P for difference		0.34	0.03	0.22	0.58
	Eggs				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.10 (0.88, 1.38)	1.08 (0.85, 1.38)	1.11 (0.88, 1.40)	1.01 (0.92, 1.11)
Non-diabetics [a]	1 (ref)	1.03 (0.87, 1.21)	1.10 (0.92, 1.31)	1.13 (0.94, 1.35)	1.05 (0.97, 1.13)
Ratio	1 (ref)	1.08 (0.81, 1.42)	0.98 (0.73, 1.33)	0.98 (0.73, 1.32)	0.96 (0.86, 1.08)
P for difference		0.61	0.92	0.90	0.53
	Vegetable oil				
	Q1	Q2	Q3		Per g
Diabetics [a]	1 (ref)	0.83 (0.69, 0.99)	0.91 (0.67, 1.24)		0.99 (0.95, 1.02)
Non-diabetics [a]	1 (ref)	0.96 (0.83, 1.12)	1.08 (0.82, 1.42)		0.99 (0.96, 1.01)
Ratio	1 (ref)	0.86 (0.68, 1.09)	0.84 (0.56, 1.27)		1.00 (0.96, 1.04)
P for difference		0.22	0.42		0.96
	Butter and margarine				
	Q1	Q2	Q3		Per 10 g
Diabetics [a]	1 (ref)	1.53 (1.19, 1.96)	1.46 (1.11, 1.93)		1.04 (0.98, 1.09)
Non-diabetics [a]	1 (ref)	1.01 (0.83, 1.22)	1.17 (0.94, 1.46)		1.04 (0.99, 1.08)
Ratio	1 (ref)	1.52 (1.11, 2.09)	1.25 (0.88, 1.78)		1.00 (0.93, 1.07)
P for difference		0.01	0.22		0.97
	Sugar and confectionary				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.10 (0.86, 1.41)	1.14 (0.85, 1.53)	1.34 (1.01, 1.77)	1.08 (1.01, 1.16)
Non-diabetics [a]	1 (ref)	1.01 (0.84, 1.23)	1.17 (0.94, 1.46)	1.18 (0.96, 1.45)	1.08 (1.03, 1.14)
Ratio	1 (ref)	1.08 (0.79, 1.48)	0.97 (0.67, 1.41)	1.13 (0.80, 1.60)	1.00 (0.92, 1.09)
P for difference		0.61	0.88	0.47	0.97
	Cakes and cookies				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	1.16 (0.84, 1.62)	1.24 (0.89, 1.72)	1.14 (0.80, 1.61)	1.01 (0.96, 1.06)
Non-diabetics [a]	1 (ref)	1.08 (0.86, 1.37)	0.85 (0.66, 1.10)	0.92 (0.71, 1.20)	0.97 (0.93, 1.02)
Ratio	1 (ref)	1.07 (0.72, 1.61)	1.45 (0,95, 2.20)	1.23 (0.80, 1.91)	1.03 (0.96, 1.11)
P for difference		0.73	0.08	0.34	0.35
	Soft drink				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.92 (0.73, 1.17)	0.86 (0.66, 1.11)	1.01 (0.76, 1.34)	0.99 (0.93, 1.06)
Non-diabetics [a]	1 (ref)	1.07 (0.88, 1.30)	0.80 (0.65, 0.98)	0.78 (0.63, 0.96)	0.96 (0.92, 1.00)
Ratio	1 (ref)	0.86 (0.64, 1.17)	1.07 (0.77, 1.50)	1.30 (0.91, 1.85)	1.04 (0.96, 1.12)
P for difference		0.35	0.68	0.14	0.37
	Juices				
	Q1	Q2	Q3	Q4	Per 10 g
Diabetics [a]	1 (ref)	0.91 (0.74, 1.13)	0.86 (0.67, 1.10)	0.89 (0.70, 1.14)	0.98 (0.94, 1.01)
Non-diabetics [a]	1 (ref)	0.98 (0.82, 1.17)	0.90 (0.75, 1.09)	0.83 (0.68, 1.01)	0.99 (0.97, 1.02)
Ratio	1 (ref)	0.93 (0.71, 1.23)	0.95 (0.70, 1.29)	1.07 (0.78, 1.47)	0.98 (0.94, 1.03)
P for difference		0.62	0.75	0.99	0.48

	Food group consumption				
	Tea				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	0.98 (0.73, 1.31)	1.01 (0.80, 1.27)	0.88 (0.70, 1.11)	0.98 (0.95, 1.01)
Non-diabetics [a]	1 (ref)	0.86 (0.68, 1.09)	0.96 (0.80, 1.14)	0.79 (0.65, 0.95)	0.99 (0.96, 1.02)
Ratio	1 (ref)	1.14 (0.78, 1.65)	1.05 (0.79, 1.40)	1.12 (0.83, 1.50)	0.99 (0.95, 1.03)
P for difference		0.51	0.74	0.46	0.62
	Coffee				
	Q1	Q2	Q3	Q4	Per 100 g
Diabetics [a]	1 (ref)	0.73 (0.55, 0.96)	0.68 (0.52, 0.89)	0.58 (0.45, 0.77)	0.95 (0.93, 0.97)
Non-diabetics [a]	1 (ref)	1.17 (0.90, 1.52)	0.96 (0.74, 1.26)	0.93 (0.72, 1.21)	0.99 (0.97, 1.00)
Ratio	1 (ref)	0.62 (0.43, 0.91)	0.71 (0.48, 1.04)	0.63 (0.43, 0.92)	0.97 (0.94, 1.00)
P for difference		0.02	0.08	0.02	0.02

[a] Age-, sex- and center-stratified and adjusted for prevalence of heart disease, cancer, or stroke, educational attainment, alcohol consumption, smoking behavior, physical activity, and disease duration and diabetes medication use (in diabetics);

3.4 Alcohol consumption

3.4.1. Associations within persons with diabetes

In men, alcohol consumption of 6 grams/day or more compared with light consumption tended to be associated with higher mortality risk, but not significantly (**Table 3.12**). Adjustment for alcohol consumption in the past only marginally changed the estimates. Non-consumers at baseline seemed to be at a higher mortality risk than men consuming up to 6 grams/day (HR 1.81, [95% CI 1.31, 2.50]). Further adjustment for alcohol consumption in the past only slightly attenuated this relationship. Compared with non-consumers at baseline, men consuming up to 60 grams/day had a lower mortality risk. Adjustment for diabetes-related factors, socio-economic status, lifestyle factors, or past alcohol consumption did not alter the associations. Lowest mortality risk was observed in men who consumed >6-12 grams/day: hazard ratio was 0.50 (95% CI 0.35, 0.71).

Among women, likewise no significant association between an alcohol consumption of 6 grams/day or more and mortality was observed compared with light consumption and with or without adjustment for past alcohol consumption (**Table 3.13**). Women who did not consume alcohol at baseline had a significant higher mortality risk, with a hazard ratio of 1.67 (95% CI 1.18, 2.36) after adjustment for diabetes-related variables, socio-economic status, lifestyle factors, and past alcohol consumption. Risk estimates changed only marginally when adjusted for past alcohol consumption. As in men, female light consumers (>0-6 grams/day) had a lower mortality risk of HR 0.60 (95% CI 0.42, 0.85) compared with non-consumers.

Table 3.14 displays mortality risk in non-consumers at baseline in sub-categories of lifetime non-consumers, always moderate consumers and sometimes heavy consumers. In men, compared with light consumption, a higher risk of death was observed in those who were categorized as persons who always consumed moderate (HR 1.64 [95% CI 1.06, 2.54]) and who sometimes consumed heavy in the past (HR 4.25 [95% CI 1.96, 9.22]). Due to small numbers, only two categories could be built for women. A higher mortality risk was seen in those categorized as former drinkers (HR 1.74 [95% CI 1.19, 2.56]) compared with light consumption.

Cause-specific mortality risks are shown in **Table 3.15**. Compared with light consumers, the higher mortality risks observed in non-consumers appeared to be driven by mortality due to other causes in both men and women and mortality due to CVD in men.

Table 3.12: Hazard Ratios (95% CI) Of The Associations Between Categories Of Baseline Alcohol Consumption And Mortality Risk In 3,453 Men With Diabetes.

	0 g/d	>0-6 g/d	>6-12 g/d	>12-24 g/d	>24-60 g/d	>60 g/d
Median	0	2.3	8.8	17.6	39.0	81.2
n	322	835	527	626	786	355
Cases/ Person-Years	73/2,921	129/7,646	76/4,790	95/5,690	113/7,164	70/3,276
Light alcohol consumption as reference						
HR (95% CI)[a]	1.86 (1.36, 2.53)	1 (ref)	0.79 (0.58, 1.06)	0.84 (0.64, 1.12)	0.94 (0.71, 1.23)	1.35 (0.98, 1.85)
HR (95% CI)[b]	1.87 (1.36, 2.57)	1 (ref)	0.84 (0.62, 1.14)	0.92 (0.69, 1.23)	1.04 (0.78, 1.37)	1.45 (1.05, 2.02)
HR (95% CI)[c]	1.81 (1.31, 2.50)	1 (ref)	0.87 (0.64, 1.18)	0.95 (0.71, 1.27)	1.07 (0.80, 1.44)	1.43 (0.92, 2.06)
HR (95% CI)[d]	1.78 (1.29, 2.46)	1 (ref)	0.89 (0.65, 1.20)	0.95 (0.71, 1.27)	1.03 (0.76, 1.39)	1.25 (0.85, 1.84)
Non-consumers as reference						
HR (95% CI)[a]	1 (ref)	0.54 (0.39, 0.73)	0.42 (0.30, 0.59)	0.45 (0.33, 0.63)	0.50 (0.37, 0.70)	0.72 (0.51, 1.04)
HR (95% CI)[b]	1 (ref)	0.53 (0.39, 0.73)	0.45 (0.32, 0.64)	0.49 (0.35, 0.69)	0.55 (0.40, 0.77)	0.78 (0.54, 1.12)
HR (95% CI)[c]	1 (ref)	0.55 (0.40, 0.76)	0.48 (0.34, 0.68)	0.52 (0.37, 0.74)	0.59 (0.42, 0.83)	0.79 (0.53, 1.18)
HR (95% CI)[d]	1 (ref)	0.56 (0.41, 0.77)	0.50 (0.35, 0.71)	0.53 (0.38, 0.75)	0.58 (0.41, 0.82)	0.70 (0.46, 1.07)

[a] Model 1: Age- and center-stratified;
[b] Model 2: Model 1 adjusted for HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment,
[c] Model 3: Model 2 additionally adjusted for smoking behavior, energy, diet, and physical activity;
[b] Model 4: Model 3 additionally adjusted for alcohol consumption in the past.

Table 3.13: Hazard Ratios (95% CI) Of The Associations Between Categories Of Baseline Alcohol Consumption And Mortality Risk In 2,931 Women With Diabetes.

	0 g/d	>0-6 g/d	>6-12 g/d	>12-24 g/d	>24 g/d
Median	0	1.4	8.4	16.3	36.7
n	787	1,339	352	257	197
Cases/Person-Years	96/7,421	110/12,238	21/3,268	27/2,423	19/1,830
Light alcohol consumption as reference					
HR (95% CI)[a]	1.69 (1.23, 2.32)	1 (ref)	0.74 (0.45, 1.19)	1.25 (0.79, 1.97)	1.46 (0.87, 2.47)
HR (95% CI)[b]	1.81 (1.29, 2.53)	1 (ref)	0.81 (0.49, 1.32)	1.24 (0.77, 1.98)	1.56 (0.91, 2.68)
HR (95% CI)[c]	1.70 (1.20, 2.40)	1 (ref)	0.88 (0.53, 1.47)	1.29 (0.79, 2.10)	1.52 (0.84, 2.75)
HR (95% CI)[d]	1.67 (1.18, 2.36)	1 (ref)	0.90 (0.54, 1.50)	1.30 (0.79, 2.14)	1.46 (0.78, 2.76)
Non-consumers as reference					
HR (95% CI)[a]	1 (ref)	0.59 (0.43, 0.82)	0.44 (0.26, 0.72)	0.74 (0.46, 1.19)	0.87 (0.50, 1.51)
HR (95% CI)[b]	1 (ref)	0.55 (0.39, 0.77)	0.45 (0.27, 0.74)	0.68 (0.42, 1.12)	0.86 (0.48, 1.54)
HR (95% CI)[c]	1 (ref)	0.59 (0.42, 0.84)	0.52 (0.30, 0.89)	0.76 (0.46, 1.27)	0.90 (0.47, 1.69)
HR (95% CI)[d]	1 (ref)	0.60 (0.42, 0.85)	0.54 (0.31, 0.93)	0.78 (0.46, 1.32)	0.88 (0.45, 1.72)

[a] Model 1: Age- and center-stratified;
[b] Model 2: Model 1 adjusted for HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment,
[c] Model 3: Model 2 additionally adjusted for smoking behavior, energy, diet, and physical activity;
[b] Model 4: Model 3 additionally adjusted for alcohol consumption in the past;

Table 3.14: Hazard Ratios (95% CI) Of The Associations Between Categories Of Non-Consumers Of Alcohol At Baseline And Mortality Risk, Compared With Light Consumers.

	Categories of non-consumers at baseline			
	Men			
	0 g/d			>0-6 g/d
	Lifetime non-consumers	Always moderate	Sometimes heavy in the past	
Number	8	226	89	
Cases /Person-Years	2/72	50/2,040	21/808	
HR (95% CI) [a]	0.23 (0.02, 2.15)	1.64 (1.06, 2.54)	4.25 (1.96, 9.22)	1 (ref)
	Women			
	0 g/d			>0-6 g/d
	Lifetime non-consumers	Former consumers		
Number	80	707		
Cases/Person-Years	5/744	91/6,677		
HR (95% CI) [a]	2.76 (0.89, 8.50)	1.74 (1.19, 2.56)		1 (ref)

[a] Age- and center-stratified and adjusted for HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment, smoking behavior, energy, diet, and physical activity.

Table 3.15: Hazard Ratios [a] (95% CI) Between Categories Of Baseline Alcohol Consumption And Cause-Specific Mortality In 6,147 Men And Women With Diabetes.

	CVD	Cancer	Other causes
Men			
0 g/d	2.07 (1.16, 3.68)	1.41 (0.64, 3.12)	2.91 (1.50, 5.63)
>0-6 g/d	1 (ref)	1 (ref)	1 (ref)
>6-12 g/d	1.09 (0.61, 1.95)	0.96 (0.50, 1.85)	0.57 (0.27, 1.21)
>12-24 g/d	1.21 (0.71, 2.07)	1.05 (0.54, 2.04)	0.74 (0.38, 1.43)
>24-60 g/d	1.41 (0.80, 2.49)	0.95 (0.46, 1.94)	1.00 (0.54, 1.85)
>60 g/d	1.35 (0.60, 3.00)	1.13 (0.42, 3.07)	1.11 (0.51, 2.42)
Women			
0 g/d	1.78 (0.87, 3.66)	1.03 (0.48, 2.19)	2.56 (1.15, 5.67)
>0-6 g/d	1 (ref)	1 (ref)	1 (ref)
>6-12 g/d	0.74 (0.23, 2.40)	0.66 (0.20, 2.21)	1.16 (0.35, 3.86)
>12-24 g/d	0.90 (0.28, 2.87)	0.95 (0.27, 3.39)	2.69 (0.86, 8.43)
>24 g/d	0.51 (0.08, 3.45)	1.00 (0.22, 4.50)	2.96 (0.84, 10.45)

[a] Age- and center-stratified and adjusted for HbA_{1c}, diabetes duration, medication use, prevalence of heart disease, cancer, or stroke, educational attainment, smoking behavior, energy, diet, physical activity, and alcohol consumption in the past;

3.4.2. Associations between persons with and without diabetes

Mortality risk in men and women with diabetes who reported to be non-consumers at baseline was higher compared with non-consumers without diabetes using light alcohol consumption as a reference category, although mortality risk was also increased in non-consumers without diabetes (**Table 3.16**). Mortality risk was HR 1.64 (95% CI 1.21, 2.23) in non-consuming men with diabetes and HR 1.61 (95% CI 1.17, 2.22) in non-consuming women with diabetes. Furthermore, a higher alcohol consumption appeared to be more detrimental in men with diabetes compared with diabetes-free men, but this difference was not significant.

Table 3.16: Hazard Ratios (95% CI) Of Associations Between Categories Of Baseline Alcohol Consumption And Mortality In 6,384 Men And Women With Diabetes And 19,152 Men And Women Without Diabetes.

	Categories of baseline alcohol consumption					
	Men					
	0 g/d	>0-6 g/d	>6-12 g/d	>12-24 g/d	>24-60 g/d	>60 g/d
Diabetics [a]	1.64 (1.21, 2.23)	1 (ref)	0.88 (0.95, 1.63)	0.98 (0.74, 1.29)	1.03 (0.78, 1.35)	1.23 (0.88, 1.74)
Non-diabetics [a]	1.24 (0.95, 1.63)	1 (ref)	0.86 (0.69, 1.08)	0.78 (0.63, 0.97)	0.79 (0.64, 0.98)	0.88 (0.66, 1.17)
Ratio	1.32 (0.88, 1.99)	1 (ref)	1.02 (0.70, 1.48)	1.25 (0.88, 1.78)	1.30 (0.92, 1.85)	1.40 (0.90, 2.19)
P for difference	0.18		0.91	0.22	0.14	0.14
	Women					
	0 g/d	>0-6 g/d	>6-12 g/d	>12-24 g/d	>24 g/d	
Diabetics [a]	1.61 (1.17, 2.22)	1 (ref)	0.80 (0.49, 1.31)	1.33 (0.84, 2.11)	1.21 (0.69, 2.11)	
Non-diabetics [a]	1.04 (0.78, 1.39)	1 (ref)	0.79 (0.58, 1.08)	0.94 (0.69, 1.28)	1.39 (0.99, 1.96)	
Ratio	1.55 (1.01, 2.40)	1 (ref)	1.02 (0.57, 1.83)	1.42 (0.82, 2.48)	0.87 (0.45, 1.66)	
P for difference	0.05		0.94	0.22	0.67	

[a] Age-, sex- and center-stratified and adjusted for prevalence of heart disease, cancer, or stroke, educational attainment, smoking behavior, physical activity, diet, alcohol consumption in the past, and disease duration and medication use (in diabetics);

3.5 Physical activity

3.5.1. Associations within persons with diabetes

Table 3.17 shows the associations between total physical activity, leisure-time physical activity, walking, and mortality risk in 6,384 individuals with diabetes. Higher levels of total physical activity as well as leisure-time physical activity were related to a lower risk of death.

Compared with physical inactive individuals, physically active individuals had a decreased risk of total and CVD mortality. The lowest hazard ratio was observed in moderately active persons: 0.60 (95% CI 0.47, 0.74) after multivariable adjustment. When excluding heavy manual workers and non-workers from the analyses, the lowest risk was still observed in the moderately active group.

Next, leisure-time physical activity was associated with lower mortality. Compared with persons in the lowest category, persons in the highest category of leisure-time activity had a mortality risk of HR 0.70 (95% CI 0.55, 0.88) in the fullest adjustment model.

The relationship of walking with total mortality was less pronounced: individuals who reported to walk for a median of 42 MET-hours/week had a hazard ratio of 0.91 (95% CI 0.73, 1.14). Of note, walking was not associated with other causes of death. Additional adjustment for vigorous physical activity did not alter the mortality risk associated with walking.

Table 3.18 shows associations of physical activity with specific causes of death. Total physical activity was in particular related to death due to CVD and other known causes. Leisure-time physical activity was in particular associated with cancer mortality. Furthermore, although walking was not significantly associated with all-cause mortality, an association with mortality due to CVD could be detected. For one quartile increase, the corresponding hazard ratio was 0.82 (95% CI 0.71, 0.95).

Among women, the associations between the several indices of physical activity and mortality were slightly stronger compared with men. Women who reported to be active had a hazard ratio of 0.57 (95% CI 0.37, 0.90) in the fullest adjustment model compared with a hazard ratio of 0.70 (95% CI 0.53, 0.92) in active men. Moreover, women who reported to be active during their leisure-time had a hazard ratio of 0.37 (95% CI 0.24, 0.57) compared with a hazard ratio of 0.73 (95% CI 0.54, 0.99) in men from the same category.

Table 3.17: Hazard Ratios (95% CI) Of The Associations Between Physical Activity And Mortality In 6,384 Persons With Diabetes.

	Physical activity				
	Total physical activity				
	Inactive	Moderately inactive	Moderately active	Active	P-Trend
n	1,863	2,006	1,312	1,203	
Cases / PY	320/16,546	240/18,285	130/12,314	140/11/521	
HR (95% CI)[a]	1 (ref)	0.65 (0.55, 0.78)	0.51 (0.41, 0.64)	0.60 (0.48, 0.76)	<.0001
HR (95% CI)[b]	1 (ref)	0.68 (0.57, 0.81)	0.55 (0.44, 0.70)	0.64 (0.51, 0.81)	<.0001
HR (95% CI)[c]	1 (ref)	0.72 (0.60, 0.86)	0.60 (0.47, 0.75)	0.71 (0.56, 0.90)	0.0001
	Leisure-time physical activity				
	Low	Medium	High	Very high	P-Trend
n	1,638	1,353	1,479	1,914	
Cases / PY	286/15,228	198/12,266	178/13,237	168/17,936	
HR (95% CI)[a]	1 (ref)	0.78 (0.64, 0.94)	0.71 (0.58, 0.87)	0.62 (0.49, 0.78)	<.0001
HR (95% CI)[b]	1 (ref)	0.80 (0.66, 0.97)	0.71 (0.58, 0.87)	0.65 (0.51, 0.82)	<.0001
HR (95% CI)[c]	1 (ref)	0.83 (0.68, 1.00)	0.74 (0.60, 0.91)	0.69 (0.54, 0.87)	0.001
	Walking (MET-hrs/wk)				
	Q1	Q2	Q3	Q4	P-Trend
Median	3.0	10.5	21.0	42.0	
n	1,778	1,596	1,414	1,596	
Cases / PY	290/16,550	195/14,703	155/12,902	190/14,512	
HR (95% CI)[a]	1 (ref)	0.79 (0.65, 0.96)	0.81 (0.65, 1.01)	0.92 (0.73, 1.15)	0.76
HR (95% CI)[b]	1 (ref)	0.83 (0.69, 1.01)	0.84 (0.84, 1.05)	0.91 (0.72, 1.14)	0.61
HR (95% CI)[c]	1 (ref)	0.85 (0.70, 1.03)	0.84 (0.84, 1.04)	0.91 (0.73, 1.14)	0.60

Abbreviations: PY, person-years.
[a] Model 1: Age- and center-stratified and adjusted for gender;
[b] Model 2: Model 1 additionally adjusted for , HbA_{1c}, diabetes duration, medication use, and prevalence of heart disease, cancer, or stroke;
[c] Model 3: Model 2 additionally adjusted for alcohol consumption, smoking behavior, energy, and diet.

Table 3.18: Hazard Ratios (95% CI) Of The Associations Between Total Physical Activity, Leisure-Time Physical Activity And Walking (Per Category Or Quartile Increase) And Cause-Specific Mortality In 6,147 Persons With Diabetes.

	CVD	Cancer	Other causes
Total physical activity	0.80 (0.69, 0.94)	0.89 (0.75, 1.06)	0.84 (0.72, 0.98)
Leisure-time physical activity	0.87 (0.75, 1.00)	0.77 (0.65, 0.91)	0.96 (0.83, 1.12)
Walking	0.82 (0.71, 0.95)	0.89 (0.76, 1.04)	1.08 (0.92, 1.26)

[a] Age- and center-stratified and adjusted for gender, HbA_{1c}, diabetes duration, medication use, and prevalence of heart disease, cancer, or stroke, alcohol consumption, smoking behavior, energy, and diet.

3.5.2. Associations between persons with and without diabetes

Table 3.19 shows the difference in associations for several physical activity indices. Leisure-time physical activity was significantly stronger associated with a lower mortality risk in person with diabetes compared to persons without. Furthermore, total physical activity was associated with a lower mortality risk in both persons with and without diabetes. However, in persons with diabetes, those who were moderately active had the lowest mortality risk, significantly lower than moderately active persons without diabetes. In both groups, walking was not associated with mortality risk, although also here the associations tended to be stronger in persons with diabetes.

Table 3.19: Hazard Ratios (95% CI) Of Associations Between Physical Activity And Mortality In 6,384 Persons With Diabetes And 19,152 Persons Without Diabetes And The Ratio Between These Associations.

	Physical activity			
	Total physical activity			
	Inactive	Moderately inactive	Moderately active	Active
Diabetics [a]	1 (ref)	0.69 (0.58, 0.83)	0.59 (0.47, 0.74)	0.70 (0.55, 0.88)
Non-diabetics [a]	1 (ref)	0.84 (0.72, 0.97)	0.82 (0.69, 0.97)	0.74 (0.62, 0.88)
Ratio	1 (ref)	0.83 (0.66, 1.04)	0.73 (0.55, 0.96)	0.96 (0.70, 1.27)
P for difference		0.10	0.03	0.71
	Leisure-time physical activity			
	Low	Medium	High	Very high
Diabetics [a]	1 (ref)	0.80 (0.66, 0.97)	0.74 (0.61, 0.91)	0.65 (0.52, 0.83)
Non-diabetics [a]	1 (ref)	0.98 (0.84, 1.14)	1.01 (0.86, 1.18)	0.95 (0.79, 1.14)
Ratio	1 (ref)	0.85 (0.64, 1.05)	0.74 (0.57, 0.95)	0.69 (0.51, 0.92)
P for difference		0.11	0.02	0.01
	Walking			
	Q1	Q2	Q3	Q4
Diabetics [a]	1 (ref)	0.87 (0.71, 1.07)	0.85 (0.69, 1.04)	0.90 (0.72, 1.12)
Non-diabetics [a]	1 (ref)	0.95 (0.80, 1.12)	1.08 (0.92, 1.26)	1.11 (0.94, 1.32)
Ratio	1 (ref)	0.92 (0.70, 1.19)	0.79 (0.61, 1.01)	0.81 (0.61, 1.07)
P for difference		0.52	0.06	0.13

[d] Age-, sex- and center-stratified and adjusted for prevalence of heart disease, cancer, or stroke, alcohol consumption, smoking behavior, energy intake, diet, and disease duration and medication use (in diabetics);

3.6 Sensitivity analyses

3.6.1. Sensitivity analysis within persons with diabetes

When excluding those who reported to have had heart disease, stroke, and cancer or had a follow-up period of less than two years, the associations between measures of adiposity and mortality risk seemed to be slightly weaker in both men and women. The associations between food groups, alcohol, and physical activity were not affected by excluding participants who were likely to be severely ill at baseline.

No large differences could be detected between the analyses performed with and without multiple imputation, indicating that the missing observations for either the exposure variables or any of the potential confounding factors did not influence the associations.

3.6.1. Sensitivity analyses within persons with and without diabetes

Excluding participants with co-morbidities at baseline did not substantially influence the risk estimates of persons with and without diabetes as well as the differences in associations. Only the observed difference in associations for coffee consumption attenuated: the ratio between the hazard ratios was 0.98 (95% CI 0.95, 1.02) and the *P*-value for difference was 0.33. Furthermore, the associations of walking and mortality strengthened among persons with diabetes to such an extent that they became significantly stronger compared with persons without diabetes.

Excluding participants classified as energy misreporters did not affect the associations as well as the difference in associations for food group consumption.

4. Discussion

4.1 Summary

The results from this prospective study show that, although diabetes mellitus confers a higher mortality risk per se, lifestyle factors could explain this to a reasonable extent. A favorable lifestyle characterized by low levels of abdominal adiposity, an overall healthy diet, alcohol consumption within the recommended limits, and higher levels of physical activity were related to lower mortality risk in men and women with diabetes mellitus. Results further suggest that the favorable associations of leisure-time physical activity and coffee consumption with mortality are stronger in persons with diabetes compared with diabetes-free individuals. Diabetes status did not substantially influence the associations between the other studied lifestyle factors and mortality risk, including adiposity, other food groups, and alcohol consumption. Overall, no indications were found that diet and lifestyle recommendations should be different in persons with diabetes compared with persons without diabetes.

4.2 Overall discussion

Despite major advances in clinical medicine, maintaining a healthy diet and lifestyle offers the largest potential to reduce CVD risk in the general population. Therefore, the American Heart Association has composed recommendations to reduce CVD risk through healthy eating habits and other lifestyle factors. In short, these diet and lifestyle recommendations include achieving a healthy weight, consuming an overall healthy diet, aim for recommended levels of lipids and normal levels of blood pressure and blood glucose, be physically active, and avoid use or exposure to tobacco products [112].

Since the discovery of insulin in 1921, diabetes mellitus has become a manageable but chronic condition. It is a well-established disease with a standardized treatment including medical and lifestyle therapies. However, due to a lack of epidemiological studies in persons with diabetes, the lifestyle advices for primary prevention of CVD in diabetes are similar to those for the general population [30]. Therefore, this thesis' first aim was to provide evidence on lifestyle and mortality risk in persons with diabetes. We found that a healthy lifestyle as recommended to the general population was also in persons with diabetes associated with lower mortality risk.

The thesis' second aim was to investigate whether associations were different between persons with and without diabetes. We observed that diabetes status did not appear to influence the relations between the studied lifestyle factors and mortality risk. Thus, no indications were found that these diet and lifestyle recommendations for persons with diabetes should be different from the general population. Favorable lifestyle behaviors, including a healthy weight, a healthy diet, and being physically active is associated with a reduced mortality risk in persons with and without diabetes. The risk reduction to be achieved with leisure-time physical activity and coffee consumption was significantly stronger in persons with diabetes than persons without a diagnosis, but the direction of the association was the same.

Diabetes develops insidiously over several years, during which the glucose metabolism progresses slowly from normal to pre-diabetes and then more rapidly to diabetes [3]. Although classic diabetes symptoms such as polyuria, polydipsia, and unexplained weight loss can be used in the diagnostic test, measurement of blood glucose or HbA_{1c} are always involved. The disease can remain asymptomatic for years, as a result it has been estimated that up to 50% of all patients with type 2 diabetes are undiagnosed [3]. The clinical diagnosis of diabetes is based on the occurrence of a complication of the disease, not on symptoms of the disease itself: the diagnosis is defined by a pre-specified cut-off point on a continuous scale of decreasing glycemic control. Pre-diabetes is defined as a state of impaired glucose tolerance or impaired fasting glucose, but below the official diagnostic criteria [2]. Pre-diabetes is already associated with modest increases in CVD risk [113] and people with pre-diabetes might benefit from lifestyle or medical interventions which can reduce or delay the progression to diabetes [3]. Furthermore, HbA_{1c} has been shown to be related to an increasing risk throughout the whole range of concentrations, even below the diabetic threshold [114]. Because diabetes is a continuously progressing condition and diabetes status did not influence the associations between lifestyle and mortality, we assume that the same recommendations also hold for persons in a pre-diabetic state as well as with undiagnosed diabetes. In conclusion, diabetes mellitus is not a clearly defined situation of "present" or "not present". There is a certain degree of randomness involved in the diagnosis of the disease: the date of diagnosis may very well be the date of a doctor's appointment. However, our findings show that these uncertainties associated with the diagnosis and the different stages of the disease do not seem relevant in terms of diet and lifestyle recommendations. Concerning primary prevention of CVD and premature mortality by diet and lifestyle, it is not necessary to know whether a person has been diagnosed with diabetes, and, thus, whether a person is at low or at high risk.

Diet, in particular carbohydrate intake, needs to be well-balanced with medication in most persons with diabetes to achieve glycemic control. Therefore, medical nutrition therapy provided by a registered dietitian is recommended. Successful nutrition therapy in diabetes is not a 'one size fits all' diet, but an approach tailored to the individual that also incorporates intensive nutrition education, active follow-up and ongoing support [115]. However, there is no optimal combination of macronutrients in diabetes [30]. Moreover, this study found no indications that the optimal diet in diabetes should be of a different composition.

Although we can conclude that no indications were found that diet and lifestyle recommendations for persons with diabetes should be different from the general population, we do not know whether persons with diabetes might benefit more from leading a healthy lifestyle. Adhering to a healthy lifestyle might be more beneficial in persons with diabetes, since they are at increased risk of CVD and premature mortality and their lifestyle behaviors are in general less healthy than the general population.

4.3 Selected lifestyle factors

4.3.1 Measures of general and abdominal adiposity

In men and women with diabetes mellitus, indicators of abdominal obesity, i.e. waist circumference, waist/hip ratio, and waist/height ratio were positively associated with mortality. These associations seemed to be independent from general obesity. Compared with other measurements, waist/height ratio showed the strongest association with mortality. Body mass index, as an indicator of general obesity, was not independently positive associated with mortality in men or women with diabetes. Associations in persons with diabetes were less strong than those observed in persons without diabetes.

Prospective studies into the relationship between body mass index and mortality in individuals with diabetes mellitus have shown heterogeneous results. Some investigations observed an inverse association between body mass index and mortality [44-47]. Two other cohort studies demonstrated that a high body mass index was related to increased mortality [41, 42] and coronary heart disease [43]. Body mass index was not associated with risk of death in two other studies when the level of exercise capacity was taken into account [48, 49] and two investigations found a U- or J-shaped relationship between body mass index and mortality [50, 51]. In the EURODIAB Prospective Complications Study, Waist/hip ratio was negatively associated with overall, CVD, and non-CVD mortality, whereas no association was observed for body mass index [52]. However, this study population was restricted to persons with type 1 diabetes. Moreover, Sone *et al.* observed that waist circumference was not associated with CVD incidence in Japanese diabetes patients [53]. Of note, associations in these studies were not adjusted for other anthropometric measurements. Finally, these inconsistent results and our findings suggest that body mass index alone is not an adequate sufficient measure when investigating the association between adiposity and mortality in individuals with diabetes.

Among the strongest associations were those observed for waist/height ratio. Waist/height ratio has not been investigated as an indicator for abdominal obesity as often as waist circumference and waist/hip ratio, but it has been shown to carry more information than the other anthropometric indices in predicting cardiovascular risk factors and mortality in the general population [116-119]. Waist/height ratio comprises two measurements: waist circumference reflects the amount of abdominal fat and height is also associated with adverse outcomes [119, 120]. Furthermore, it has been shown that individuals with a shorter stature have a higher percent body fat compared with people of the same body mass index and a longer stature [121]. Moreover, height is inversely related to overall mortality [122]. Therefore, the waist/height ratio is suggested to be a relevant measurement of relative fat distribution among participants of different ages and statures [120]. In two cross-sectional studies in persons with diabetes, Waist/height ratio suggested the strongest association with coronary artery disease [123] and adverse cardiorenal outcomes [124] compared with body mass index, waist circumference, and waist/height ratio. To our knowledge, this is the first prospective study investigating the relationship between waist/height ratio and mortality in individuals with diabetes.

The observed associations between measures of abdominal adiposity and mortality tended to be stronger after adjustment for body mass index. Furthermore, a higher body mass index – independent of waist/height ratio – was associated with decreased mortality. When waist circumference is held constant, body mass index may indicate lean body mass, whereas waist measurements, independent of body mass index, are indices of abdominal fat mass [125]. Adjusting the relationship of waist circumference and mortality for body mass index means the modeling of waist circumference when body mass index, and thus body weight, is kept constant. An increase in the waist circumference, without an increase in weight, would, therefore, indicate an increase in peripheral fat mass and a decrease in muscle mass.

Associations for general and abdominal adiposity measures and mortality tended to be stronger in persons without diabetes. The diabetic subjects with low body mass index might have been more severe cases of diabetes, since the proportion of insulin users was higher and diabetes duration was longer. Severe illness will lead to a decrease in fat mass as well as muscle mass and will, therefore, be more reflected in body mass index. Moreover, persons with a higher body mass index probably benefited from their energy stores [126]. This can explain why some studies observed that a high body mass index was related to a decreased mortality risk [44-47]. Thus, reverse causality from their disease or other prevalent diseases might explain that adiposity measures were stronger associated with mortality in persons without diabetes compared with diabetic persons [127]. Pischon *et al.* investigated the association between general and abdominal obesity and risk of death in the overall EPIC study population (*n* = 359,387) [39]. Participants in the lower and upper body mass index categories had an increased risk of death and abdominal obesity as measured by waist circumference and waist/hip ratio was strongly associated with mortality after adjustment for body mass index. Results of the present study suggest that abdominal adiposity plays a more important role for mortality risk in persons with diabetes than general adiposity. This can be due to the fact that abdominal adiposity is strongly related to development of diabetes mellitus type 2 [128] and heterogeneity of body mass index might be lower than heterogeneity in measures of abdominal obesity in this population. Obesity is estimated to account for approximately 60% of the cases of type 2 diabetes [129].

In conclusion, measurements of abdominal but not general adiposity were associated with increased risk of death in diabetic men and women. Associations tended to be weaker compared with persons without diabetes.

4.3.2 Food group consumption

In men and women with diabetes, higher consumption of vegetables, nuts and seeds, pasta, rice, bread, cakes and cookies, and coffee was associated with a lower mortality risk. The strongest risk reduction was observed for coffee consumption. Moreover, high intakes of butter and margarine and soft drinks were related to an increased mortality risk. In addition, a moderate consumption of cheese, vegetable oil, sugar and confectionary, and juices were associated with a lower mortality risk in persons with diabetes. These associations were independent from various lifestyle factors, including other food groups and body size.

The associations tended to be stronger in persons with diabetes compared with diabetes-free individuals, but only a significant difference was observed for coffee consumption.

Compared with other food groups, the strongest protective associations were observed for coffee consumption. Moreover, these associations were significantly stronger in diabetic persons compared with diabetes-free individuals. Coffee consumption has been consistently associated with a lower risk of type 2 diabetes [130, 131]. The protective effect of coffee is unlikely to be the solely effects of caffeine, but rather the broad range of antioxidant components and other constituents such as magnesium, lignans, and chloreogenic acids. These components have been found to have beneficial effects on biological pathways intimately involved in glucose homeostasis and insulin secretion [130]. Furthermore, it has been suggested that oxidative stress is a common factor leading to insulin resistance, beta cell dysfunction, impaired glucose tolerance, and finally type 2 diabetes [132]; thus, coffee consumption may also be beneficial in the diabetes patient. It appears that the mechanisms involved in coffee consumption and diabetes incidence are also valid for the treatment of diabetes and its complications. The present study confirms this hypothesis, but evidence from other prospective studies in persons with diabetes is not conclusive. Bidel *et al.* reported that coffee consumption was associated with a reduced risk of total mortality in 3,837 Finnish diabetes patients [56], but a cohort study in 3,497 diabetic men from the Health Professionals Follow-up Study [62] and an observational study in 7,170 women from the Nurses' Health Study [61] did not show a protective effect of coffee consumption.

Next, a higher consumption of nuts and seeds was associated with a lower mortality risk, independent of other lifestyle factors, as well as body size and consumption of other food groups. Nuts are low in saturated fat and rich in unsaturated fatty acids as well as vegetable protein, fiber, phytosterols, polyphenols, vitamins and minerals. These compounds may be held responsible for improving endothelial function, blood pressure, and serum lipid profile, as well as lowering oxidative stress and inflammation [133, 134]. Observational studies in the general population have consistently shown that nut consumption is related to reduced risk of CHD [133]. An analysis of women with type 2 diabetes showed that those consuming five or more servings of nuts and peanuts per week had more favorable LDL-cholesterol levels and overall a 44% lower risk of developing CVD [57]. Although evidence in persons with diabetes is less conclusive, there are indications that nut consumption is also associated with diabetes incidence by their favorable effects on glycemic control, but long-term effects are not clear [134]. Due to their high fat content and energy density, a moderate consumption of nuts as part of a healthy diet may be recommended to persons with diabetes.

Vegetables were also favorably related to a lower mortality risk. Within EPIC, it was already shown that an increment in vegetable, legume and fruit intake was associated with a reduced mortality risk of 0.94 (95% CI 0.90, 0.98); when analyzed separately, vegetables and legumes were associated with a significantly reduced risk [60]. In the Greek arm of the EPIC study, no significant associations were found for vegetable consumption and mortality [35]. The effects of fruit and vegetable intake on the incidence of diabetes are less conclusive; a systematic review and meta-analysis of six prospective cohort studies showed no significant benefits of fruit and vegetables [135]. However, numerous mechanisms explaining the

beneficial effects on CVD and overall mortality have been suggested in persons with and without diabetes, such as the antioxidant effects of vitamins, minerals, and polyphenols [136].

Higher intakes of the carbohydrate-rich foods pasta, rice, and bread were related to a reduced mortality risk. There is a large body of evidence that whole grain foods protect against the development of diabetes and improve glycemic control in diabetes patients [137]. A meta-analysis of six cohort studies showed that an increment of 2 servings of whole grain per day was associated with a 21% risk reduction for type 2 diabetes [138]. Moreover, among 7,822 women with diabetes from the Nurses' Health Study, consumption of whole-grain, cereal fiber, bran and germ was associated with a 16% to 31% lower overall mortality risk. However, only the associations for bran intake were independent from other lifestyle factors [59]. Whole-grains are known to have beneficial effects on serum lipids and blood pressure, improve glucose and insulin metabolism, endothelial function, and reduce inflammation and oxidative stress [137].

A higher consumption of butter and margarine were associated with higher mortality, whereas a moderate vegetable oil consumption was related to a lower risk. These findings are in line with results from other observational studies among persons with diabetes. Among Greek adult with diabetes, it was shown that saturated fat was associated with significant increase in mortality [35]. Moreover, analyses of the Nurses' Health Study reported that a higher intake of saturated fat and cholesterol were related to increased CVD risk among diabetic women [139]. In addition, within the Nurses' Health Study and an investigation among Finnish men and women with diabetes, a lower ratio of polyunsaturated fat to saturated fat was related to a lower risk of CVD. Saturated fats may induce insulin resistance and thus worsen glycemic control. Moreover, a favorable lipid profile has also been related to lower CVD incidence in diabetic subjects. Furthermore, effects on endothelial function and thrombogenesis are behind these beneficial effects [55, 139]. Thus, choosing food groups high in polyunsaturated fatty acids over saturated fatty acids is likely to reduce mortality risk in persons with diabetes.

Soft drink consumption was related to higher mortality risk. To our knowledge, no other studies have investigated soft drink consumption and mortality in persons with diabetes. A prospective study among 4,304 men and women did show that higher intakes of fructose, glucose and sweetened beverages were related to increased risk of type 2 diabetes [140]. The detrimental effects of soft drinks are most likely to be due to the high glycemic index of glucose and a subsequent increased stress to insulin secretion. Furthermore, higher intake of glucose and fructose may lead to a positive energy balance and may therefore play a role in body weight increases. Moreover, it has been observed that a high consumption of liquid foods with a high energy density is usually not compensated by a reduction in food and energy intake; thus leading to a positive energy balance [141].

Paradoxically, higher consumption of sugar and confectionary as well as cake and cookies were associated with reduced mortality risk. These associations were only apparent in the analyses within persons with diabetes, not in the combined analyses of persons with and without diabetes. In an analysis of the Nurses' Health Study, it was reported that homemade pie and cake were inversely related to diabetes incidence among women with a body mass index <29 kg/m^2 [142]. A larger body of evidence on the detrimental

effects of fats and sugars contradict these findings. Our results might be an artifact: the result of systematic underreporting of high consumers. It has been shown that obese subjects with diabetes tend to underreport their energy intake to a greater extent than obese subjects without diabetes [143]. An inverse association might also have occurred if persons with diabetes have reduced their cake and cookie consumption after diagnosis and before baseline as a result of their ill health. In that case, persons with a higher consumption had in general a better health status. This confounding effect was accounted for in a sensitivity analysis by excluding participants who reported co-morbidities or had a follow-up of less than two years and findings remained. However, since we do not know whether diabetic persons have changed their consumption after their diagnosis, it could have been due to their diabetes status.

In general, adherence to the nutrition recommendations for disease management and prevention of complications was associated with a lower mortality risk in persons with diabetes. No indications were found that these nutrition recommendations should be different compared with the general population. More research is needed to assess whether a higher coffee consumption is truly more beneficial in persons with diabetes.

4.3.3 Alcohol consumption

No association between current alcohol consumption over 6 grams per day and mortality risk compared with light consumption could be shown, also when past alcohol consumption was accounted for. Men and women with diabetes who abstained from alcohol at baseline had a higher mortality risk compared with light consumers. This observed association was more apparent in persons with diabetes compared with diabetes-free individuals. This study suggests that the increased risk in non-consumers was influenced by their past alcohol consumption rather than their current abstinence.

Several studies investigated the association between alcohol and mortality in individuals with diabetes. A meta-analysis pooled six prospective studies and showed that mortality risk was decreased for a consumption of >0 and <6 grams/day compared with non-consumers (RR 0.64, 95% CI 0.49, 0.82). Furthermore, risks of fatal and total CHD were decreased with an alcohol consumption of >0 and <6, 6-18, and ≥18 grams/day compared with non-consumers [83]. Moreover, among 404 diabetic and glucose-intolerant Japanese men, non-daily consumers had a decreased mortality compared with never consumers. No association was observed for former or daily consumers [66]. Considering the different reference category, these results seem to be in line with the current findings.

Regardless of pre-existing diabetes, moderate alcohol consumption has been linked to a lower risk of atherosclerotic diseases and overall mortality compared with non-consumers, which could be explained by beneficial changes in lipid metabolism, endothelial function, inflammation, haemostatic balance, insulin sensitivity, and blood pressure [144]. These favorable effects are particularly relevant in individuals with diabetes, in whom coronary risk factors are highly prevalent [87, 145]. In the general population, the relationship between alcohol and mortality has been consistently described as a J- or U-curve. This was

confirmed in a meta-analysis of 34 prospective studies, where consumption of up to four drinks per day in men and up to two drinks per day in women was inversely associated with total mortality compared with non-consumers [82].

We did not observe an association between a current alcohol consumption of more than 6 grams/day and mortality risk compared with light consumers. However, the meta-analysis of Koppes *et al.* has shown that consumption of 0 to 6 grams/day may already give protection compared with abstinence [83]. These findings demonstrate that consumption above 6 grams/day is not associated with mortality compared with a condition that is already considered beneficial. Thus, this does not mean that alcohol consumption is not associated with mortality in diabetic persons, but that the difference between the protection associated with light consumption and a higher consumption is not significantly different.

These results show that the choice of reference category can have a substantial influence on the interpretation of an observed association between alcohol consumption and mortality. We chose light alcohol consumers as a reference group, because it has been shown that non-consumers - including former drinkers - as well as lifetime abstainers do not constitute a useful reference category. First, lifetime abstinence of alcohol is in many high-income countries not normative. As a consequence, this group is relatively small and members of this group differ from consumers in many other health determinants [85]. Second, the inclusion of former drinkers in the reference group when investigating alcohol consumption has been under discussion for over two decades [86, 89]. We observed that non-consumers had a higher mortality risk compared with light consumers at baseline when controlled for confounders including co-morbidities. In general, this can be explained by: 1) these persons were lacking the favorable physiological effects of alcohol reported above, or 2) these persons quit due to health reasons. The second explanation supports the hypothesis that the group of non-consumers may include the so-called “sick-quitters”, which originates from findings of Shaper *et al.* [89]. This hypothesis reads: a separation of abstainers into lifelong abstainers and former consumers leads to less pronounced or to a complete disappearance of beneficial effects observed in moderate consumers relative to non-consumers. Persons who quit consuming alcohol due to health reasons are more vulnerable to mortality and, thus, may be responsible for some or most of the higher risk of abstainers [89, 146]. However, Constanzo *et al*. conclude in a review that the protective effect seen for moderate alcohol consumption does not appear to be substantially related to the fact that former consumers are included in the reference group [86]. In their meta-analysis, Di Castelnuovo *et al.* showed that the protective effect of alcohol among the general population was lower when former consumers were excluded, but still significant [82]. On the other hand, Friesema *et al.* found that lifetime alcohol consumption was not related to mortality or CVD incidence, whereas current consumption was associated with lower CVD and mortality risk compared with never drinkers [88]. Because our population consisted of individuals with diabetes, their diagnosis or the existence of co-morbidities are plausible explanations for their decision to quit consuming alcohol. This would mean that their ill health rather than their alcohol consumption drove the association. When comparing the associations to persons without diabetes, this theory is being further confirmed. The observed mortality risk in non-consumers was stronger in persons with diabetes, suggesting that it was due to their diagnosis or ill health in general that they quitted consuming alcohol.

In conclusion, these results are in support of the current advice that persons with diabetes mellitus can consume alcohol within the recommended upper limits. The increased mortality risk among non-consumers appeared to be affected by their past alcohol consumption rather than their current abstinence. In addition, this study supports the hypothesis that former consumers, abstinent at point of entry into the study, do not constitute a useful reference category.

4.3.4 Physical activity

Higher levels of total physical activity, leisure-time physical activity, and walking were associated with a lower risk of total mortality in individuals with diabetes mellitus. Diabetic persons who reported being moderately physically active had lowest mortality risk compared with those who reported being physically inactive. These associations were stronger in persons with diabetes compared with diabetes-free individuals, in particular those associations observed for leisure-time activities.

In persons with diabetes, an increase in physical activity has shown to reduce HbA_{1c} [95, 147] and improve insulin sensitivity [91]. Moreover, physical activity has been shown to have beneficial effects on inflammation, hypertension, dyslipidemia, endothelial function, and abdominal adiposity in persons with and without diabetes [148-151].

The association between total physical activity and mortality appeared to be slightly J-shaped. This could have been due to misclassification of activity levels which may be higher in the most physically active group due to labeling bias. This result is in contrast with other studies, which showed linear inverse associations with the lowest observed hazard ratio in the highest quantile [35, 73, 75, 76, 78, 79]. To our knowledge, at least two of them did not consider occupational activity [73, 78]. In the present study, participants reporting heavy manual physical activity at work were automatically assigned to the “active” category. Mortality risk in these participants tended to be higher compared with sedentary workers, but not significantly. People with an occupation that involves heavy manual work are more likely to be more frequently exposed to occupational risk factors and to have a lower socio-economic status, and, therefore, may have more unfavorable risk factors [152]. However, excluding heavy manual workers and non-workers from the analyses did not change the estimates. An alternative explanation for these findings is that high physical activity levels could be linked to increased risk of hypoglycemia and injuries in particular in insulin users [93, 94]. In the present study, the proportion of insulin users was highest in the most active persons, but excluding insulin users did not alter the findings. However, additional data on presence of hypoglycemia and injuries was not available. Thus, diabetic individuals who are physically inactive appear to have a higher risk of early death and being moderately active may already improve survival. In contrast to persons with diabetes, being moderately active did not confer the lowest mortality risk in the analyses in persons without diabetes. In a dose-response meta-regression [153] and a large prospective cohort study [154] among the general population, moderate activity was also associated with the lowest mortality risk.

Walking may reduce the risk of CVD in people with diabetes by improving glycemic control and other risk factors [94]. Persons in the highest quartiles of walking had a lower risk of CVD mortality compared with the lowest. In contrast, walking was not related with significant lower total mortality risk in the present study, whereas the other studies included in the meta-analysis reported strong inverse relationships [70, 73, 77, 78]. In the present study, persons in the highest category reported walking more than 27 MET-hours per week. Walking levels were lower in the other included studies: in comparison, persons in the active category in the study of Tanasescu *et al.* walked more than 16 MET-hours per week [78]. It is known that Europeans are more active than North American populations [155] and it has been observed in a Dutch population that activities of at least moderate intensity, but not lower intensity, such as walking were related to CVD incidence [156]. This appears to be in contrast to the findings on walking and CVD mortality. However, because no information on walking pace was available, we cannot draw conclusions on walking intensity. In conclusion, although our results failed to reach statistical significance, from the existing literature in persons with diabetes the potential benefits of walking on mortality are well established.

Reverse causality could have overestimated the mortality risks if diagnosed or undiagnosed co-morbidities at baseline were responsible for inactivity. However, when excluding participants with self-reported heart disease, stroke, or cancer at baseline or a follow-up of less than two years, risk estimates were even lower, indicating that it is not likely that reverse causality is an explanation for the results.

Compared with persons without diabetes, results suggested that leisure-time physical activity was stronger related to a lower mortality risk in persons with diabetes. Higher levels of physical activity are also associated with diabetes incidence; physical activity has shown to reduce HbA_{1c} and improve insulin action [91, 95]. This suggests that the underlying mechanisms involved are likely to be beneficial in the prevention as well as the treatment of diabetes mellitus. Moreover, mortality risk observed in those categorized as moderately active was significantly lower in persons with diabetes. Given this was seen specifically for persons with diabetes, it is in support of the theory that higher levels of physical activity could be linked to a higher risk of hypoglycemia, other diabetes- and CVD-related adverse events, or injuries. It also underlines the finding that being moderately active is already associated with a lower mortality risk in persons with diabetes.

In conclusion, these findings underline the importance of the recommendation that diabetic persons should engage in regular physical activity [91]. Because not many diabetes patients adhere to the physical activity recommendations [34] – only 39% of the American adults with diabetes are physically active, compared with 58% in the general American population [91] – future research should focus on identifying and elucidating the determinants of physical inactivity and designing successful intervention strategies to promote active lifestyles.

4.4 Methods

4.4.1 Study design and population

The prospective analyses into physical activity and mortality were conducted within a cohort study, EPIC. In a cohort study, a group of exposed individuals and a group of non-exposed individuals is selected and followed up to compare the incidence rate of disease (or death). A strength of cohort studies is that the exposure of interest has been assessed before the occurrence of the outcome because it limits the effect of reverse causality and avoids recall bias [157]. Potential sources of bias in cohort studies include loss to follow-up and informative censoring, the latter might occur if censoring is caused by the exposure of interest. A cohort study enables a long follow-up period, which is needed to assess mortality as an outcome [157]. The most appropriate method of data-analysis in a cohort study is survival analysis using Cox proportional hazard regression. Survival analysis uses person-time data, which takes the timing of occurrence of the event into account. Cox proportional hazard regression assumes that the ratio of the two hazards is constant over time, i.e. the hazards are proportional [103]. This assumption was tested and met in our data.

EPIC is a large European collaborative effort aimed at investigating the association between diet, lifestyle, and cancer, although the possibility of other outcomes of interest has been considered since the beginning of the project [158]. Therefore, it was possible to verify self-reports of diabetes diagnoses at baseline with a second information source for most of the participants and study mortality as an outcome. Self-reports of diabetes at baseline were confirmed with a second information source, but when no additional information source was available, we were unable to discriminate true- from false-positive case classifications, which might have introduced selection bias into our study. Moreover, although a few false negative cases were found, no systematic screening was conducted. Therefore, this cohort of prevalent diabetic individuals can best be considered as a convenience sub-sample. This could have reduced the external validity of our study. However, selective participation should not impair etiological associations between a lifestyle factor and an outcome. Since this study's main aim was to study associations, it was not considered likely that the lack of a representative sample of the general diabetic and non-diabetic population has biased the results.

We were not able to differentiate between type 1 and type 2 in our study. However, all diet and lifestyle recommendations of the American Diabetes Associations are also valid for type 1 and type 2 diabetes patients, which is why we still consider our analysis meaningful collapsing type 1 and type 2. Although absolute CVD risk in type 1 diabetes patients is lower in type 2 diabetes patients - partly due to their younger age and lower prevalence of other CVD risk factors - the relative risk of CVD is still higher compared with non-diabetic individuals. Furthermore, no data suggest that the lifestyle interventions aimed to reduce CVD are less effective in type 1 diabetes than type 2 diabetes patients [30].

4.4.2 Exposure assessment

4.4.2.1 Questionnaires

Questionnaires, including interviews, are the most common tools for lifestyle assessment in cohort studies. The methodology is inexpensive and feasible in large study populations. They are based on self-report and are subjective; therefore, they will reflect common perceptions rather than precise measures, but can be adequately used to rank individuals according to their lifestyle. However, more objective measurements of lifestyle factors are needed to clarify the physiological mechanisms behind the associations with mortality.

Due to the lack of objectivity of the measurement, random measurement error could have occurred. Random measurement error means that the recorded level of the lifestyle factor fluctuates randomly around true habitual level and when it occurs in an exposure variable it may in some cases bias the effect estimates towards the null; thus, true risk reductions associated with lifestyle factors might have been underestimated [159].

Lifestyle factors were not updated, using only the participants' lifestyle behavior at the beginning of the follow-up period, which would also attenuate associations. Using repeated exposure measurements would be more powerful for addressing possible causal associations; however, repeated measurements were not available in the present study.

4.4.2.2 Anthropometry

Some differences existed between study centers in measuring waist and hip circumference. Waist circumference was measured either at the narrowest circumference of the torso or at the midpoint between the lower ribs and iliac crest. Next, hip circumference was measured either horizontally at the widest circumference of the hips or over the buttocks. A systematic review of 120 studies conducted to investigate whether measurement protocol influenced the relationship of waist circumference and multiple outcomes concluded the influence was not substantial [160]. Therefore, it was not anticipated that differences in measurement methods would affect the results. Furthermore, it was controlled for differences between study centers in the statistical analysis by stratification.

In addition, there is debate whether or not to include mutual adjustments of anthropometric measurements. Because the measurements were highly correlated in this study population, adjustment may induce collinearity. However, modeling the residual variables of the measurements as a method to overcome this high correlation did not change the results. Furthermore, the effect estimates derived from mutual adjustments warrant careful interpretation.

4.4.2.3 Dietary assessment

Habitual dietary intake of the preceding year was assessed using country-specific food frequency questionnaires (FFQ). The FFQ is a widely used dietary assessment instrument, particularly in large epidemiological studies. A general limitation of the questionnaire is that participants are required to have good memory to accurately report frequency and portion size of their food consumption. Furthermore, food lists may be limited. Various pilot studies have assessed the relative validity and reproducibility of the FFQ's used in EPIC, which found that the repeatability was generally good, while the validity ranged from modest to good [161-167]. Moreover, food group consumption as measured in the FFQ was calibrated with a highly standardized reference dietary measurement taken from an 8% age-stratified random sample of the cohort using a computerized 24-hour dietary recall [98].

Food group consumption is highly correlated with total energy intake and may therefore be non-causally related to disease as a result of confounding by energy intake. Therefore, it was adjusted for energy by the residual method. In this procedure, the food groups of the participants were regressed on their total energy intakes. The residuals from the regression represent the differences between each participant's actual intake and the intake predicted by their total energy intake. Because measurement errors in the assessment of nutrient or food group intakes are strongly related with measurement errors of total energy intake, control for variation in total energy intake will also reduce the errors in the measurement for specific nutrients. Thus, energy adjustment will not only control for confounding by energy intake, but also reduce extraneous variation [105].

4.4.2.4 Assessment alcohol consumption

Information on current and past alcohol consumption was based on self-report, which might have introduced recall bias. Due to misreporting or the fact that the questions asked about alcohol consumption at defined ages only, misclassification into categories of lifelong abstainers, former, and current consumers may have occurred. Moreover, no information was available about the onset and times and reasons for cessation of alcohol consumption. However, in a large cohort study, methods of assessing current and past alcohol consumption are restricted and a self-administered questionnaire has been judged to generate reliable and valid estimates [100, 168].

4.4.2.5 Physical activity assessment

In general, physical activity questionnaires have a low reliability and low validity. Furthermore, domestic and commuting activities have shown to be most difficult to report [169]. The Cambridge Physical Activity Index, which was used as a measure of total physical activity, has shown to have a high repeatability and validity in middle-aged persons [101]. Moreover, the index was also associated with a reduced mortality risk in the EPIC-Norfolk cohort: risk reduction was 32% (95% CI 19-43%) in active persons compared

with those who reported to be inactive [170]. A meta-analysis of physical activity and mortality among the general population found that studies using questionnaires to assess physical activity reported more conservative risk reductions than studies using more objective measurements of fitness; probably the effect of random measurement error [159, 171] . An accelerometer validated with the doubly labeled water method has been suggested as the "gold standard" to assess habitual physical activity in daily life. Doubly labeled water is an excellent method of assessing total energy expenditure and accelerometers can provide objective information about the frequency, the intensity, and the duration of physical activity [169]. However, this method is also costly and requires a high effort from the participant and may therefore not be feasible in large cohort studies. More valid and objective methods to measure physical activity are now becoming available [169], but have not yet been applied in large scale epidemiological studies. Nevertheless, they could be used to validate physical activity questionnaires. In addition, more studies into the dose-response relationship between types of physical activity and mortality are needed to elucidate the specific type, frequency, duration, and intensity of activities which will offer persons with diabetes the most benefits.

4.4.3 Outcome

Present study focused predominantly on all-cause mortality as an outcome. Use of such a composite endpoint can enhance statistical power if a risk factor has a fairly uniform effect on each component of the outcome, but cannot identify differences between the associations of a risk factor with the different components [172]. Thus, it may limit interpretations of the causes of the associations. Diabetes not only confers a higher risk of CVD but also a wide range of other diseases, including cancer, renal and liver disease, and pneumonia [12]. Using overall mortality as an outcome will capture this wide range of morbidities associated with diabetes.

Considering that about 65% of the deaths in diabetes is due to CVD [5, 8], CVD mortality was low in this diabetic population from EPIC, namely 28%. It has been reported that for diabetes-related deaths, it may be difficult for the certifying physician to report whether diabetes directly caused the death or contributed to death [173]. It might have occurred that deaths due to CVD were improperly reported as deaths due to diabetes mellitus; however, this hypothesis is highly speculative and in the present population only eleven deaths were reported with diabetes mellitus as the underlying (i.e. official) cause of death and CVD as the immediate cause of death. Therefore, it is unlikely that this explains the low CVD death rate.

Because a majority of the deaths in diabetes are due to CVD, most diet and lifestyle recommendations are aimed at reducing CVD incidence. In the present study, no data were available on fatal and non-fatal CVD events, only on mortality, which is why we have focused on the overall mortality risk. Moreover, cause-specific mortality risks did not provide meaningful results to put more focus on the different causes.

4.4.4 Confounder selection and adjustment

Although several definitions of confounding exist, it can be described as the effect of an extraneous factor that is mistaken for or mixed with the actual exposure effect which may be null [174]. The goal of most observational research is to estimate this actual exposure effect. When all existing confounders are adequately dealt with, only the causal effect between exposure and disease will remain. The goal of etiologic observational research is to estimate the causal effect and a way to eliminate confounding is to adjust, stratify, or condition on the common cause [175]. In epidemiological studies, confounders are usually not clearly defined and often no structural approach for confounder selection is undertaken. Several methods for confounder identification exist, e.g. the "change-in-estimate" strategy or the "significance-test-of-the-covariate" strategy [176].

To ensure appropriate adjustment in the present study, confounders were selected using directed acyclic graphs or causal diagrams. The use of causal diagrams in epidemiology has been proposed by Greenland *et al.* [106]. Causal diagrams are graphical models for causal relations that underlie a research question. They are a useful way to summarize, clarify, and communicate one's qualitative beliefs about the causal model. Adjustment for the covariates from the identified minimal sufficient adjustment set minimizes bias when estimating the total effect from exposure to outcome. However, it should be kept in mind that causal diagrams are qualitative and do not give information about the strength and direction of the confounding or interaction and they require extensive knowledge about all pathways from exposure to outcome [106]. Furthermore, due to the observational nature of the study, residual confounding cannot be excluded.

4.4.5 Multiple imputation

Missing data are ubiquitous in epidemiological studies, but often neglected or not properly handled during data-analysis. Inappropriate methods of handling missing data may induce bias. Several approaches of dealing with missing data exist, for instance including in the analysis only "complete cases", that is those who have no missing data in any of the variables required for the analysis. However, complete-case analyses are inefficient, since often a substantial proportion of the original sample is excluded, which leads to a loss of precision and power. Furthermore, complete-case analyses are only unbiased when there are no systematic differences between the missing and observed values, which is rarely true [109, 177]. Because the missing values in our study were most likely to be missing at random, multiple imputation was performed. Multiple imputation assumes that any systematic difference between the missing and the observed values can be explained by differences in observed data. It is not an easy or routine technique; however, when the procedure is carried out appropriately and carefully, multiple imputation can improve the validity of the results [109, 178]. Multiple imputation is usually only performed on missing observations in the covariates, not in the exposure or outcome variables, although there are no guidelines. Because several exposures were used in the analyses, we have decided to also impute exposure variables. Proportions of missing observations for these variables were very small; therefore, it is not likely that the imputation of exposure variables has induced bias. Moreover, results from the analyses without

imputation were similar to those derived from the multiple imputation procedure in the current study. Thus, it can be concluded that missing values for any of the exposure variables or covariates did not influence the effect estimates.

4.4.6 Test for equality hazard ratios

To the best of our knowledge, our study is the first to use the methodology of the competing risk model and a statistical test for the equality of hazard ratios to quantify and test for differences in epidemiological associations between populations. Lunn and McNeil developed a method for the joint estimation of parameters in models of competing risks in survival analysis with Cox's proportional hazards regression model fitted using a data duplication method [110]. In the competing risk model, the risks for the different failure types are assumed to be independent and the hazard functions for the types of risks to be additive. Thus, the hazard of failure is the sum of two component risk processes and the time to failure of either type is the minimum of the two failure times associated with these risk processes. When the baseline hazard functions are expected to have no constant ratio, stratifying the analyses for failure type will treat the survival times separately and allows for the estimation of separate associations with each outcome. The advantage of the competing risk approach is that the effects of each risk factor can be estimated and formally compared across different causes of death. Unlike standard Cox proportional hazards regression, in which risk factors are constrained to have common associations with all components of the outcome, this method allows for some risk factors to have different associations with different causes of death [172]. In the present study, instead of multiple outcomes, we have built a joint model with one exposure and one outcome, but where different associations were assumed of persons with and without diabetes. Because we have not duplicated the data, the observations could be considered independent and we have therefore not estimated robust estimates for standard errors of regression coefficients, which is appropriate in a competing risk model. Using a data duplication method similar to the one of Lunn and McNeil, Hoffmann *et al.* developed a statistical test for the equality of differently adjusted incidence ratios and provided a confidence interval for their ratio [111], which we have used to test for differences. A disadvantage of the equality test is that it can be misleading when misclassification is present. We refrained from estimating model fit by a likelihood ratio test, since any significance obtained from this test will not say anything about the difference between the two models [111].

Three other studies were found in which it was tested whether associations between lifestyle and mortality risk in persons with diabetes were statistically different from persons without. Batty *et al.* explored whether diabetes status modified the effect of physical activity on mortality in 352 men with type 2 diabetes compared with 6,056 normoglycemic men [70]. The magnitude of the association between walking pace and leisure-time physical activity and CVD outcomes was stronger in men with diabetes compared with the normoglycemic men; the *P*-value for test for interaction was significant. These results were confirmed in our study, where leisure-time physical activity was significantly more protective for mortality risk in persons with diabetes. Furthermore, in an analysis of NHANES I, it was tested for

interaction by diabetes status for the associations between the lifestyle factors smoking, body mass index, physical activity and mortality [71]. None of the interaction terms were significant. Moreover, in our study of adiposity and mortality, we tested for statistical interaction between measures of adiposity and diabetes status in relation to mortality within the general EPIC population [179]. No statistical significant interaction was detected.

Although we are the first to use this approach to statistically compare hazard ratios, we believe this was the most appropriate method to answer our study question. Other methods we considered was to test for interaction and for heterogeneity. However, these tests will only give an indication whether the relationship might be different between two groups, whereas our method directly tested and quantified the magnitude of the differences. Unlike standard Cox proportional hazard regression, this method allows the associations between lifestyle factors and mortality to be different between persons with and without diabetes. This competing risk approach enabled us to compare and quantify differences in strength and direction of epidemiological associations between persons with and without diabetes.

We aimed to create a reference group of persons without diabetes as comparable as possible to the persons with diabetes. By matching and adjusting for the same covariates - which were also subject to the same measurement error since they stem from the same study population - any observed difference in associations between the two groups would be due to diabetes status. Yet underreporting of energy intake has been widely acknowledged in obese persons, and it has also been reported that obese persons with diabetes underreport their energy intake more than obese persons without diabetes [143]. Indeed, a larger proportion of persons with diabetes was classified as energy misreporters compared with those without diabetes. However, associations were not affected when those classified as energy misreporters were excluded. Energy adjustment seems to minimize the problems related to selective misreporting [180]. Moreover, although persons with diabetes are supposed to undergo nutrition and health counseling, this was not reflected in their lifestyle behaviors in this study as well as others [34, 36].

4.5 Strengths and limitations

4.5.1 Strengths

These analyses benefitted from the large sample size, multi-centric design, verification of diabetes diagnoses, availability of a wide range of variables, and a long follow-up period. Potential bias through inappropriate adjustment was addressed with a suitable method for confounder selection. Moreover, it was dealt with missing values in any of the covariates in an effective and appropriate way using the multiple imputation procedure. In addition, it was tested for differences in associations with a new method which enabled statistical comparisons between epidemiological associations in two populations.

4.5.2 Limitations

One of the limitations of the prospective study was that due to the selection of the study population, the prevalent diabetes cohort might not be completely representative of the general diabetes population. However, this does not bias any etiological associations. Furthermore, it was not possible to take into account changes in lifestyle patterns over time, since only one baseline measurement was available. Moreover, information on exposure variables as well as diabetes medication was self-reported, which may have induced misclassification and random measurement error.

5. Conclusion

Diabetes mellitus is a chronic disease that requires continuing medical care and patient self-management education to achieve glycemic control and to reduce the risk of complications. In our study, diabetes conferred a higher mortality risk per se, but lifestyle factors could explain this increased risk to some extent. Up till now, efforts to reduce the impact of diabetes have been predominantly aimed at controlling hyperglycemia, hypertension, and dyslipidemia by medication strategies. However, diabetes management should be an overall intervention strategy including lifestyle modification. Compared with medication strategies, persons with diabetes can actively reduce their overall mortality risk in a cost-effective way by leading a healthy lifestyle. We have provided evidence that a favorable lifestyle characterized by low levels of abdominal adiposity, an overall healthy diet, alcohol consumption within the recommended limits, and higher levels of physical activity were related to lower mortality risk in a European cohort of men and women with diabetes mellitus. We found no indications that there is a need for diabetes-specific advices. Diet and lifestyle recommendations for primary prevention of premature mortality written for the general population appear also to be valid in persons with diabetes. A healthy diet and lifestyle allows people with and without diabetes to live healthier and longer.

5.1 Public health implications

In terms of primary prevention of premature mortality by means of diet and lifestyle, it is not necessary to know whether a person has been diagnosed with diabetes: no indications were found that associations for persons without diabetes, persons with pre-diabetes, undiagnosed or diagnosed diabetes are different. If these results are confirmed in further studies, the implications for general practitioners and public health professionals include that a healthy diet and lifestyle can and should be advised and communicated to an even larger proportion than the general population.

5.2 Outlook

Since associations between the studied lifestyle factors and mortality risk were similar for persons with and without diabetes, our findings do not support the conduct of epidemiological studies investigating lifestyle factors and mortality specifically in persons with diabetes. However, since persons with diabetes are at high risk of CVD and premature mortality and their lifestyles are less healthy than the general population, it is of interest to examine whether persons with diabetes will benefit more from adherence to the general diet and lifestyle recommendations than the general population. Calculating population attributable fractions can provide exact percentages of the mortality cases which can be explained by unfavorable lifestyle factors. If the population attributable fractions are larger in persons with diabetes, this would call for diabetes-specific risk communication.

Because only one baseline lifestyle measurement was available in our study, we were not able to take into account lifestyle change. These analyses have shown that a favorable lifestyle at baseline was associated with a lower mortality risk. Nevertheless, it remains unknown whether lifestyle modification is related to a lower mortality risk in persons with diabetes as well as persons without diabetes. Future studies are needed to investigate whether moving from an unfavorable to a favorable lifestyle improves survival rates.

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Hiermit erkläre ich an Eides statt, dass ich die Dissertation selbständig verfasst habe; die von mir benutzten Hilfsmittel und Quellen sind aufgeführt und die Arbeit ist nicht in Zusammenarbeit mit anderen Wissenschaftlern oder Wissenschaftlerinnen erstellt worden. Alle Teile, die wörtlich oder sinngemäß einer Veröffentlichung entstammen sind als solche gekennzeichnet. Weiterhin erkläre ich, dass ich weder früher noch gleichzeitig eine Anmeldung der Promotionsabsicht gemäß § 4 der Promotionsordnung für die TUB oder ein Promotionsverfahren bei einer anderen Hochschule oder bei einer anderen Fakultät beantragt habe. Teile dieser Arbeit sind in ähnlicher Form veröffentlicht worden; Kopien der folgenden Veröffentlichungen lege ich bei:

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