Diabetes and hypertension – entangled chronic conditions in primary care

Time trends and determinants for mortality and cardiovascular complications

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Cover: Early summer morning in Skaraborg County
Photo by Tobias Andersson

To my family

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ABSTRACT

Diabetes and hypertension are chronic, often coexisting conditions with increased risk of premature death and cardiovascular complications. This thesis aimed to study different epidemiological aspects regarding risk of mortality and cardiovascular complications among individuals with diabetes, hypertension, and hypertension with concomitant diabetes in primary care.

The thesis includes four cohort studies. In Study I, people with new-onset type 2 diabetes registered in the Skaraborg Diabetes Register (SDR) 1991–2004 were followed until 2014 to assess causes of death and mortality trends compared to controls from the population, and in Study II to evaluate C-peptide as a predictor of mortality and cardiovascular complications. In Study III, people with hypertension registered in primary care and included in the Swedish Primary Care Cardiovascular Database (SPCCD) 2001–2008 were followed until 2012 to estimate the risk of mortality and cardiovascular complications with regard to diabetes status, educational level and income, and in Study IV with regard to diabetes status and country of birth.

In the SDR, excess mortality was driven by cardiovascular and endocrine causes of death and decreased by 2% per calendar year of diagnosis between 1991 and 2004. Also, C-peptide was associated with risk of all-cause and cardiovascular mortality. In the SPCCD, diabetes and low income versus no diabetes and high income was associated with almost 4-fold increased risk of mortality and 2-fold risk of myocardial infarction and stroke. Compared to Swedish-born, Non-European country of birth was associated with decreased risk and being born in Finland with increased risk of mortality.

In conclusion, excess mortality in patients in Skaraborg with type 2 diabetes has decreased. In diabetes and hypertension, socioeconomic factors and C-

peptide are associated with risk of mortality and cardiovascular complications and could potentially be used to identify patients at high risk of adverse outcomes, to allocate health care resources, and to strengthen individual risk factor control with the aim to improve prognosis.

Keywords: Diabetes mellitus, hypertension, C-peptide, mortality, cause of death, myocardial infarction, stroke, cohort studies, primary health care, socioeconomic factors, emigrants and immigrants, Sweden

SAMMANFATTNING PÅ SVENSKA

Diabetes och hypertoni (högt blodtryck) är två kroniska och ofta samtidigt förekommande tillstånd med förhöjd risk för förtida död och hjärtkärlkomplikationer. Syftet med denna avhandling var att studera olika epidemiologiska aspekter kring risk för död och hjärtkärlkomplikationer hos individer med diabetes, hypertoni och hypertoni med diabetes i primärvård.

Avhandlingen bygger på fyra kohortstudier med uppföljning via det svenska Dödsorsaksregistret och Patientregistret. I den första studien följdes individer som insjuknat i typ 2 diabetes 1991–2004, och som registrerats i Skaraborgs Diabetesregister (SDR), till och med 2014 för att studera dödsorsaker och trender i dödlighet, jämfört med matchade kontrollindivider från befolkningen. I den andra studien studerades C-peptid (som avspeglar insulinnivån i blodet) som riskmarkör för död och hjärtkärlkomplikationer hos individer i SDR som var yngre än 65 år då de insjuknade i typ 2 diabetes 1996–1998. I den tredje studien följdes individer med hypertonidiagnos, som registrerats i primärvård 2001–2008 i The Swedish Primary Care Cardiovascular Database (SPCCD), till och med 2012 för att studera sambandet mellan diabetes, utbildningsnivå och inkomst samt risk för död och hjärtkärlkomplikationer. I den fjärde studien studerades motsvarande samband mellan diabetes och födelseland samt risk för död och hjärtkärlkomplikationer.

I SDR framkom överdödlighet på grund av hjärtkärlsjukdom och endokrina sjukdomar (framför allt diabetes). Överdödligheten var 47% vid diabetesdiagnos år 1991 och minskade därefter med 2% per kalenderår för diabetesdiagnos mellan 1991 och 2004. Det framkom även ett samband mellan hög nivå av C-peptid i blodet och ökad risk för förtida död oavsett orsak, samt för död orsakad av hjärtkärlsjukdom. I SPCCD framkom att låg inkomst i kombination med hypertoni och diabetes, jämfört med hög inkomst i kombination med hypertoni utan diabetes, var associerat med nästan 4-faldigt ökad risk för död och 2-faldigt ökad risk för hjärtinfarkt och stroke. Jämfört med att vara född i Sverige var utomeuropeiskt födelseland associerat med minskad risk för förtida död, och Finland med ökad risk för förtida död.

Sammanfattningsvis så har överdödligheten bland individer med typ 2 diabetes i Skaraborg minskat. Socioekonomiska faktorer och C-peptid var associerade med risk för död och hjärtkärlkomplikationer vid diabetes och hypertoni, och skulle kunna användas som hjälp för att identifiera individer med hög risk för komplikationer, i syfte att kunna rikta sjukvårdsresurser och för att kunna intensifiera individuell riskfaktorkontroll, med förbättrad prognos som mål.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Andersson T**, Hjerpe P, Carlsson AC, Pivodic A, Wändell P, Manhem K, Bengtsson Boström K. Mortality trends and cause of death in patients with new-onset type 2 diabetes and controls: A 24-year follow-up prospective cohort study. *Diabetes Research and Clinical Practice.* 2018;138:81-89.

II. Pikkemaat M, **Andersson T**, Melander O, Chalmers J, Rådholm K, Bengtsson Boström K. C-peptide predicts all-cause and cardiovascular death in a cohort of individuals with newly diagnosed type 2 diabetes. The Skaraborg diabetes register. *Diabetes Research and Clinical Practice.* 2019;150:174-183.

III. **Andersson T**, Pikkemaat M, Schiöler L, Hjerpe P, Carlsson AC, Wändell P, Manhem K, Kahan T, Hasselström J, Bengtsson Boström K. The impact of diabetes, education and income on mortality and cardiovascular events in hypertensive patients: A cohort study from the Swedish Primary Care Cardiovascular Database (SPCCD). *PLoS One.* 2020;15:e0237107.

IV. **Andersson T**, Pikkemaat M, Schiöler L, Hjerpe P, Carlsson AC, Wändell P, Manhem K, Kahan T, Bengtsson Boström K. Country of birth and mortality risk in hypertension with and without diabetes: the Swedish Primary Care Cardiovascular Database. *Journal of Hypertension.* 2020 December 5, Online ahead of print.

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CONTENT

ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DBP	Diastolic blood pressure
EASD	European Association for the Study of Diabetes
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HbA1c	Glycated hemoglobin A1c
HDL	High density lipoprotein
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence rate ratio
LDL	Low density lipoprotein
NDR	National Diabetes Register
PH	Proportional hazards
PURE	Prospective Urban Rural Epidemiologic study
SBP	Systolic blood pressure
SDR	Skaraborg Diabetes Register
SPCCD	Swedish Primary Care Cardiovascular Database

WHO   World Health Organization

1 INTRODUCTION

Diabetes mellitus and hypertension (high blood pressure) are worldwide widespread chronic conditions with increased risk of cardiovascular complications and premature death [1]. Hypertension has been the most important risk factor globally for all-cause mortality during the last decades, followed by smoking and high fasting plasma glucose according to the Global Burden of Disease Study in 2017 [2]. In addition, those three risk factors were the most important ones with respect to disability-adjusted life years i.e., the combination of years lost due to premature mortality and years of healthy life lost due to disability. In a global pooled analysis of 1479 population-based studies, 1.13 billion people were estimated to be affected by hypertension in 2015, with the majority of people living in low or middle-income countries [3]. The prevalence of diabetes is rising globally and was estimated to affect 463 million people in 2019, with projections of 700 million affected people in 2045 [4].

In Sweden as well as many other countries, the majority of patients with hypertension and diabetes are managed in primary care.

1.1 DIABETES MELLITUS

Symptoms of what is today known as diabetes mellitus are thought to have been first described in ancient Egypt in the Ebers Papyrus 3500 years ago as a polyuric syndrome [5]. Circa 100 BC, Aretaeos of Kappadokia, a disciple of Hippocrates was the first to use the word *diabetes* (derived from the Greek word diabainein meaning siphon or "to pass through") in his description "Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine…" [6, 7]. Sweet tasting urine attracting flies and ants was described already in 500-600 BC by ancient Hindu physicians and was later described by the Latin word *mellitus* meaning sweetened by honey.

1.1.1 CLASSIFICATION

Nowadays diabetes mellitus or diabetes is recognized as a diverse group of diseases with hyperglycemia (high blood glucose) as the common denominator [8]. The subgroups of diabetes are classified and have been continuously revised by the World Health Organization (WHO) and the American Diabetes Association (ADA).

The first WHO classification of diabetes was published in 1965 [9]. Revised versions were published in 1980 [10], 1985 [11], 1999 [12], and most recently in 2019 [13]. The current classification divides diabetes in 6 major subgroups.

- **Type 1 diabetes** [14], which is caused by autoimmune destruction of the insulin producing beta-cells in the pancreas. The destruction of beta-cells can progress at various speed but eventually usually result in total insulin deficiency, leading to lifelong need of insulin therapy. Type 1 diabetes accounts for 5–10% of cases of diabetes. Autoantibodies can be detected among 85–90% of individuals with type 1 diabetes, and include antibodies reactive against insulin (IAA), glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8A). Type 1 diabetes is in most cases a polygenetic disease with strong association with certain HLA (human leukocyte antigen) regions. However, for a minority of patients with type 1 diabetes the etiology is unknown, with no evidence of autoimmunity or HLA association.

  Type 1 diabetes was previously termed insulin dependent diabetes (IDDM) or type 1 in the 1980 classification. In the 1985 classification, type 1 was omitted, and it was just termed IDDM. Later, in the 1999 classification, the term type 1 was reintroduced and IDDM omitted. It has also been known as juvenile onset diabetes.

- **Type 2 diabetes**, which is caused by loss of adequate beta-cell secretion of insulin in combination with insulin resistance. This is the major subgroup of diabetes and globally accounts for 90–95% of diabetes. This thesis mainly focuses on individuals with type 2 diabetes whose characteristics will be described in more detail in the forthcoming sections.

  In parallel with type 1 diabetes, type 2 diabetes has changed names over the years. In the 1980 classification it was termed non-insulin dependent diabetes (NIDDM) or type 2. In the 1985 classification, type 2 was omitted, and it was just called NIDDM. In the 1999 classification, type 2 was reintroduced and NIDDM dropped. It has previously also been known as adult-onset diabetes.

- **Hybrid forms of diabetes.** *Slowly evolving immune diabetes* is a form of diabetes that is presented clinically first as type 2 diabetes, but where antibodies against the pancreas can be detected resulting in progressive loss of beta-cell function and insulin production. This form of diabetes has also been termed latent autoimmune diabetes in adults (LADA). The LADA term is debated [15] and in the 2020 ADA classification, LADA is classified as type 1 diabetes. There are no distinct diagnostic criteria for this type of diabetes, but it usually includes age over 35 years at diagnosis, positivity for GAD autoantibodies, and no need for insulin therapy during the first 6–12 months after diagnosis. *Ketosis-prone type 2 diabetes* is a rare form of type 2 diabetes that initially presents with ketosis and transient insulin deficiency that goes in remission with recovery of the beta-cell function and no further need of insulin therapy. The pathogenesis is unclear with no evidence of autoimmunity and no known genetic markers.

- **Other specific types of diabetes.** This group include *monogenic diabetes* (for example neonatal diabetes and maturity-onset diabetes of the young [MODY]), *monogenic defects in insulin action*, *drug- or chemical induced diabetes* (for example due to glucocorticoids), *endocrine disorders* (for example Cushing's syndrome, hyperthyroidism, and acromegaly), *diabetes due to diseases of the exocrine pancreas* (for example cystic fibrosis, pancreatitis, trauma, infection, and cancer of the pancreas), and *uncommon forms of immune-mediated diabetes*.

- **Unclassified diabetes.** The classification of diabetes has become more complex over the years with increasing overlapping clinical features between type 1 and type 2 diabetes e.g., obese children and young adults with accompanying type 2 diabetes, and more overweight or obese adults with type 1 diabetes. In uncertain cases, the unclassified diabetes subgroup can be used until the diagnosis is conclusive.

- **Hyperglycemia first detected during pregnancy.** This type of diabetes is subgrouped in *diabetes during pregnancy* which is diagnosed using the same diagnostic criteria as in non-pregnancy, and in *gestational diabetes* which is diagnosed

according to the WHO 2013 criteria with lower cut offs than for diabetes.

Since 1988, the ADA has published annually updated recommendations and classifications in its "Standards of medical care in diabetes". The current 2020 ADA classification divides diabetes in four general categories [16, 17]: type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types of diabetes due to other causes. The four subgroups mainly overlap with the 1999 WHO classification.

Five novel subgroups of adult-onset diabetes have recently been proposed in a Swedish data-driven cluster analysis based on six variables (pancreatic islet antibodies, age at diagnosis, body mass index [BMI], glycated hemoglobin A1c [HbA1c], and homeostatic model assessment 2 estimates of beta-cell function and insulin resistance) [18]. Cluster 5 (mild age-related diabetes [MARD]) was the largest cluster (40%) and included older patients with modest metabolic derangements and the most benign clinical course. Cluster 4 (mild obesity-related diabetes [MOD]) included younger patients with obesity without insulin resistance. Cluster 3 (severe insulin resistant diabetes [SIRD]) included patients with insulin resistance, high BMI and high risk of diabetic kidney disease. Cluster 2 (severe insulin deficiency diabetes [SIDD]) included patients with insulin deficiency, high HbA1c but no islet antibodies, whereas cluster 1 (severe autoimmune diabetes [SAID]) overlaps with type 1 diabetes.

1.1.2 DIAGNOSIS

Diabetes may debut with clinical signs and symptoms such as weight loss, polyuria (abnormal large production or passage of urine), blurred vision, fatigue, thirst, or genital infections. It can also debut with severe symptoms such as ketoacidosis and hyperosmolar syndrome which can lead to death if untreated. However, in type 2 diabetes the debut is generally less dramatic, and patients are often asymptomatic when diagnosed as they have gradually adapted to the slowly evolving hyperglycemia.

The diagnostic criteria of diabetes, and the diagnostic tests used for diagnosis of diabetes have changed over time. According to the current WHO and ADA guidelines, diabetes can be diagnosed using any of four diagnostic tests.

- Fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl).

- HbA1c ≥ 48 mmol/mol (≥ 6.5% NGSP [National Glycohemoglobin Standardization Program]).

- 2-hour plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) after ingestion of 75 g glucose in an oral glucose tolerance test (OGTT).

- A random non fasting plasma glucose ≥ 11.1 mmol/l in the presence of signs and symptoms of diabetes.

In asymptomatic individuals, a repeat diagnostic test is recommended to confirm the diagnosis. The repeat test can be from the same blood sample e.g., a combination of abnormal fasting glucose and HbA1c. It can also be from two separate samples from different occasions e.g., two abnormal fasting glucose or HbA1c, a combination of abnormal fasting glucose and HbA1c, or a combination of abnormal OGTT, fasting glucose, or HbA1c.

The addition of the HbA1c diagnostic criteria was recommended in 2009 by the ADA, the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation [19]. It was also recommended by the WHO in 2011 [20] and has been used in Sweden since 2014 [21].

The historical WHO glucose concentration values for diagnosis of diabetes during the last four decades are shown in Table 1. During this period, the OGTT cut off for diabetes has remained unchanged. However, in 1999 the fasting plasma glucose threshold for diabetes was lowered from ≥ 7.8 mmol/l (≥ 140 mg/dl) to ≥ 7.0 mmol/l (≥ 126 mg/dl). This was done to better correspond to the OGTT threshold, and to better correspond to increased risk of micro- and macrovascular disease [12].

Table 1. World Health Organization glucose concentration values for diagnosis of diabetes.

	Glucose concentration, mmol/l (mg/dl)		
	Venous whole blood	Capillary whole blood	Venous plasma
Fasting			
WHO 2019			≥ 7.0 (≥ 126)
WHO 1999	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
WHO 1985	≥ 6.7 (≥ 120)	≥ 6.7 (≥ 120)	≥ 7.8 (≥ 140)
WHO 1980	≥ 7.0 (≥ 120)	≥ 7.0 (≥ 120)	≥ 8.0 (≥ 140)
2 hours after OGTT			
WHO 2019			≥ 11.1 (≥ 200)
WHO 1999	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
WHO 1985	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
WHO 1980	≥ 10.0 (≥ 180)	≥ 11.0 (≥ 200)	≥ 11.0 (≥ 200)

OGTT: oral glucose tolerance test. WHO: World Health Organization.

1.2 TYPE 2 DIABETES

1.2.1 PATHOPHYSIOLOGY

In short, type 2 diabetes is characterized by a relative insulin deficiency caused by dysfunction of the insulin producing beta-cells in the pancreatic islet in combination with insulin resistance in insulin sensitive organs [22]. The pancreatic islet pathophysiology leading to impaired insulin secretion is complex and also involves glucagon-secreting alfa-cells and somatostatin-secreting delta-cells in addition to the insulin-secreting beta-cells [23].

The glucose homeostasis system keeps the concentration of glucose within a narrow optimal range and engages intricate biological feed-back loops between the insulin producing beta-cells and insulin sensitive tissue such as liver, muscle, and adipose tissue [24]. Insulin mediates the uptake of glucose, fatty acids and aminoacids in muscle and adipose tissue, whereas it inhibits the production of glucose in the liver. The insulin sensitive tissues signal the need of insulin to the pancreatic islets. Insulin resistance often follows obesity and leads to increased demand of insulin by the insulin sensitive tissues. The glucose homeostasis is maintained as long as the beta-cells can produce enough insulin to compensate the increased demand. However, once the beta-cells fail to meet the demand of insulin, the glucose concentration starts to increase

leading first to prediabetes and later development of type 2 diabetes. This can be a slowly evolving process – increased fasting and OGTT glucose, as well as decreased insulin sensitivity and beta-cell function have been observed several years before the diagnosis of type 2 diabetes [25].

The mechanisms of the glucose homeostasis feed-back loops are not fully understood, but the brain is proposed to play a role and to be part of the link between obesity and the development of type 2 diabetes [26].

Type 2 diabetes is a multifactorial disease, and although more than 400 genetic signals have been associated with risk of type 2 diabetes [23], obesity and unfavorable lifestyle have been shown to be strongly associated with increased risk of type 2 diabetes regardless of genetic predisposition [27].

1.2.2 C-PEPTIDE

The distinction between type 1 and type 2 diabetes usually involves clinical evaluation of patient characteristics such as age at onset, family history of diabetes, obesity, and other features of the metabolic syndrome [28]. Sometimes the distinction can be puzzling, for example in young obese people or in lean older people. In these and other situations, evaluating beta-cell autoantibodies and beta cell function can be valuable.

The pancreatic beta-cells produce pro-insulin which is cleaved by an enzyme to insulin and C-peptide (connecting-peptide) in equimolar quantities [29]. There are several advantages to measure C-peptide instead of insulin to assess beta-cell function and insulin secretion [30, 31]. First, the half-life of C-peptide is longer, 20-30 minutes as compared to 3-5 minutes for insulin. Also, approximately 50% of the endogenously produced insulin is first pass metabolized by the liver whereas C-peptide is not cleared by the liver. In addition, the peripheral clearance of C-peptide is constant while the clearance of insulin is more variable.

C-peptide can be measured in venous blood in a random non fasting state, in fasting, or after glucagon stimulating. Random or fasting sampling are the most convenient approaches in everyday clinical practice. In type 1 diabetes, the C-peptide is usually low, reflecting low or no endogenous secretion of insulin. In type 2 diabetes, C-peptide is usually within the normal range or increased, reflecting increased secretion of insulin to balance insulin resistance. However, C-peptide can also be low in type 2 diabetes with long duration, where the beta-cell function has been extensively impaired resulting in only low endogenous secretion of insulin. In these cases, low C-peptide suggest initiation of exogenous insulin therapy.

C-peptide has attracted interest as a biomarker to predict diabetes complications. In type 1 diabetes, where C-peptide is generally low, even modest C-peptide secretion was associated with reduced risk of retinopathy, nephropathy [32, 33], and foot ulcers [34]. The protective effect of C-peptide secretion in type 1 diabetes has been proposed to be linked to better glycemic control and reduced glucose variability. In people without diabetes, elevated C-peptide has been associated with increased risk of myocardial infarction and coronary artery disease [35], cardiovascular and all-cause mortality [36, 37].

Studies of the association between C-peptide level and complications in type 2 diabetes have provided somewhat contradictory results. In one small study, no difference was seen in C-peptide levels between patients with and without diabetic complications [38]. Another larger study found no association between C-peptide levels and all-cause mortality or mortality due to diabetes, cancer, or cardiovascular disease [39]. However, in this study elevated C-peptide levels were associated with decreased risk of microvascular complications (neuropathy, retinopathy, and nephropathy). In contrast, one study including people with "older-onset"-diabetes revealed an association between raised C-peptide levels and all-cause and ischemic heart disease mortality [40], and other studies have also reported associations between elevated C-peptide levels and macrovascular complications [41] as well as cardiovascular mortality [42].

None of the above-mentioned studies were based on people with new-onset type 2 diabetes. However, in a previous Swedish study from Skaraborg, 399 individuals with new-onset type 2 diabetes were followed for up to 13 years [43]. This study found an association between all-cause mortality and C-peptide levels in the highest versus lowest quartile with a hazard ratio (HR) of 2.75 (95% CI 1.17–6.47, p=0.04).

Whether the increased risk of mortality associated with elevated C-peptide levels in new-onset type 2 diabetes was driven by cardiovascular disease remains to be further studied, as well as if an increased risk also can be found for myocardial infarction and stroke.

1.2.3 GLOBAL EPIDEMIOLOGY OF TYPE 2 DIABETES

The global prevalence of diabetes was estimated by the International Diabetes Federation Diabetes Atlas 9th edition to be 9.3% or 463 million people in 2019 [4]. Of those people, half were diagnosed, and half were yet undiagnosed. Type 2 diabetes constitutes around 90% of the total cases of diabetes. During the last

10 years the global prevalence of diabetes has increased by 62%. The reasons behind the steep increase are complex and include higher incidence of type 2 diabetes among both young people and adults partly due to sedentary lifestyle and excessive intake of high energy food. In addition, the overall ageing of the global population contributes to the increased prevalence of type 2 diabetes which is more common in the elderly, affecting roughly 20% of those 65 years and older globally. Also, earlier detection of type 2 diabetes, improved management of the disease, and overall longer life-expectancy contribute to higher prevalence.

The Diabetes Atlas also reveals large regional differences in the prevalence of diabetes. The age-standardized prevalence in 2019 among people 20-79 years old were estimated to be highest in the Middle East and North Africa (12.2%), Western Pacific (11.4%), South-East Asia (11.3%), and North America and Caribbean (11.1%). By country, the prevalence of diabetes was estimated to be highest in the Marshall Islands (30.5%), followed by other Western Pacific Islands, Sudan and Pakistan with prevalence around 20%. In absolute terms, the largest number of people with diabetes were living in China (116 million), India (77 million), and the United States (31 million). By 2045 Pakistan is projected to overtake the third place from the United States. In contrast, the regional prevalence of diabetes was estimated to be lowest in Africa (4.7%) and in Europe (6.3%).

Similar estimates of the worldwide prevalence of diabetes have been calculated by the Non-Communicable Diseases Risk Factor Collaboration (NCD-RisC) and the Global Burden of Disease (GBD) study. According to the NCD-RisC, the prevalence of diabetes was estimated to have increased from 118 million in 1980 (4.3% in men and 5.0% in women) to 422 million in 2014 (9.0% in men and 7.9% in women) [44]. The highest prevalence was found in some of the Western Pacific Islands (about 25%) and the lowest prevalence was found in northwestern Europe (less than 5%). In the GBD study, the prevalence of diabetes was estimated to be 476 million in 2017 [45].

1.2.4   EPIDEMIOLOGY OF TYPE 2 DIABETES IN SWEDEN

From a global perspective, the prevalence of diabetes in Sweden is relatively low. The prevalence and incidence of diabetes in Sweden have been estimated in several studies. According to the Swedish National Diabetes Register (NDR) the current prevalence of diabetes in Sweden is approximately 5.5%, of which type 2 diabetes constitutes 90% [46].

In another study the prevalence of diabetes was estimated for people of all ages in Sweden [47], using data from the Swedish Prescribed Drug Register [48] on pharmacologically treated diabetes, and data from the NDR regarding non-pharmacologically treated diabetes. During the study period 2005–2013, the prevalence of pharmacologically-treated diabetes increased annually by 2.4% in men and by 1.9% in women. The increase could however not be explained by increased incidence, which actually in overall decreased annually by 0.6% in men and 0.7% in women. In 2012–2013 the age-standardized prevalence of pharmacologically treated diabetes was estimated to 5.1% in men and 3.5% in women (4.3% in total). When also including non-pharmacologically treated diabetes, the prevalence was estimated to 5.6% in men and 3.9% in women (4.7% in total). The prevalence of diabetes was strongly associated with high age. The prevalence was 16.9% in men, and 12.0% in women aged ≥ 65 years old, as compared to 0.95% in men and 0.90% in women aged 15–39 years.

Comparable results were found in another study using similar methodology with data from the Swedish Prescribed Drug Register and the NDR [49]. Here the prevalence of diabetes in adults ≥ 20 years old was estimated to have risen from 5.8% in 2007 to 6.8% in 2013, with a constant annual incidence of 0.44%. This study projects that conditional on constant incidence, the prevalence of diabetes in Sweden will increase to 10.4% by 2050, affecting 940 000 people. Changes in age structure with an ageing population and increasing population size, as well as decreased gap in mortality between people with and without diabetes are projected to drive this increase in prevalence.

The finding of constant or near constant incidence of diabetes has also been reported in earlier Swedish studies. In Skaraborg the incidence of type 1 and 2 diabetes remained fairly constant in 1991–1995, whereas the total prevalence of diabetes increased by 6% per year and was estimated to 3.2% in 1995 [50]. In a study of people with type 2 diabetes in Uppsala, the incidence 1996–2003 was approximately constant, and the prevalence increased from 2.2% to 3.5% [51]. A biphasic pattern of initial 3% annual rise of incidence of diabetes in 1990–2002, and thereafter stabilized incidence until 2010 was seen in a study from Stockholm County [52]. Also, during 30 years of follow up 1972–2001 in rural Laxå, no increased incidence of type 1 or 2 diabetes was detected, and the age-standardized prevalence remained rather stable around 4.5% over the last 13 years of the study [53].

1.2.5 MORTALITY AND CARDIOVASCULAR COMPLICATIONS

Complications of diabetes are traditionally classified as microvascular and macrovascular [54, 55]. Microvascular complications are neuropathy, retinopathy, and nephropathy. Macrovascular complications are stroke, ischemic heart disease, and peripheral vascular disease. The rates of these classic diabetes complications have declined substantially during the last decades in high income countries [56]. In addition to the classic complications, diabetes also confers increased risk of heart failure [57, 58], certain cancers [59], and geriatric conditions such as Alzheimer's disease, vascular dementia, mobility decline, and disability [60].

Historically the risk of death by cardiovascular disease (CVD) has been substantially increased for people with diabetes versus people without diabetes. In the Multiple Risk Factor Intervention Trial (MRFIT) study where CVD mortality was assessed among middle aged men recruited in the United states during the 1970s, diabetes was associated with overall 3 times higher risk of CVD mortality [61]. When also exposed to smoking, elevated systolic blood pressure levels, and elevated cholesterol levels, the age adjusted absolute risk of CVD mortality increased for men both with and without diabetes. Considerable elevated excess mortality in people with diabetes versus people without diabetes has also been reported from middle-income countries. In a study from Mexico City including patients with diabetes 1998–2004 with follow-up until 2014, just over 5-fold excess mortality was seen in patients 35–59 years old, and near 2-fold excess mortality in patients 75–84 years old, as compared to people without diabetes [62].

Mortality rates in overall, and CVD mortality rates in particular, have declined considerably in the general population in Western countries during the last decades. For example, in Finland, where cardiovascular mortality was the highest in the world during the 1960s, coronary heart disease mortality decreased by over 80% in 1972 to 2012. Two thirds of the decline is estimated to be attributed to changes in smoking habits and lowered cholesterol and systolic blood pressure levels [63].

Declining mortality rates in Western countries have also been reported in people with diabetes. In an US study of people with diabetes, the all-cause mortality rates declined by 23%, and the CVD death rates by 40% between 1997 and 2006 [64]. In the same study, the mortality gap between people with diabetes versus people without diabetes also declined during the study period with all-cause mortality HR declining from 1.94 to 1.54, and CVD mortality

HR from 2.38 to 1.64. A similar trend of closing mortality gap between people with versus without diabetes was seen in Canada and the United Kingdom, where the mortality rate ratios decreased from 1.90 in 1996 to 1.51 in 2009, and from 2.14 to 1.65, respectively [65]. In a Norwegian study from the Nord-Trøndelag health study (HUNT), coronary heart disease mortality rates in 70–79 year old people with diabetes who were recruited in 1984–1986 and 1995–1997, declined by 54% in men and 59% in women [66]. However, in this study the excess risk of mortality among people with versus without diabetes remained fairly stable with approximately 2-fold risk in men and nearly 3-fold risk in women. Lower excess mortality for people with diabetes was found in a Swedish 33-year longitudinal study from Laxå, reporting age-adjusted HR of 1.17 for all-cause mortality, and HR 1.33 for CVD mortality [67]. Similar excess all-cause mortality of 29% in 2002–2014 was seen in a recent large US study, presenting lower excess mortality for people with diabetes than in earlier US studies [68].

Mortality trends have also been studied specifically for type 2 diabetes. In an Australian national cohort study, using data from an administrative database, the standardized mortality ratio declined from 1.40 in 1997 to 1.21 in 2010 for men, and from 1.56 to 1.22 for women [69]. Two recent nationwide Swedish observational studies from the NDR have examined temporal trends of mortality in type 2 diabetes. In the first study, the overall all-cause fully adjusted mortality HR was 1.17 in 1998-2005, with slightly lower HR 1.13 in 2005-2012 [70]. The risk of CVD mortality was similar, and the study showed that excess mortality increased with younger age, worse glycemic control, and renal impairment. The second study showed a 21% reduction in all-cause mortality among people with type 2 diabetes from 1998–2014, whereas the reduction was 31% among matched controls [71]. As a result, the mortality gap widened between people with versus without type 2 diabetes during follow up in this study.

Mortality and mortality trends in people with new-onset type 2 diabetes have not been extensively studied. In a Scottish observational study using record-linkage data the all-cause mortality HR for people with new-onset type 2 diabetes in 1993–2004 versus age and sex matched controls was 1.32 when adjusting for material deprivation, and 1.15 when also adjusting for pre-existing cardiovascular disease [72]. The corresponding HR for cardiovascular mortality was somewhat higher, 1.51, and 1.23, respectively. In a UK observational study using data from the United Kingdom General Practice Research Database, the age-standardized mortality rates declined from 1996 to 2006 for people with new-onset type 2 diabetes, compared to a reference population derived from official population statistics [73]. The relative

mortality declined in this study from 1.38 in 1997 to 1.27 in 2006 for men with type 2 diabetes, and from 1.62 to 1.44 for women.

In summary, declining mortality rates have been observed in many studies for people with and without diabetes, and excess mortality linked to diabetes seem to have become less pronounced over time. However, population based prospective data to assess temporal mortality trends and causes of death are still lacking in people with clinically new-onset type 2 diabetes compared to the background population.

1.3 HYPERTENSION

According to the Global Burden of Disease study, hypertension was the leading risk factor for all-cause mortality between 1990 and 2017 [2]. In 2010 hypertension was reported to be the major risk factor of mortality due to cardiovascular disease, chronic kidney disease, and diabetes [1]. Together with high BMI, elevated levels of glucose and cholesterol it was estimated to be responsible for 67% of those deaths. In the INTERHEART study of potentially modifiable risk factors for myocardial infarctions in 52 countries, hypertension alone was estimated to be responsible for 17.9% of all myocardial infarctions worldwide, and together with 8 other risk factors for 90.4% of all myocardial infarctions [74]. Potentially modifiable risk factors for stroke were similarly evaluated in the INTERSTROKE study [75]. Here, hypertension alone was estimated to be responsible for 47.9% of all stroke worldwide, and together with 9 other risk factors for 90.7% of all stroke. The leading role of hypertension as a modifiable risk factor for cardiovascular disease and mortality was recently further emphasized in the Prospective Urban Rural Epidemiological (PURE) study including over 155 000 individuals in 21 high-, middle-, and high-income countries [76]. In this study, metabolic risk factors were estimated to be responsible for 41.2% of all cardiovascular disease and deaths, with hypertension alone being responsible for 22.3%.

1.3.1 PREVALENCE

The age standardized worldwide prevalence of raised blood pressure (BP) has decreased during the last decades [3]. In 1975 the prevalence was estimated to be 29.5% in men and 26.1% in women. In 2015 it had decreased to 24.1% and 20.1%, respectively. The decline in prevalence has been most marked in high income western and Asia Pacific countries. In contrast to the decline in age standardized prevalence, the absolute number of adults with hypertension have increased from 594 million to 1.13 billion during the same time period. This

increase is due to the net effect of population growth and ageing in combination with declining age-standardized prevalence.

In Sweden, the prevalence of detected and undetected hypertension was estimated to 27% of the adult population in a systematic review from 2007, corresponding to 1.8 million people [77]. Of those people, 60% was estimated to have mild hypertension (140–159/90–99 mm Hg), 30% moderate hypertension (160–179/100–109 mm Hg), and 10% severe hypertension (≥180/≥110 mm Hg). The prevalence of hypertension increased with age and among retired people more than half had elevated BP.

The prevalence of diagnosed hypertension in Stockholm County was reported to be 12.2% in the total population in 2011 [78], and 14% among adults in 2013 [79]. This is in line with previous population studies and the "rule of halves", where approximately half of the cases of hypertension are undetected [80]. An alternative "rule of thirds" was stated in a report from a population study in Skaraborg County 2001–2005 [81]. Here, the prevalence of detected and undetected hypertension in adults 30–75 years old was estimated to 20%. One third were unaware of their high BP, one third were aware but had uncontrolled BP, and one third were aware with controlled BP.

1.3.2   HISTORY OF HYPERTENSION

Hypertension has however not always been considered important. In a historical expose of the management of hypertension, high blood pressure was viewed during the 1930s as a natural and necessary compensatory mechanism that should be left alone [82]. Later, in the late 1940s, the management of hypertension was described in the textbook *Diseases of the heart* [83] as follows: "In a patient with mild benign hypertension— [defined as a] blood pressure < 200/< 100 mm Hg, there is no indication for use of hypotensive drugs. Continued observation is desirable and conservative treatment consisting of reassurance, mild sedatives, and weight reduction is indicated."

The natural course of untreated hypertension has been exemplified in the case of US president Franklin D. Roosevelt [82]. In 1937, at the age of 54, his BP was measured at 162/98 mm Hg, and in concordance with the view of high BP at that time he received no treatment. His BP increased further, and in 1941 after a BP reading of 188/105 mm Hg he was prescribed phenobarbital and massage. In 1943–1944 the President's health worsened with signs and symptoms of congestive heart failure, and digitalis therapy and low salt diet was prescribed in combination with reduced use of alcohol and cigarettes. However, even higher BP were recorded in 1944, 180–230/110–140 mm Hg,

and the President suffered several cardiovascular events [84]. In 1945, before the Yalta conference, his BP was recorded at 260/150 mm Hg. Later the same year on the 12th of April, Roosevelt lost consciousness and died after complaining about severe headache. His BP was recorded at > 300/190 mm Hg, and the cause of death was certified, without autopsy, as cerebral hemorrhage.

During the 1950s and 1960s more antihypertensive drugs were discovered and used, some with considerable side-effects. During the late 1960s, evidence of the correlation between elevated BP and congestive heart failure, myocardial infarction, and kidney disease emerged in the Framingham Heart Study [85]. Also, reduced risk of congestive heart failure, stroke, and kidney damage was demonstrated in the Veterans Administrations Study, where male patients with diastolic BP (DBP) 115–129 mm Hg were treated with antihypertensive drugs [86]. Soon afterwards in 1970, a second Veterans Administrations study was presented where similar beneficial results were found when treating males with DBP 90–114 mm Hg [87].

In 1977, the first report was published from the US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) [88, 89]. In this brief 6-page report antihypertensive treatment was recommended to almost all persons with DBP > 105 mm Hg, and individualized antihypertensive treatment for those with DBP 90–104 mm Hg. The goal with antihypertensive treatment was set to DBP < 90 mm Hg. In version 5 of the JNC in 1993, the report had grown to 29 pages and the importance of systolic hypertension in the decision to initiate drug therapy was first addressed. In this report, antihypertensive drug therapy was recommended for persons with BP 140–149/90–94 mm Hg in combination with target organ damage or other risk factors, after trying lifestyle modifications [90].

1.3.3 HYPERTENSION TODAY

Over the years the knowledge of hypertension and its treatment has grown rapidly. The current *Guidelines for the management of arterial hypertension* from the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) were presented in 2018 [91]. The recommendations are complex and have expanded to 84 pages.

Currently, hypertension is defined as office (measured at the doctor's office) systolic BP (SBP) ≥ 140 and/or DBP ≥ 90 mm Hg. Repeated elevated BP measurements are recommended to confirm the diagnosis unless the BP is substantially elevated. In more detail BP levels are classified as:

- Optimal: < 120/ < 80 mm Hg

- Normal: 120–129/80–84 mm Hg

- High normal: 130–139/85–89 mm Hg

- Grade 1 hypertension: 140–159/90–99 mm Hg

- Grade 2 hypertension: 160–179/100–109 mm Hg

- Grade 3 hypertension: ≥ 180/≥ 110 mm Hg

- Isolated systolic hypertension: ≥ 140/< 90 mm Hg

In previous guidelines, office blood pressure was recommended for screening and diagnosis of hypertension. Now, in addition to repeat office BP, ambulatory 24-hour BP measurement, and/or home BP measurement are recommended for diagnosis of hypertension. In ambulatory BP measurement the diagnostic threshold for hypertension is defined as a mean BP of ≥ 130/80 mm Hg over 24 hours, ≥ 135/85 mm Hg at daytime, and ≥ 120/70 at nighttime. The diagnostic threshold for hypertension using home BP is ≥ 135/85 mm Hg.

The use of unattended office BP measurement by automated BP monitors has become more frequent and can reduce the "white coat effect" (elevated BP in the office but normal BP when measured with home or ambulatory BP measurement) sometimes seen in office BP measurement [92]. However, the automated SBP readings are also 5–15 mm Hg lower than in conventional office BP reading [93]. After the SPRINT trial, advocating SBP target < 120 mm Hg, and where unattended automated BP readings were used [94], controversies have emerged on how to compare those BP readings to conventional office BP measurement previously used in epidemiological studies and clinical trials [95].

The current ESC/ESH guidelines stress the importance of individual cardiovascular risk assessment (for example by using the SCORE system [96]), and detection of hypertension mediated organ damage (HMOD) e.g., arterial stiffness, left ventricular hypertrophy, microalbuminuria, chronic kidney disease, retinopathy, and ankle-brachial index < 0.9.

It is recommended that drug treatment is initiated for patients < 80 years old with grade 1 hypertension (140–159/90–99 mmHg) even without HMOD if hypertension persist after a period of lifestyle modification. Drug treatment is

recommended in parallel with lifestyle modifications for patients with grade 1 hypertension and high cardiovascular risk or HMOD, and for patients with grade 2 hypertension or higher. Fit older patients > 80 years with SBP ≥ 160 mm Hg are recommended drug treatment if well tolerated.

If treatment with antihypertensive drugs is initiated, the target BP for most patients is < 140/90 mm Hg, and if well tolerated < 130/80 mm Hg. However, the SBP should not be lower than 120 mm Hg. For old patients ≥ 65 years, and very old patients ≥ 80 years, the SBP target is 130–139 mm Hg and the DBP target is < 80 mm Hg, if tolerated.

1.3.4 BLOOD PRESSURE TARGET IN TYPE 2 DIABETES

The BP level goal to achieve in type 2 diabetes is a moving target and has been much debated the last decade [97-99]. In the Swedish National Board of Health and Welfare's national guidelines for diabetes in 2010, the overall BP target in type 2 diabetes was set at < 130/80 mm Hg [100]. In 2015 the guidelines were revised [101], and the overall BP target was raised to < 140/85 mm Hg based on consensus decision and following the 2013 ESC/ESH guidelines [102]. According to the current Swedish guidelines which were last updated in 2018, lower BP target is advised to be considered in some circumstances e.g., in younger patients or in the presence of albuminuria.

Compared to the Swedish guidelines, the 2018 ESC/ESH and the 2019 ESC/EASD [103] guidelines recommend lower BP target in type 2 diabetes. Here, the SBP target is 130 mm Hg, and lower if tolerated, but not below 120 mm Hg. For patients ≥ 65 years old, the SBP target is 130–139 mm Hg. The DBP is recommended to be lowered to < 80 mm Hg but not below 70 mm Hg.

From a Swedish viewpoint, a nationwide observational study from the National Diabetes Register of patients with type 2 diabetes and no previous cardiovascular disease showed that SBP 110–119 mm Hg was associated with reduced risk of several cardiovascular complications, but also increased risk of heart failure and all-cause mortality, as compared to SBP 130–139 mm Hg [104].

1.4 TYPE 2 DIABETES AND HYPERTENSION IN PRIMARY CARE

Primary care is the cornerstone in the management of type 2 diabetes and hypertension in Sweden [105] and other European countries [106, 107].

According to the NDR more than 95% of patients with type 2 diabetes were managed in primary care in 2019 [46]. Hypertension has been reported to be the second most common diagnosis in primary care in Stockholm County [108] and one of the most common reason for visit in primary care in developed countries [109].

Type 2 diabetes and hypertension are entangled companions that share several common risk factors e.g., obesity, sedentary lifestyle, insulin resistance, hyperinsulinemia, and familial history of the conditions [110]. Coexistence of the conditions is common and approximately 75% of patients with diabetes in Swedish primary care were treated with antihypertensive treatment in 2019 [46]. Circa 57% of those patients reached the BP target < 140/85 mm Hg. In previous studies from former Skaraborg County, 51% of patients with type 2 diabetes in the 1990s also had hypertension, and 22% of patients with hypertension also had type 2 diabetes [111, 112]. In a hypertensive mixed rural/urban Swedish primary care population 21.9% of the patients were also diagnosed with diabetes or prescribed antidiabetic medication in 2001–2008 [113]. Similar overlap of the diseases has also been reported from other western countries and Japan [114], and developing countries [115].

In Sweden, patients with type 2 diabetes and hypertension are often treated by general practitioners and diabetes specialist nurses in cooperation with other health care professionals such as dieticians, chiropodists, physiotherapists and ophthalmologists. In a recent nationwide Swedish primary care observational study, higher number of whole-time-equivalent general practitioners devoted to diabetes care was associated with lower mortality risk in patients with diabetes [116]. Also, diabetes specific education of registered nurses, and the length of patients' visit to registered nurses were associated with lower HbA1c levels in patients with type 2 diabetes indicating better glycemic control [117].

Historically, in the 1970s and the 1980s economic resources were allocated to primary care in former Skaraborg County to develop the decentralized "Skaraborgsmodellen" [118]. The rationale was to ease secondary hospital care utilization and to provide cost effective primary health care to the citizens. The model consisted of decentralized team-based primary health care clinics where general practitioners worked in close collaboration with specialist trained nurses, physiotherapists, dieticians and other health care professionals to provide care for patients with hypertension, diabetes, asthma, as well as for geriatric patients and maternity and infant care. Since then, "Skaraborgsmodellen" has gradually been dismounted. First, the primary responsibility for geriatric care was transferred from primary care to the municipalities in "Ädelreformen" 1992. Second, in 1999 Skaraborg County

was incorporated as one of five primary care regions into the larger administrative unit Västra Götaland Region. Third, in 2009 the economic conditions in primary care were standardized in the Västra Götaland Region as a new universal and central governed reimbursement system was introduced. Although many aspects of the local "Skaraborgsmodellen" have been dismounted, the foundation of multi professional management of patients with type 2 diabetes persists and is guided by national guidelines [119].

Of note, although most patients with type 2 diabetes and hypertension are seen and treated primarily in primary care, only a small fraction of diabetes related research emanates from a primary care setting [120].

1.5 SOCIOECONOMIC DETERMINANTS OF HEALTH AND MORTALITY

It has long been known that socioeconomic status (SES) such as income, educational level, occupation, marital status, social class, and area of residence is strongly associated with disease and mortality [121-124].

This also holds true for cardiovascular disease and mortality. In the contemporary PURE study including 20 low-, middle-, and high-income countries, low educational level was associated with increased risk of cardiovascular disease and mortality, with the largest effect seen in low- and middle-income countries [125]. Similar results with elevated risk of cardiovascular disease mortality in people with low occupational and educational class has previously been shown in the United States and Western European countries [126]. In Sweden, low neighborhood socio-economic status has been associated with increased risk of stroke also after extensive adjustment for other markers of SES [127].

The importance of SES regarding risk of cardiovascular disease and mortality has been studied in patients with diabetes living in high-income countries. In Scotland, area deprivation has been associated with increased risk of cardiovascular mortality [128]. Unemployment, low educational level, and low income are other socio-economic determinants that have been associated with increased risk of mortality in Finland [129]. Similar findings of socio-economic position and risk of mortality has been shown in Denmark [130]. In a nationwide Swedish study of patients with type 2 diabetes, living alone, low income, and low educational level were all associated with increased risk of mortality [131].

However, the interplay and relative importance of diabetes and socioeconomic status in relation to mortality and cardiovascular disease in patients with hypertension has not been extensively studied, and not in a primary care setting.

1.5.1 COUNTRY OF BIRTH

There are various studies on the influence of country of birth on mortality. A general immigrant mortality advantage i.e., lower mortality among immigrants than in the general population was reported in a recent systematic review and meta-analysis across various disease categories [132]. However, immigrant mortality patterns are not homogenous, with variations according to country of birth and host countries, as seen in different European [133] and Nordic countries [134].

An overall pattern of 2-fold higher diabetes mortality has been reported in immigrants compared to the local born population in some European countries, with higher mortality especially seen in immigrants from less developed countries [135]. This is in contrast with findings from a Swedish nationwide study of patients with type 2 diabetes where being born in a low-income European or a non-European country was associated with reduced risk of mortality, as compared to being born in Sweden [131]. The reduced mortality risk could be considered paradoxical since a higher cardiovascular risk than in Swedish born have been reported in immigrant groups in Sweden with higher prevalence of diabetes [136], worse glycemic control [137], and higher prevalence of cardiovascular disease [138, 139].

Today roughly 20% of the Swedish population is foreign born [140]. Historically, from the 1950s Finnish born immigrant workers has been the largest immigrant group in Sweden, culminating at approximately 250 000 individuals around 1980 and thereafter declining to approximately 145 000 in 2019 [140]. The top position was overtaken in 2016 by Syrian immigrants, following the Syrian civil war and refugee crisis. In 2019 the growing Iraqi immigrant group was roughly of equal size as the Finnish immigrant group. Previously, excess risk of mortality [134] and myocardial infarction [141], as well as increased prevalence of hypertension [142] have been reported in Finnish immigrants in Sweden. Lower prevalence of hypertension has been reported in Iraqi immigrants in Sweden, as compared to local-born people [143]. In Europe varying BP levels have been seen among different non-European immigrant groups, as compared to people born in Europe: lower BP levels in immigrants from South Asia, and higher among immigrants from sub-Saharan African [144].

So far, there are no studies exploring the association between immigrants' country of birth and risk of mortality and cardiovascular disease in hypertensive individuals in primary care. Moreover, the effect of concomitant diabetes on mortality and cardiovascular disease in this setting has not been studied.

1.6   REGISTER BASED RESEARCH

Everyone who is registered in the Swedish Population Register is assigned a unique personal identity number (PIN [in Swedish personnummer]) by the Swedish Tax Agency [145]. The PIN was introduced in 1947, states the date of birth and 4 additional digits, and is used unchanged throughout the whole life of an individual. It is widely used in Swedish society in contacts with health care providers, in commercial and financial situations, in contacts with various societal authorities, and in public administration. Besides being used as a personal identifier, the PIN can be used to trace individuals over time and geographically, both within the country but also to keep record of individual emigration and reimmigration. The PIN has enabled formation of various high-quality national registries kept by the Swedish state at the National Board of Health and Welfare and at Statistics Sweden, with almost complete coverage of the population.

The transition from paper based medical records to near complete use of electronic health records started gradually in Swedish primary care in the 1990s [146]. Since then, the transition to electronic health records has also been made in hospitals. This means that, technically, clinical data from electronic health records registered in routine health care, or any other form of computerized medical data, can be linked with data from national registries by using the PIN as the key identifier to form a combined data set. However, challenges in register-based research have emerged after the introduction of the European Union's General data Protection Regulation in 2018, with uncertainty of how it should be interpreted in practice in secondary research e.g., research that was not prespecified at the start of a study, or research using data from routine clinical care [147].

Research using register-based observational data has its pros and cons [148] in relationship to randomized controlled trials (RCTs) which are considered the gold standard in medical research. Pros include that longitudinal data can be made available at start, with no need of costly and time-consuming collection of research data as in a RCT. There is also no need to wait maybe several years for study outcomes. Cons include that the data is not primarily collected for research, meaning that all variables of interest might not be available, or

available with quality issues such as missing data or inconsistent coding. In longitudinal studies spanning over years or decades, variables relating to for example diagnoses or laboratory tests can also have changed multiple times. In RCTs, a causal relationship is assumed between exposure and outcome, whereas causality is much harder to assess in an observational study due to risk of potential biases and reverse causality. For both RCTs and register-based research, know-how on different aspects of study design, database handling and statistics is needed.

This thesis is based on 2 studies of prospectively collected data linked to national registers for assessment of study outcomes, and 2 studies with data collected from electronic health records in routine primary care linked to national registers for additional individual data and assessment of study outcomes.

2 AIM

The overall aim of this thesis was to study different epidemiological aspects regarding risk of mortality and cardiovascular complications among individuals with diabetes, hypertension, and hypertension with concomitant diabetes in primary care. The specific aims of the individual studies were:

I. To assess causes of death and long- term changes in mortality among patients in the Skaraborg Diabetes Register with new-onset type 2 diabetes clinically diagnosed between 1991 and 2004 compared to the general population.

II. To evaluate C-peptide concentration at the time of diagnosis of type 2 diabetes among patients in the Skaraborg Diabetes Register 1996–1998 as a possible biomarker to detect individuals at high risk of all-cause death, cardiovascular death and cardiovascular complications.

III. To estimate the effect of diabetes, educational level and income on the risk of mortality, myocardial infarction and ischemic stroke among hypertensive patients in primary care, using the Swedish Primary Care Cardiovascular Database.

IV. To investigate associations between mortality risk and country of birth among hypertensive patients in primary care with and without concomitant diabetes, using the Swedish Primary Care Cardiovascular Database. In addition, we also aimed to study the corresponding risks of myocardial infarction and ischemic stroke.

3 PATIENTS AND METHODS

This thesis is based on four cohort studies analyzed using various types of survival analyses. Study I-II originate from the Skaraborg Diabetes Register, and study III-IV from the Swedish Primary Care Cardiovascular Database. Key elements of the study design and methodology are summarized in Table 2, and statistical methods in Table 3.

Table 2. Study design.

	Study I	Study II	Study III	Study IV
Study design	Prospective cohort with historical controls	Prospective cohort	Retrospective cohort	Retrospective cohort
Setting	The Skaraborg Diabetes Register	The Skaraborg Diabetes Register	The Swedish Primary Care Cardiovascular Database	The Swedish Primary Care Cardiovascular Database
Inclusion criteria	Clinically new-onset type 2 diabetes. Matched population controls.	< 65 years old at diagnosis of clinically new-onset type 2 diabetes	≥ 30 years old and diagnosis of hypertension registered in primary care	≥ 30 years old and diagnosis of hypertension registered in primary care
Number of participants	7461 patients 37 271 controls	398 patients	62 557 patients	62 557 patients
Years of inclusion	1991-2004	1996-1998	2001-2008	2001-2008
Years of follow-up	1991-2014	1996-2014	2001-2012	2001-2012
Exposure	Type 2 diabetes and calendar time	C-peptide	Diagnosis of diabetes, level of education, and income	Diagnosis of diabetes and country of birth
Study outcome	All-cause, and cause-specific mortality	All-cause mortality, cause specific mortality, myocardial infarction, and ischemic stroke	All-cause mortality, myocardial infarction, and ischemic stroke	All-cause mortality, myocardial infarction, and ischemic stroke
Outcome assessment	Cause of death register	Cause of death register, Patient register	Cause of death register, Patient register	Cause of death register, Patient register

Table 3. Statistical methods.

	Study I	Study II	Study III	Study IV
Survival analysis	Incidence rates, Incidence rate ratios, Kaplan Meier curves, Log-rank test, Poisson regression for time-varying data, Fine and Gray competing risk regression	Incidence rates, Cox-regression	Incidence rates, Cox-regression with time-updated variable	Incidence rates, Cox-regression with time-updated variable
Analysis time scale	Time in study	Time in study	Age	Age
Covariate adjustment	Age, sex, calendar year of study entry	Age, sex, smoking, BMI, systolic blood pressure, antihypertensive treatment, HbA1c, eGFR, c-reactive protein, total cholesterol, previous myocardial infarction, previous ischemic stroke	Sex, calendar year of study entry, educational level, income, country of birth, preexisting conditions at baseline, systolic and diastolic blood pressure, creatinine, smoking, BMI, cholesterol, LDL, HDL, triglycerides	Sex, calendar year of study entry, educational level, income, diabetes status, preexisting conditions at baseline, systolic and diastolic blood pressure, creatinine, smoking, BMI, cholesterol, LDL, HDL, triglycerides
Handling of missing data	No missing data	Multiple imputation with chained equations	Multiple imputation with chained equations	Multiple imputation with chained equations
Other statistical methods	Fisher's exact test, Mann-Whitney U test		Restricted cubic splines	Restricted cubic splines

BMI: body mass index. HbA1c: hemoglobin A1c. eGFR: estimated glomerular filtration rate. LDL: low density lipoprotein. HDL: high density lipoprotein.

3.1 THE SKARABORG DIABETES REGISTER

The Skaraborg Diabetes Register (SDR) was active between 1991 and 2004 and is described in detail by its founder Bo Berger, MD, PhD, in his 2006 thesis: "Epidemiology of diabetes in a well-defined population in Sweden: the Skaraborg Diabetes Registry" [149].

When SDR was founded, Skaraborg was as it is today a mainly rural county with approximately 280 000 residents in 17 municipalities: Essunga, Falköping, Gullspång, Grästorp, Götene, Habo, Hjo, Karlsborg, Lidköping, Mariestad, Mullsjö, Skara, Skövde, Tibro, Tidaholm, Töreboda, and Vara. In 1998, fifteen of the municipalities in Skaraborg county were incorporated in Västra Götalandsregionen and the remaining two, Habo and Mullsjö were incorporated in Jönköpings län.

Starting 1 January 1991, prevalent cases of diabetes and new-onset cases of diabetes were registered in the SDR by hospital and primary care physicians, private practitioners, and specialized diabetes nurses in primary care. Gestational diabetes was excluded. In addition, cases of diabetes were added from an administrative hospital registry, the Skaraborg retinopathy screening program, and from an inventory of expedited insulin and antidiabetic drugs from pharmacies in Skaraborg. In 1992-1994, the capture rate of the SDR was estimated to $88.4 \pm 1.3\%$, and the prevalence of diabetes was estimated to $3.20 \pm 0.08\%$ [150].

The SDR includes individual and clinical data such as date of birth, sex, date of diagnosis of diabetes, clinical type of diabetes (type 1 and 2), age at diagnosis, systolic and diastolic blood pressure, HbA1c, smoking status, weight, height, BMI, antihypertensive treatment, renal function, total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), treatment with insulin, and treatment with oral antidiabetics. Registration of variables in the SDR differed to some extent over the 14 years of registration, e.g., blood lipids or usage of insulin pump were not reported during the first years. Some variables were registered only at clinical debut of diabetes (polyuria, weight loss, ketoacidosis), while other variables were registered longitudinally, e.g., blood pressure, HbA1c, and weight.

To assess the sensitivity of the SDR during its later period we validated the SDR against electronic medical health care records in 24 out of 25 primary health care centers in Skaraborg (data not previously published). A custom-built software was used to extract data from the medical records to find patients

with diabetes registered between 1 January 2000 and 31 December 2002. Diabetes was defined as fulfillment of any of the following criteria:

1. A registered diagnosis of diabetes (International Statistical Classification of Diseases and Related Health Problems [ICD] 10th revision: E108P, E109, E118P, E119, E14-P).
2. Prescription of insulin (any A10A Anatomical Therapeutic Chemical (ATC) code).
3. Prescription of any oral antidiabetic medication (any A10B ATC code).
4. Fasting whole blood glucose ≥6.1 mmol/L repeated at minimum 2 occasions.

Vitality status per 31 December 2002 was assessed by the Cause of Death Register for patients in the SDR, and by administrative census data or date of laboratory testing for the patients at the health care centers. In total, vitality status could not be ascertained for 207 patients at the health care centers. Assuming those 207 patients were alive 31 December 2002, the sensitivity or capture rate of the SDR to include patients with diabetes at the health care centers would be 83.1% (7079/8515), see Table 4. Assuming all those 207 patients were dead, the sensitivity would be 85.2% (7079/8308).

Table 4. Crosstabulation of number of patients with diabetes, alive on the 31 December 2002 in the SDR versus health care centers. The numbers within parenthesis refer to uncertain vitality status regarding 207 patients.

	Record of diabetes at health care center		Total
Included in the SDR	No	Yes	
No	0	1436 (1229)	1436
Yes	2726	7079	9805
Total	2726	8515 (8308)	11241

3.2 THE SWEDISH PRIMARY CARE CARDIOVASCULAR DATABASE

The Swedish Primary Care Cardiovascular Database (SPCCD) includes 74 751 patients 30 years or older with diagnosis of hypertension (ICD-10: I10, I13, and I15), registered in primary care 2001-2008 in any of 24 primary health care centers in the rural area of Skaraborg, or 24 primary healthcare centers in a mixed urban area of south-western Stockholm [113]. The total population in the two geographical areas were approximately 592 000 in 2008 (256 000 in Skaraborg and 336 000 in Stockholm).

Data on clinical and laboratory variables, diagnoses and prescribed medications from the primary care medical records (Profdoc Journal III [Profdoc AB, Uppsala, Sweden]) were extracted using a custom-made software extraction tool. The clinical variables include the last recorded data on body weight, height, smoking habits, and all recorded systolic and diastolic blood pressures. The laboratory variables include the first and last recorded data on creatinine, HbA1c, glucose, microalbuminuria, and the last recorded data on blood lipids. Diagnoses from primary care include hypertension, ischemic heart disease (I20-25), diabetes mellitus (E10-11, E14), congestive heart failure (I50), atrial fibrillation/flutter (I48), ischemic and hemorrhagic stroke (I60-69), and transient ischemic attack (G 45). Prescribed medications from primary care include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and beta-adrenergic receptor blockers.

Using the unique Swedish personal identification number [145], additional data was merged from national registers. Mortality data was added from the Cause of Death Register (see 3.3.1). Data on hospitalizations from 1997 and onwards, and hospital-based outpatient visits 2001 and onwards were added from the National Patient Register (see 3.3.2). Data on dispensed drugs from July 2005 were added from the Swedish Prescribed Drug Register [48]. Socioeconomic data on level of education (highest reported level of education in 2005 and 2010), income (reported in 2005 and 2009), and country of birth were added from national registers at Statistics Sweden.

3.3 REGISTERS USED FOR ASSESSMENT OF STUDY OUTCOMES

Study outcomes in the four studies were assessed using the Swedish Cause of Death Register and the Swedish National Patient Register which were linked to other study data using the Swedish unique personal identification number.

3.3.1 THE SWEDISH CAUSE OF DEATH REGISTER

Documentation of cause of death statistics as part of population statistics was introduced in Sweden by Tabellverket as early as 1749 [151, 152]. Initially, cause of death registration was a duty of the clergies and included limited causes of deaths such as smallpox, plague, maternal deaths, accidents, suicides, and violent deaths. In 1860 death certificates signed by a physician became mandatory in some instances for example in cities, and when the deceased had been cared by a physician. Since 1911 all causes of death have been included in the cause of death statistics. From 1911 to 1993 Statistics Sweden was responsible for the cause of death register, until the responsibility shifted to the Swedish National Board of Health and Welfare in 1994.

In 1991 the administrative procedures of certifying deaths and reporting cause of deaths were altered. After death is confirmed, the confirming physician must immediately send a "notification of death" (dödsbevis) to the Swedish Tax Agency (Skatteverket). Without this notification burial is not allowed. Within three weeks of death, a medical death certificate (intyg om dödsorsak) must also be sent to the National Board of Health and Welfare. In most cases the death certificate is completed by the patient's physician, or the last physician the patient was in contact with before death. The death certificate includes a version of the International Form of Medical Certificate of Cause of Death which is divided in 2 parts. The first part reports conditions that led directly to death as well as antecedent conditions contributing to death, and the second part reports unrelated but contributory conditions.

The underlying cause of death presented in official cause of death statistics is defined according to WHO in ICD-10 [153] and previous versions as "(a) the disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstance of the accident or violence which produced the fatal injury." However, for some diseases or injuries, special rules apply. Thus, classification of the underlying cause of death can in some cases be uncomplicated and straightforward, but in some cases also a very complex procedure as described in the ICD-10 instruction manual [153]. Up to 48 multiple causes of death can be reported on the death certificate, including both

the underlying cause of death as well as contributing causes of death, which are not presented in order of importance. Data completeness in the Cause of Death Register is high with only a small proportion of death certificates lacking an underlying cause of death (0.9% in 2019), or with an insufficiently specified cause of death (3.1% in 2019) [154].

The validity of the reported cause of death varies upon the circumstances in which the death occurred. In a Swedish study [155] validating death certificates against hospital case summaries, the death certificate accuracy was high for malignant tumors (90%) and ischemic heart disease (87%), but low for chronic obstructive and other pulmonary diseases (47%), and benign, other and unspecified tumors (40%). The accuracy also decreased with higher age at death, with 98% accuracy for age 15–44 years and 72% for age 85 and older. Autopsy as a method to clarify causes of death have become more uncommon in Sweden over the past decades [156], with autopsy rates declining from 41% in men and 31% in women in 1987, to 14% in men and 7% in women in 2019. Autopsy rates also generally decrease with age, and in 2019 only 5% of men and 3 % of women 75 years and older were autopsied after death. However, better diagnostic tools and practices preceding death have been reported to counterbalance the effect of decreasing autopsy rates [157]. Probably the validity of death certificates is lower for deaths occurring out of hospitals i.e., among multimorbid elderly receiving end-stage care in their own homes or at nursing homes. Even though the reporting physician could have followed these patients clinically for a long time, the cause of death is sometimes not obvious and can involve some qualified guesswork.

3.3.2   THE SWEDISH NATIONAL PATIENT REGISTER

The National Patient Register [158] was founded in 1964 and initially covered hospital discharge data including ICD-diagnoses concerning somatic inpatient care in six Swedish counties. Data on psychiatric inpatient care was added in 1973. Complete national coverage on somatic and psychiatric inpatient care was reached in 1987. In 1997 data was added on surgical day care procedures, and data on other hospital-based outpatient physician visits were added in 2001. The National Patient Register does not include data from primary health care, or data from caregivers other than physicians. The validity of diagnoses in the National Patient Register is high for some but not all diagnoses, with studies showing positive predictive values of 98–100% regarding myocardial infarction and 68.5–98.6% regarding stroke/transient ischemic attacks [158].

3.4 DATA ON SOCIOECONOMIC STATUS

Individual longitudinal data on socioeconomic status such as income, level of education, civil status, employment, occupation, and country of birth are available in Swedish national registries with high coverage. Many of the variables are available in multiple versions using alternative definitions. For example, data on income is available in several versions including taxed income, earnings, business income, allowances to parents, sick leave, disability pension, unemployment benefits, social welfare, and other incomes such as income from capital. Data on disposable income is often used in research and is defined as the sum of all incomes minus taxes and is available on individual and family level.

The socioeconomic variables mentioned above, and many more variables are collected with annual updates at Statistics Sweden in the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA, Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknads-studier). LISA was initiated in 2003 and includes longitudinal data since 1990 for over 600 variables concerning individuals, firms and workplaces.

3.5 STATISTICS

The common statistical theme of the studies building this thesis is time to event, or survival analysis. In survival analysis we are not only looking at the occurrence of a binary event of interest or *failure*, for example death or myocardial infarction, but also the length of time the subject or individual has been at risk until experiencing the event – *the failure time*. Elapsed time from study start to failure can be measured in any quantity of time, for example hours, days, months, or years. In this section, statistical concepts and methods used in this thesis are briefly described and discussed from a clinician's viewpoint.

3.5.1 RATES AND RATE RATIOS

An incidence rate describes the number of events or failures per unit of time. In survival analysis, time is usually measured as the sum of follow-up time for all individuals being at risk of experiencing an event or failure, and is expressed as person-time e.g., person-days or person-years. Often, especially if the number of events is low, person-time is expressed as a multiple e.g., 100 or 1000 person-years. Thus, the incidence rate of myocardial infarction can be expressed as

$$\frac{number\ of\ myocardial\ infarctions}{1000\ person-years}$$

A rate ratio is calculated by dividing one rate with another rate. For example, a mortality incidence rate ratio (IRR) is calculated by dividing the mortality rate in population *A* with the mortality rate in population *B*. IRR > 1 indicates higher mortality rate in population *A* compared to population *B*, whereas IRR < 1 indicates the opposite. If the mortality rates are equal in both populations, the IRR is 1.

3.5.2 CENSORING

In cohort studies it is common for individuals to enter the study at different calendar periods. The period of study entry or inclusion can be short, a few days, but also prolonged for several years. It is also common that the follow-up period varies between individuals. Some individuals may be followed from study entry until the prespecified end of study, while others may have shorter follow-up due to different reasons unrelated to failure itself, such as voluntarily withdrawal from the study, emigration, death, or any other reasons for loss of follow-up. In survival analysis, the observation time of individuals that do not experience failure during follow-up are *right-censored* (commonly described

as just censored) at the last date of follow up. After right-censoring it is unknown for the observer if, and when failure will occur.

Although right-censoring is the most common type of censoring in epidemiology, other forms of censoring may apply. If the exact timepoint of failure is unknown, but failure is known to have occurred between two distinct timepoints the observation is *interval-censored*. This could be the case for an individual with diabetes attending yearly clinical follow-up visits revealing no signs of proteinuria or retinopathy at year 1, but with signs of complication at the follow-up year 2. The exact timepoint where the complication developed is unknown, but it occurred sometime between year 1 and 2. *Left-censoring* is also possible and occurs when failure happened before the observation time begun. In mortality studies this is not an issue as dead people cannot be included in a study. For other outcomes, people who have already experienced the outcome of interest are usually excluded from the study.

3.5.3   SURVIVAL AND HAZARD

The survival probability, or the survival function *S(t)*, is the probability that an individual has survived i.e., not experienced the failure event, from the start of observation or inclusion in a study until the specified timepoint *t*. Survival could be freedom from death but could also be freedom from any other prespecified failure event. The survival probability can range between 1 at the start of observation before any failures has occurred, and 0 as the observation time approaches infinity.

The survival probability can be estimated using the Kaplan Meier method [159] which takes both censored and uncensored survival time into account. The survival probability is often visualized by using a Kaplan Meier survival curve where the survival probability is stepwise plotted against time, and for example the median survival time easily can be estimated. In epidemiological studies the occurrence of a study outcome or failure e.g., death or a specific disease, is often more of interest than survival or freedom from the study outcome and therefore the failure proportion *1-S(t)* is plotted rather than S(t). See Figure 1 for example.

Statistical tests can be used to test for equality or difference in survival curves. The most commonly used test is the non-parametric log rank test which assess the observed number versus the expected number of failures to test if there is a statistically difference between survival curves [160]. The log rank test produces a p-value of the statistical significance, but no information on how large the difference is in absolute or relative terms.
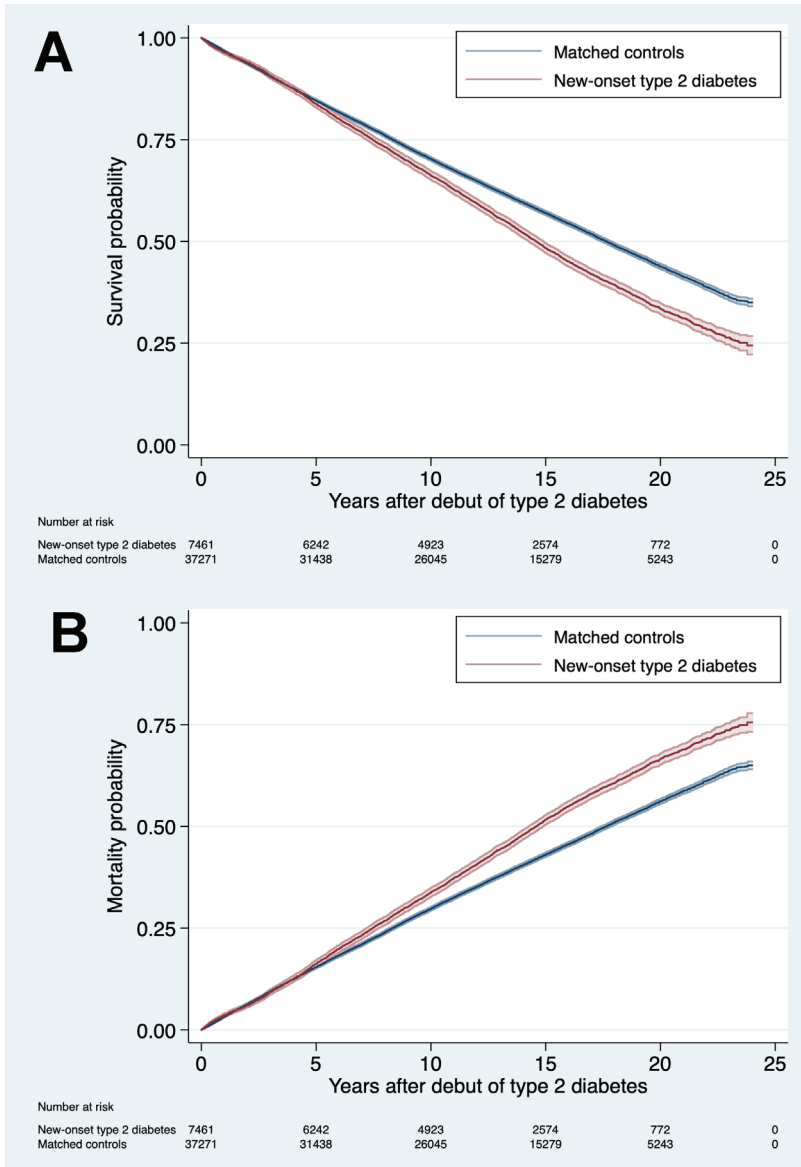
Figure 1. Examples of Kaplan-Meier curves. Panel A depicts the survival probability with 95% confidence interval for patients in Study I with new-onset type 2 diabetes versus matched control individuals. Panel B shows the mortality probability (1-survival) for the same cohorts. The number of individuals at risk of study outcome is presented at the start of the study and for every 5 years of follow-up. Median survival time after study start can be estimated at survival or mortality probability 0.50.

The hazard *h(t)* may seem less intuitive than the survival function, but is the instantaneous failure rate at time t for an individual who has survived (i.e., not experienced failure) until time t. It can also be described as the rate of change in the survival function, or in mathematically terms as the derivate of the negative logarithm of the survival function. Perhaps the easiest way for a clinician to understand the concept of hazard is to think of it as the instantaneous incidence rate of a disease or other clinical event (i.e., failure) at a specified time point, under condition that the individual has survived (i.e., not experienced failure) up until that timepoint. The unit of the hazard is number of events per time unit, and the hazard can take any value from 0 to infinity.

3.5.4 CONFOUNDING

The Kaplan Meier method and the log rank test are examples of univariate analysis i.e., they describe the survival with respect to one factor or exposure, such as an age group, gender, a pharmacological treatment, or a specific disease. In epidemiological studies there is often a need to take additional factors into account for proper evaluation of the factor or exposure of interest. Age and gender are factors often associated with both the exposure of e.g., diabetes or hypertension, and the outcome e.g., death or a myocardial infarction. With advancing age, the risk of the exposure of diabetes or hypertension increase, as well as the risk of the outcomes of death or myocardial infarction. In this example age and sex are examples of *confounders*, see Figure 2. According to Rothman [161] confounders are characterized by three properties:

- "A confounder must be associated with the disease (either as a cause or as a proxy for a cause, but not as an effect of the disease)."

- "A confounder must be associated with the exposure."

- "A confounder must not be an effect of the exposure."

One way of dealing with confounding is to restrict the analysis according to the confounding factor. If gender is a confounder, survival could be analysed with Kaplan Meier curves and the log rank test, stratified for gender i.e., with separate analyses performed for men and women. Similarly, if age is a confounder, stratified analyses could be performed for each age or age interval. However, in a situation with more than a few stratification variables, the number of subgroup analyses can be large, resulting in fewer samples in each

group and lower statistical power. Also, the complexity involved in disentangling the effect of an exposure increases with the number of subgroup analyses.
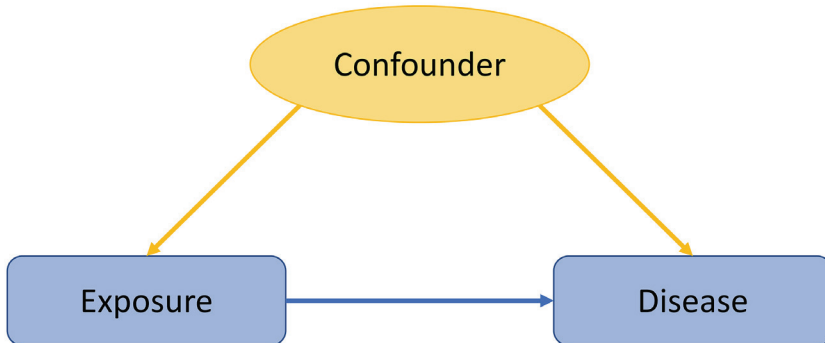
Figure 2. A confounder is a factor associated with both the exposure and the outcome/disease of interest. To be able to estimate the effect of the exposure on the outcome/disease, the confounder must be considered.

Other approaches to deal with confounding are randomization and matching. In randomization, individuals are chosen by chance in two or more study groups where, in theory and with sufficiently large study samples, known as well as unknown confounding factors are balanced within the study groups, resulting in equalization of confounding. In matching, individuals with similar characteristics, for example age and gender, are selected one to one or in any other ratio into the study groups. Matching provides good control of known confounders but doesn't control for unknown confounding.

3.5.5   THE COX PROPORTIONAL HAZARDS MODEL

A popular technique for handling confounding in survival analysis is to use the Cox proportional hazards model, which was developed and presented by Sir David Roxbee Cox in 1972 [162]. The Cox model makes it possible to calculate the effect of an exposure while controlling or adjusting for other variables or *covariates*. Variables in the model are allowed to be continuous or categorical (binary, nominal, or ordinal), and their effects are expressed as hazard ratios. According to Cox, the hazard function can be described as

$$h(t) = h_0(t) \times \exp{(b_1 x_1 + b_2 x_2 + \cdots + b_p x_p)}$$

where h(t) (the hazard at time t), is dependent on a baseline hazard h_0 and p number of covariates (x_1, x_2,…, x_p) with different effect sizes (b_1, b_2,…, b_p).

The hazard ratio is the rate of two hazards and is thus a relative, and not an absolute measure.

The Cox model assumes proportional hazards (PH), meaning that the hazards can vary over time, but their ratio must be proportional or constant over time. If the hazard or the momentaneous incidence of an event such as myocardial infarction is higher in study group A compared to study group B, the hazard ratio for study group A versus B exceeds 1 which is interpreted as increased risk of the event. If the hazards are equal in group A and B the hazard ratio is 1 i.e., equal risks. Lower hazard in group A versus B results in a hazard ratio less than 1 i.e., decreased risk of the event.

The PH assumption can be validated in several ways [163]. An initial quick and easy, although less formal method to assess obviously non-PH is to check for the occurrence of crossing Kaplan Meier survival curves. A more formal graphical method is to plot log-log survival curves. Parallel curves demonstrate proportionality, whereas crossing curves imply non proportionality. Another graphical approach is to plot Kaplan Meier curves together with predicted survival curves from the Cox model. Proportional hazards result in curves plotted closely together. If the curves are far from each other the PH assumption is considered violated.

Yet another way of assessing PH is to evaluate the so called Schoenfeld residuals, either graphically or in a statistical test (see chapter 3.6.3 for example in Study I). The PH assumption is considered violated if Schoenfeld residuals for a certain covariate correlate with survival time, depicted graphically as a non-horizontal pattern, or in the test statistics as a significant p-value. Finally, the PH assumption can be evaluated by introducing an interaction term between time and the covariate of interest. A statistically significant interaction term means that the effect of the covariate varies over time and is thus not constant i.e., the PH assumption is violated.

The described methods to assess PH all have their pros and cons. The graphical methods are somewhat subjective as the evaluator must decide how parallel is parallel, how close is close, and how horizontal is horizontal? The Schoenfeld test statistics also has its drawback as large sample sizes e.g., studies with tens of thousands of participants as typically seen in registry-based research, can result in statistical significances even for a minor deviance from PH. However, in general, the Cox PH model is considered rather robust and a conservative approach is often practiced, where violation of the PH assumption is deemed only at clear deviations.

3.5.6   NON-PROPORTIONAL HAZARDS

Several alternative analytical approaches are possible if the assumption of PH is violated, and it is judged not suitable to apply the standard Cox proportional hazards model.

It is possible to stratify the Cox model on the covariate not fulfilling the PH assumption. The drawback of this approach is that the effect of the stratified covariate cannot be estimated. However, stratifying is a viable option if we are not primarily interested in the effect size of the stratified covariate, but just want to control for potential confounding.

Another option is to use the extended Cox model for time-dependent or time updated variables [164]. In this model, the HR of covariates are allowed to vary over time. One scenario is that the HR of a covariate interacts with time, for example that the HR of an event such as death is highest in the first period of follow up and then decreases during follow-up time. The value of a covariate can also be time-updated, for example in a categorical variable describing the addition of a diagnosis of diabetes at some timepoint during follow up, or in a continuous variable describing blood pressure levels measured at repeated timepoints during follow up.

Beyond the Cox model other regression models such as Poisson regression can be used for survival analysis [165]. In Poisson regression, the follow up time can be split in multiple shorter time intervals. A new time interval could for example start every day, month, year, or at the timepoint of a study outcome event. As separate incidence rate ratios or HRs can be estimated for each time interval, the incidence rate ratios or HRs are not restricted to be constant during follow-up but can vary over time.

3.5.7   COMPETING RISKS

A competing risk is an event that preclude the outcome of interest [166]. In standard survival analysis right-censoring is assumed to be independent or noninformative, meaning that individuals being followed in a study should have the same future risk of an outcome event as censored individuals that are no longer followed. However, an individual who is participating in a study where the occurrence of myocardial infarction is assessed, and whose follow-up time is censored due to death cannot later also have a myocardial infarction. In this example death preclude myocardial infarction and is thus a competing risk. Similarly, if cause specific mortality due to cardiovascular disease is assessed, all other causes of death are competing risks. The downside of not taking competing risks such as death in account is the risk of overestimating

the probability of an outcome event to occur, especially if the proportion of individuals experiencing a competing risk is high [167]. As a consequence, if the probability of cardiovascular mortality and non-cardiovascular mortality are plotted as Kaplan-Meier curves and the probabilities are added, the combined probabilities will exceed the probability of all-cause mortality [166].

Although competing risks are often handled just by censoring, there are statistical methods available to address the difficulties of competing risks. The cumulative incidence function (CIF) takes competing risk into account and can be used instead of Kaplan Meier estimates and the survival function. The CIF can be calculated by competing risk regression according to Fine and Gray [168]. From this method the so called subhazard function and subdistributional hazard ratios (which are similarly presented but not as easily interpreted as Cox regression hazard ratios) are derived, and can be used to plot the CIF [169].

3.5.8 MISSING DATA

Missing data is a common problem encountered in research dealing with electronic health care records collected from routine health care [170]. In prospective RCTs, various prespecified data for participants fulfilling the inclusion criteria is meticulously recorded in a controlled environment. In comparison, studies using "real world data" extracted from routine health care can include a large number of individuals, with heterogenous characteristics representing the complexity and multimorbidity typically seen in a primary care setting. However, "real world data" is often incomplete, as data later needed in a particular study has not always been recorded due to various reasons.

Three separate mechanisms for the occurrence of missing data have been described by Rubin [171, 172]: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). MCAR occur when missing data is totally by chance and is independent of both the observed and the unobserved data. For example, a questionnaire being lost in the postal service, or a study participant being struck by lightning on his way to a clinical follow-up visit. MAR occur when data is systematically missing and is dependent on other known data. For example, data on smoking or BMI could have been less frequently recorded, intentionally or unintentionally, in elderly individuals, in either sex, or in individuals with certain socioeconomic position. Finally, MNAR also occur systematically but is dependent only on unknown data including the missing data itself. For example, in a survey of self-reported income, participants with high income could be less likely to report their income. The distinction between MAR and MNAR cannot easily

be made by examining the study data, and the toolbox to handle MNAR is much more limited than for MAR [173].

The easiest way to handle the problem of missing data is to exclude individuals with any missing variable – "listwise deletion", and to include only individuals with complete data regarding all variables of interest in the study to perform a "complete case analysis". This approach will have two drawbacks [174]. First, a reduction in study sample size will result in lower statistical power to detect statistically significant findings. Even a small proportion of missing data per variable can result in a large reduction in sample size if the pattern of missing data is non overlapping, e.g., 3% missingness in 20 variables without overlap equals 60% missing data in total. Second, unless data is MCAR, listwise deletion can introduce bias of unknown direction and magnitude. Although the exact mechanism of missing data in electronic health care records is frequently unknown, it is often assumed to be MAR and less likely to be 100% MCAR or MNAR [170].

Multiple imputation by chained equations (MICE) is a widely used method to handle missing data assuming MAR [175, 176]. MICE is possible to use for missing data that is continuous, as well as for binary, nominal, and ordinal missing categorical data. The method involves three steps. First, a number of multiple imputed datasets are generated where the unknown data is replaced by data derived from other data in the dataset, for example by using linear regression for continuous data, and logistic regression for categorical variables. Second, each dataset (which is now complete without missing data after step 1) is analysed separately using the complete cases analysis approach. Third, the estimates from the separate analyses in step 2 are combined in overall estimates using Rubin's rules [177].

The first step in the MICE procedure involves a substantial amount of tweaking. The number of separate datasets needed is debated and, as a rule of thumb, has been suggested to be at least equal to the percentage of incomplete cases [178]. Further, the imputation model used to derive "new" values for missing data must include all covariates that will later be used in the analyses carried out in the second step. The outcome of the study must also be included, and for survival analysis some measure of time to outcome. For the Cox proportional hazard model, it has been recommended to include an indicator of the outcome and to include the Nelsen-Aalen estimate of the cumulative hazard instead of simply time to outcome [179]. In addition, any other variable predicting either the value of missing variable or that the variable is missing is allowed to be included in the imputation model, even though the variable will not be included in the analyses in the second step. Before inclusion in the

imputation model, skewed variables may be logarithmically transformed and then transformed back before analysis.

The MICE procedure is an iterative process and the stability of the results of the imputation model can be checked visually by "trace plots" where the variable estimate is plotted against the number of iterations. Ideally, the estimate should converge rapidly towards a stable estimate without any trending against the number of iterations, see Figure 3.
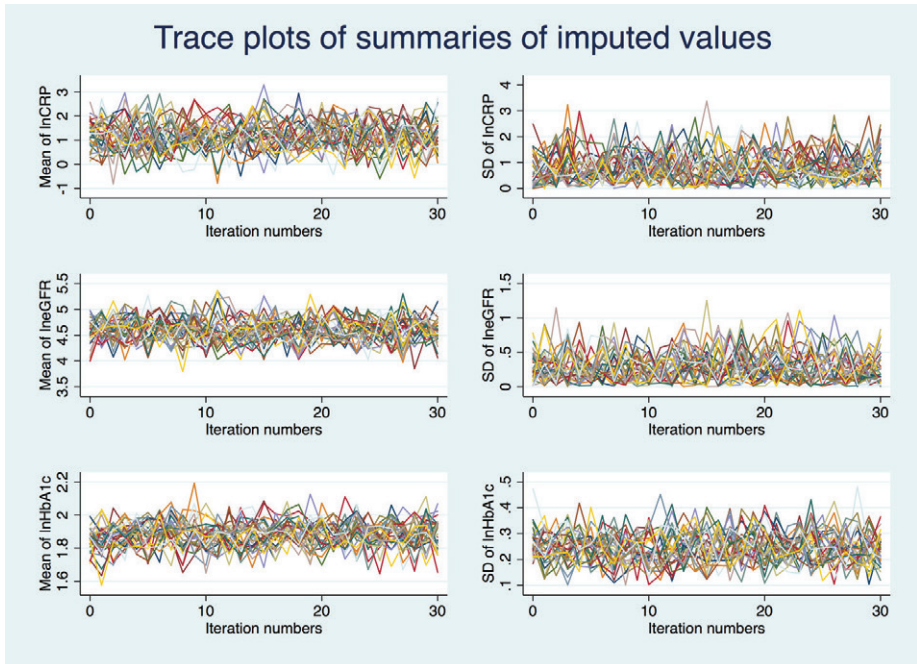
Figure 3. Trace plots can be used to visually evaluate the mean values and the standard deviation of values that have been imputed by multiple imputation by chained equations (MICE). Here, MICE has been used in Study II to impute missing data regarding the variables CRP, e-GFR, and HbA1c. As the variables were non-normally distributed the values were ln-transformed before imputation. Convergence with intermingled streams is seen without any specific trending.

3.5.9   FUNCTIONAL FORM

The ideal approach to model or assess the association between a continuous variable, for example systolic blood pressure, and an outcome event such as myocardial infarction or death is debated [180]. Historically, continuous variables have often been modeled assuming a linear relationship between the

exposure and the outcome. However, biological associations are frequently non-linear, but rather U or J shaped as in the association between systolic blood pressure and mortality risk [181].

Categorization of continuous variables is another common approach which can be used if the functional form (linear, exponential, J-shaped, U-shaped, or any other form) of the association between exposure and outcome is unknown. Benefits of categorization include that data often is straightforward to analyze, and the results easy to interpret and compare to similar studies. However, categorization has some drawbacks. First, loss in data information reduces the statistical power. Second, the number of categorical cut points and where to place them risk being rather subjective if not prespecified. For example, a non-recommended "optimal cut point strategy" could be used where cut points are placed at locations resulting in the largest differences between the subcategories leading to biased results [182].

Martingale residuals can be used to assess the functional form of a covariate in a Cox regression model [169, 183]. The martingale residual can be interpreted as the difference in the observed number of outcome events compared to the number of outcome events predicted by the model. In practice, the martingale residuals are smoothly plotted against the covariate of interest x, or different transformations of the covariate, for example x^2, e^x, $log\ x$, $1/x$, or any other likely functional form. When evaluated visually, a straight curve indicates the transformation that best describe the functional form of the covariate (see chapter 3.7.3 for example in Study II).

By using splines, non-linear functional forms can be modeled without the drawbacks of categorization of data [184]. Restricted cubic splines are a set number of intervals with piecewise cubic polynomial functions smoothly joined together at the split points of the intervals which are called "knots". Restricted refers to that the functional form must be linear before the first, and after the last knot. The number of knots can be specified by the analyst and is often between 3 and 7. The location of the knots can be specified as well, or default locations used as described by Harrel [185]. For example, if using 5 knots which is the default number using the statistical software Stata, the locations of the knots are at the 5th, 27.5th, 50th, 72.5th, and 95th percentile of the data. The use of restricted cubic splines versus linear modeling is exemplified in Figure 4.

The use of splines is not without drawbacks. The effect size of a variable of interest that has been transformed using splines can be hard to interpret and the effect size is often better visualized in a graph. However, this is less of a

problem if the spline transformed variables are merely used to adjust for confounding where the effect sizes of the confounders are not of primary interest. This could be the case in a study assessing mortality risk among patients with, versus without diabetes where the effect of diabetes could be adjusted for various continuous confounders with possible non-linear associations with mortality such as blood pressure [181] and BMI [186]. Another drawback with splines is that it can be harder to describe and communicate complex results from analyzes with splines, as compared to categorized data or if a linear association is assumed.
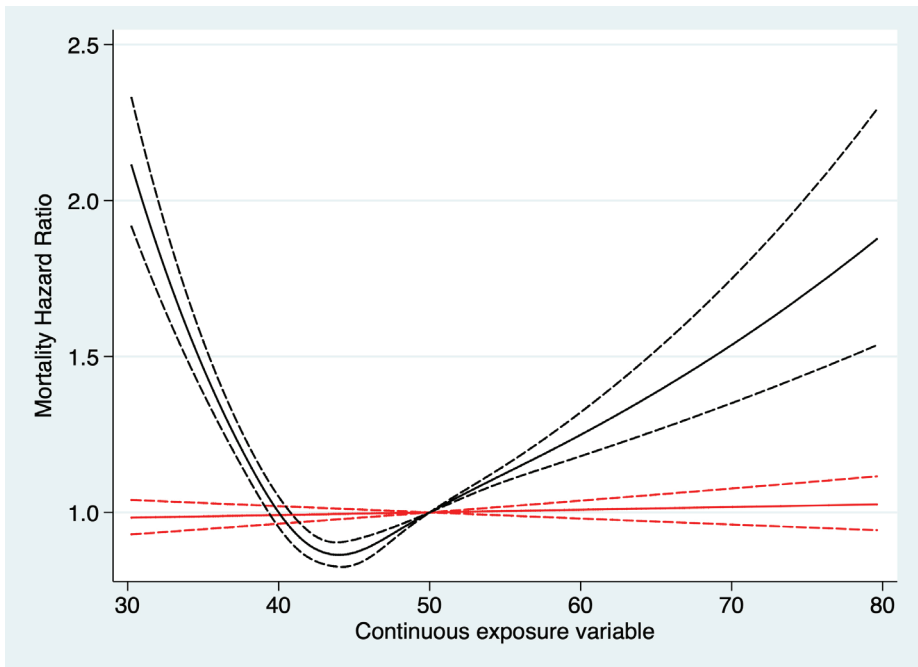
Figure 4. In this hypothetical example of functional form, the association between a continuous exposure variable and mortality has been estimated by Cox regression modeling. The red solid and red dotted lines represent the mortality hazard ratio with 95% confidence intervals for various values of the exposure variable when modeled assuming a linear association between exposure and mortality risk. Using this approach, no significant association is seen between exposure and risk of mortality as the 95% confidence intervals include mortality hazard ratio 1 for all values of the exposure. In contrast, when the association is modeled using restricted cubic splines with 5 knots, a highly significant U-shaped association is seen between the exposure variable and mortality, as depicted by the black solid and dotted lines. In this example, the numerical value 50 was arbitrary defined as reference for the exposure.

3.6 STUDY I

3.6.1 STUDY DESIGN, SETTING AND PARTICIPANTS

In this cohort study, we included patients > 18 years old prospectively registered in the Skaraborg Diabetes Register, with debut of clinically new-onset type 2 diabetes between 1991 and 2004. With assistance from Statistics Sweden, patients were matched with up to 5 individual controls from the general population in Skaraborg County. The controls were matched for sex and age on the calendar year and month of patients' study inclusion.

3.6.2 OUTCOME ASSESSMENT AND FOLLOW UP

The study outcomes were all-cause, and cause-specific mortality, assessed by the Cause of Death Register. Participants were followed from study inclusion until the first of the following events: emigration (data obtained from Statistics Sweden), death, or end of study 31 December 2014.

3.6.3 STATISTICAL METHODS

In order to study temporal changes in baseline characteristics, we split the cohort in two calendar periods based on new-onset type 2 diabetes debut in 1991-1997 and 1998-2004, respectively. Fisher's exact test was used to test for differences in dichotomous variables, and Mann-Whitney U test for continuous variables.

We calculated crude outcome incidence rates with 95% confidence intervals (CI) for patients and controls. Thereafter, we used the incidence rates to calculate incidence rate ratios with 95% CI for patients versus controls. Rates and ratios were calculated stratified for calendar periods, sex, and age at diagnosis. Kaplan-Meier curves were used to plot cumulative incidences of mortality, and differences in mortality were tested by the log-rank test.

Initially, we planned to use Cox regression models for multivariable survival analysis. However, the proportional hazard assumption was not fulfilled when evaluated by Schoenfeld residuals (see Figure 5), and by log(-log(survival) versus log(time) plots. This means that mortality hazard ratios were not constant but varied during follow up time. To analyze and plot time-varying hazard ratios, we instead fitted Poisson regression models based on previously developed methodology [187]. We included the following variables: time since diagnosis, age at diagnosis, sex, calendar year at diagnosis, and significant interactions of the aforementioned variables. Age, and time since diagnosis

were modelled as piecewise linear continuous variables, with cut points for age at 55, 65, 75, and 85 years, and for time since diagnosis at 1, 4, and 15 years.
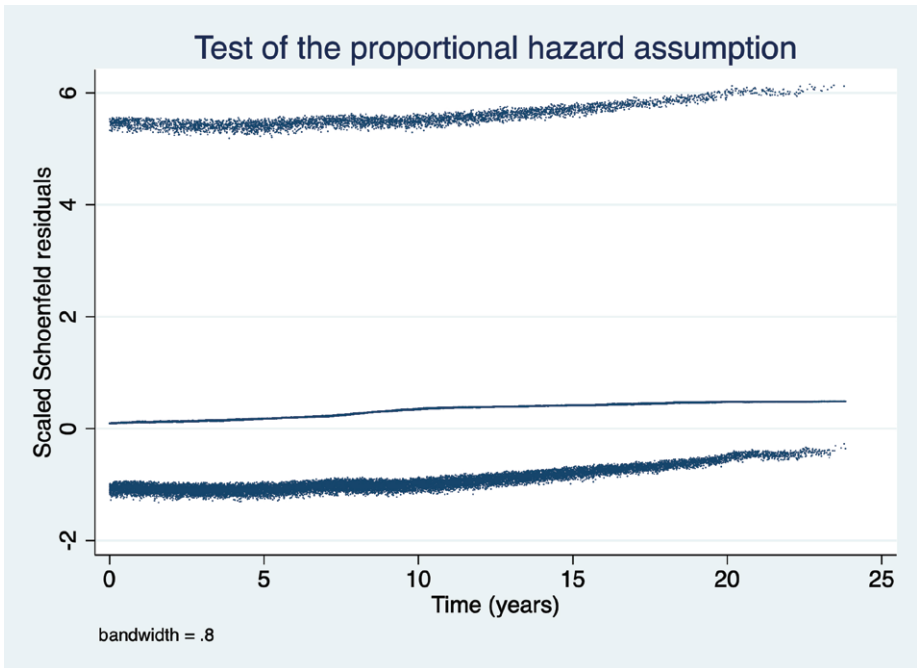
Figure 5. Graphical test using scaled Schoenfeld residuals to check the Cox proportional hazard assumption regarding excess mortality in patients with type 2 diabetes versus population controls. The blue line is non-horizontal indicating violation of the proportional hazard assumption i.e., that the excess mortality risk is not constant during follow-up.

Using the Poisson models, we estimated the adjusted overall all-cause mortality hazard ratio with 95% CI, for patients versus controls, and for men versus women among patients and controls. We also estimated the adjusted annual decrease in all-cause mortality risk for patients and controls, and the adjusted annual decrease in all-cause mortality hazard ratio for patients versus controls.

We calculated cause-specific mortality incidence rate ratios with 95% CI for patients versus controls, in total and stratified for sex. For each cause of death subcategory, we estimated the subdistribution hazard ratios using competing risk regression models according to Fine and Gray, using all other causes of death subcategories as competing risks. Using the subdistribution hazard

ratios, we plotted the cumulative mortality incidence, for patients and controls, for each cause of death subcategory.

Analyses were performed using STATA version 14.2 (StataCorp., College station, TX, US), and SAS version 9.4 (SAS Institute Inc., Cary, NC, US). Tests were two-tailed with significance level 0.05, or 0.0014 (0.05/36) after Bonferroni correcting for multiple comparisons of causes of death.

3.7 STUDY II

3.7.1 STUDY DESIGN, SETTING AND PARTICIPANTS

From 1 September 1996 to 31 August 1998, patients in the Skaraborg Diabetes Register younger than 65 years at diagnosis of clinical new-onset type diabetes were invited to an additional study investigating beta-cell function and pancreatic islet antibodies [188]. Within 3 months (median 1 month) after the diagnosis of diabetes, fasting blood samples including C-peptide, glucose, HbA1c and islet antibodies, were drawn from the participants and collected in a biobank. In 2012, the biobank was used to add laboratory analyses of renal function (creatinine and cystatin C), and C-reactive protein (CRP) which is an indicator of inflammation. In this cohort study, we included all participating patients characterized as type 2 diabetes, and with blood samples collected in the biobank.

3.7.2 OUTCOME ASSESSMENT AND FOLLOW UP

Study outcome were assessed by the Cause of Death Register, and the National Patient Register. The primary study outcome was all-cause mortality. Secondary mortality outcomes were underlying cardiovascular cause of death (ICD 9: 390–459, ICD 10: I), contributing cardiovascular cause of death, underlying cancer cause of death (ICD 9: 140–239, ICD 10: C), contributing cancer cause of death, and non- cardiovascular non-cancer death (ICD 9: all codes except 390–459 and 140–239, ICD 10: all codes except I and C). Secondary outcomes also included fatal and non-fatal myocardial infarction (ICD 9: 410, ICD 10: I21), fatal and non-fatal ischemic stroke (ICD 9: 433–434, ICD 10: I63), and a combined endpoint of fatal and non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, and cardiovascular death. Participants were followed from study inclusion until the first of the following events: study outcome, death, or end of study 31 December 2014.

3.7.3 STATISTICAL METHODS

We calculated number of study outcomes, and study outcome rates with 95% CI. Missing data was handled by using multiple imputation with chained equations (MICE) in 30 datasets.

We investigated the association between C-peptide concentration at baseline and study outcomes using Cox regression models, with time in study as timescale. The functional form of the association between C-peptide and outcomes could be described as linear when evaluating Martingale residuals graphically (see Figure 6).
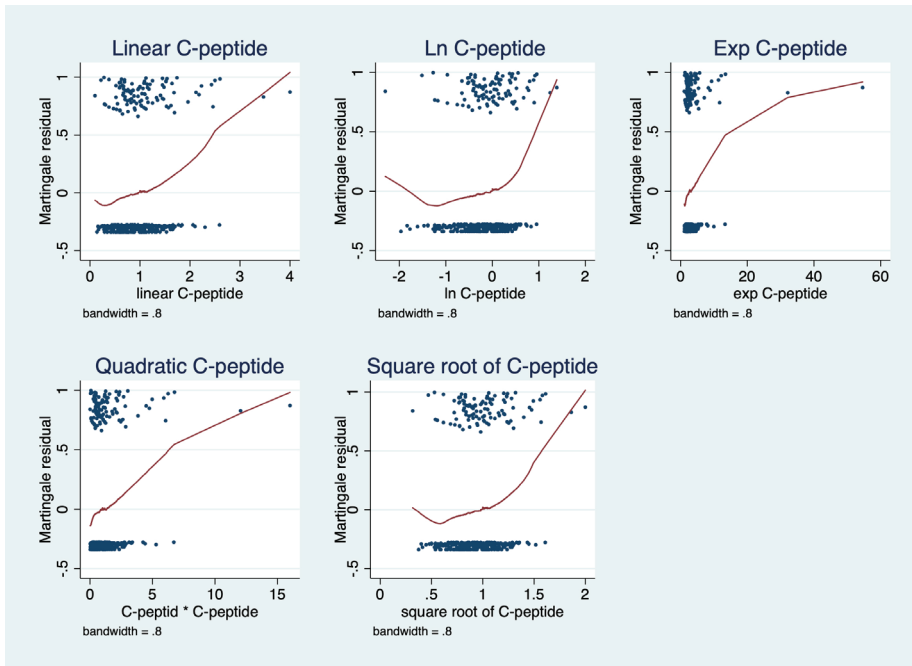
Figure 6. Test of the functional form of the association between C-peptide and mortality by plotting martingale residuals against different transformations of the C-peptide concentration. Non transformed linear concentration of C-peptide was compared to ln, exponential, quadratic, and square root transformations of the C-peptide concentration. The transformation resulting in the straightest red line describes the functional form best. Here, the straightest lines are seen for linear and quadratic C-peptide concentrations. Test of model fit by the Akaike information criterion favored linear C-peptide which is also easier to understand intuitively.

In the first Cox regression model, we estimated unadjusted HRs. In the second model HRs were adjusted for sex and age. In the third model, HRs were estimated for patients with complete data for all covariate adjustments: age, sex, BMI, smoking, SBP, antihypertensive treatment, HbA1c, CRP, eGFR, total cholesterol, and previous ischemic stroke or myocardial infarction. In the fourth and final model, to minimize the effect of missing data, we used imputed data to estimate HRs adjusted for the same covariates as in model 3. Subgroup analyses were done for patients without prior ischemic stroke or myocardial infarction at baseline.

Analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, US), and Stata version 15.1 (StataCorp., College station, TX, US). Tests were two-tailed with significance level 0.05.

3.8 STUDY III

3.8.1 STUDY DESIGN, SETTING AND PARTICIPANTS

In this retrospective observational cohort study, we included hypertensive individuals in the Swedish Primary Care Cardiovascular Database without previous diabetes (ICD 10: E10–11, E14), myocardial infarction (ICD 10: I21), or ischemic stroke (ICD 10: I63). We defined diabetes as prescription of antidiabetic medication from primary care in 2001–2008, or a registered diagnosis of diabetes in the primary care medical records or the National Patient Register. The study participants were included in the study on the date of the first registration of a diagnosis of hypertension in primary care 2001–2008.

3.8.2 OUTCOME ASSESSMENT AND FOLLOW UP

The study had three separate outcomes: all-cause mortality, myocardial infarction, and ischemic stroke. Data on mortality was collected from the Cause of Death Register, and data on myocardial infarction and ischemic stroke was collected from the National Patient Register. The study participants were followed-up until the first occurrence of: study outcome, death, or end of study 31 December 2012.

3.8.3 STATISTICAL METHODS

Missing data was handled by using multiple imputation with chained equations (MICE) in 70 datasets. We calculated number of study outcomes using complete cases, and unadjusted outcome rates with 95% CI by Poisson regression using imputed data. The calculations were stratified for educational level, income, and as shown in Figure 7 for time-updated diabetes status. Educational level was categorized in 3 groups based on the highest reported educational level: ≤ 9 years of school, 10-12 years of school, and > 12 years of school. Income was grouped in fifths by quintiles.

We used Cox regression proportional hazard models to investigate the association between study outcomes and educational level, income, and time-updated diabetes status. Age was used as timescale in the analyses, and continuous covariates were modeled using restricted cubic splines with 4–7 knots, with the exception of calendar year which was modeled linear. We determined the number of knots by evaluating model fit according to Akaike information criterion, and we placed the knots at recommended percentiles [185].
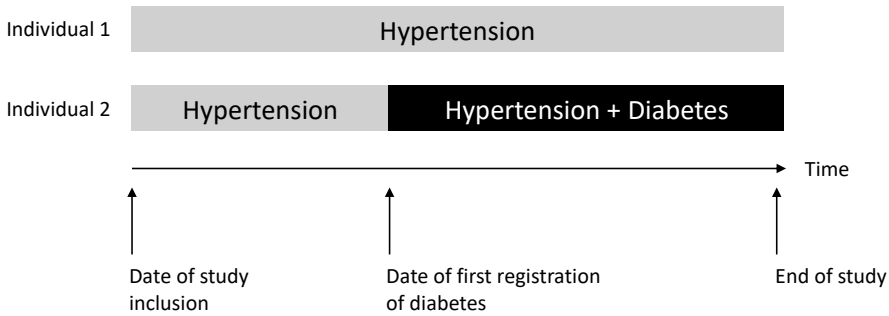
*Figure 7. Both individual 1 and 2 are included in the study at the first date of diagnosis of hypertension in primary care. Individual 1 is followed-up with hypertension. Individual 2 is followed-up with hypertension during the first period and with hypertension **and** diabetes during the second period i.e., with diabetes as a time-updated variable.*

In the first model the hazard ratios were adjusted for sex and calendar year of study inclusion. The second model was also adjusted for educational level and income. The third model was additionally adjusted for country of birth and preexisting conditions at study inclusion (atrial fibrillation [ICD 10: I48], ischemic heart disease [ICD 10: I20–25], congestive heart failure [ICD 10: I50], cerebrovascular disease [ICD 10: I60–69], transient global attack [ICD 10: G45], kidney failure [ICD 10: N18], cancer [ICD 10: C00–97], percutaneous coronary intervention [procedure code: FNG], and coronary artery bypass grafting [procedure codes FNA–FNE]). Country of birth was categorized in 6 groups (Sweden, Finland, Other Nordic countries, European Union except the Nordic countries, Europe except the European Union and the Nordic countries, and outside of Europe). The fourth model was additionally adjusted for SBP, DBP, creatinine, smoking, BMI, total cholesterol, LDL, HDL, and triglycerides.

Analyses and data management was performed using R software version 3.5.1 using the package "forestplot", Stata version 15.1 (StataCorp., College station, TX, US), and SAS version 9.4 (SAS Institute, Cary, NC, US). Tests were two-tailed with significance level 0.05.

3.9 STUDY IV

3.9.1 STUDY DESIGN, SETTING AND PARTICIPANTS

This retrospective observational cohort study included the same cohort of individuals as in study III, previously described in 3.8.1.

3.9.2 OUTCOME ASSESSMENT AND FOLLOW-UP

The primary outcome was all-cause mortality. Secondary outcomes were myocardial infarction, and ischemic stroke. Data on mortality was collected from the Cause of Death Register, and data on myocardial infarction and ischemic stroke was collected from the National Patient Register. The study participants were followed-up until the first occurrence of: study outcome, death, or end of study 31 December 2012.

3.9.3 STATISTICAL METHODS

As in study III, missing data was handled by using multiple imputation with chained equations (MICE) in 70 datasets. We calculated number of study outcomes, and study outcome rates with 95% CI. The calculations were stratified for country of birth and time-updated diabetes status. Country of birth was categorized in 6 subgroups: Sweden, Finland, other Nordic countries, high-income Europe, low-income Europe, and non-European.

We used four Cox regression proportional hazard models to investigate the association between study outcomes, and diabetes status and country of birth categories. As in study III, age was used as timescale in the analyses, and continuous covariates were modeled using restricted cubic splines with 4–7 knots, with the exception of calendar year which was modeled linear. We estimated the associations between diabetes status and study outcomes for each country of birth category in separate models. We also estimated the hazard ratios for each study outcome according to diabetes status and country of birth categories, with being born in Sweden as reference.

The first Cox regression model was adjusted for sex and calendar year of study entry. The second model was additionally adjusted for income and educational level. The third model was additionally adjusted for time-updated diabetes status where appropriate, preexisting conditions at baseline (as in study III), SBP, DBP, and creatinine. The fourth and fully adjusted model was additionally adjusted for smoking status, total cholesterol, LDL, HDL, triglycerides and BMI.

Analyses and data management was performed using Stata version 15.1 (StataCorp., College station, TX, US), and SAS version 9.4 (SAS Institute, Cary, NC, US).

3.10 ETHICAL CONSIDERATIONS

The Skaraborg Diabetes Register was originally approved in 1996 by the Ethics Committee of Sahlgren's University Hospital in Gothenburg (reference 474-96) and the Swedish Data Inspection Board. A new approval was made by the Regional Ethical Review Board in Gothenburg in 2006 (reference 208-06) with subsequent additional approvals (references T564-10, T832-15, T632-16, and T965-16).

The studies from the Swedish Primary Care Cardiovascular Database were approved by the Regional Ethical Review Board in Gothenburg in 2008 and 2015 (references 568-08 and T457-15).

As with all studies, the key ethical consideration is that the benefit must outweigh any potential harm. Potential risks with register-based studies include the possible violation of study participants' privacy and integrity, and the possible misinterpretation of results due to non-valid data. For the studies presented here validated data was used and all study results are presented on aggregated level, no individual data is disclosed, and no individual can be identified directly or indirectly.

In general, in Sweden the need for individual consent is waived in observational register-based research that have been approved by the appropriate ethical committee [189]. The reasoning behind this position include that it would be nearly impossible and very costly to gain informed consent in studies potentially including tens of thousands or even millions of individuals. There would also be risk of selection bias, and retrospective mortality studies would not be possible as consent postmortem is not possible. The patients in study II who had study-specific blood samples drawn, were informed of the study and gave individual consent before entering the study.

4 RESULTS

4.1 STUDY I

In this study we included and followed 7 461 patients with clinically new-onset type 2 diabetes registered in the SDR 1991–2004, and 37 271 matched controls from the general population (see flowchart Figure 8).
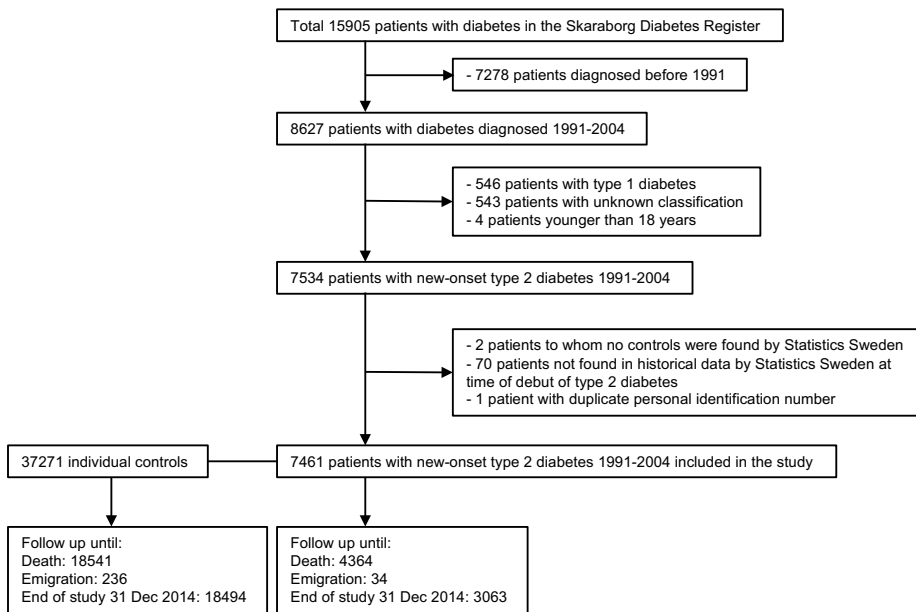
Figure 8. Flowchart of patients and controls included in the study.
(With permission from the Publisher)

Baseline characteristics for patients and controls during the early 1991–1997, and the late 1998–2004 study cohorts are presented in Table 5. Patients in the late cohort were younger at diagnosis, had better glycemic control, lower blood pressure, but were more often smoker, and had higher BMI, as compared to the early cohort.

Table 5. Baseline characteristics study I.

	1991–1997 cohort		1998–2004 cohort		
	Patients (n=4361)	Controls (n=21 785)	Patients (n=3100)	Controls (n=15 486)	p
Age, years	66.0 ± 13.1	66.0 ± 13.1	63.0 ± 13.2	63.0 ± 13.2	<0.0001
Male sex	53.2%	53.1%	53.8%	53.8%	0.57
HbA1c, mmol/mol	58 ± 16		56 ± 17		<0.0001
SBP, mmHg	148.5 ± 21.6		143.8 ± 19.7		<0.0001
DBP, mmHg	82.3 ± 10.4		79.9 ± 10.1		<0.0001
Smoking, yes	17.8%		20.0%		0.023
BMI, kg/m^2	29.1 ± 5.1		30.1 ± 5.4		<0.0001

Numbers are presented as mean ± standard deviation or %. SBP: systolic blood pressure. DBP: diastolic blood pressure. BMI: body mass index. P-values refer to tests of the 1991–1997 versus 1998–2004 patient cohorts. (With permission from the Publisher)

4.1.1 ALL-CAUSE MORTALITY

Patients were followed for a median of 12.7 years, and controls for 13.6 years. During follow-up, 4364 patients (58.5%, [48.2 deaths/1000 person-years]) and 18 541 controls (49.7%, [38.7 deaths/1000 person-years]) died.

The crude mortality rates were higher among patients compared to controls in the 1991–1997 cohort and in the 1998–2004 cohort, with unadjusted mortality incidence rate ratios (IRR) of 1.27 (95% CI 1.22–1.32) and 1.21 (95% CI 1.14–1.29), respectively. The increased relative mortality risk was most pronounced, almost 2-fold, among younger patients < 55 years old at diagnosis, and decreased with increasing age at diagnosis. Among older patients > 75–85 years old at diagnosis, no or just a slightly increased relative mortality risk was seen.

The overall adjusted mortality HR in the total cohort for patients versus controls, estimated by Poisson modeling, was 1.32 (95% CI 1.28–1.37). Higher mortality HR was seen among women (HR 1.37, 95% CI 1.31–1.44) compared to men (HR 1.28, 95% CI 1.23–1.34), p for interaction = 0.041. The adjusted mortality HR for patients versus controls declined with increasing calendar year at diagnosis. For patients diagnosed with new-onset type 2 diabetes in 1991, the mortality HR was 1.47 (95% CI 1.39–1.57), and thereafter dropped by 2% per calendar year at diagnosis until 2004.

The mortality HR, modelled by Poisson regression, varied with follow-up time and according to calendar year at diagnosis, as illustrated in Figure 9 for calendar years 1992, 1998, and 2004. The mortality HR early after diagnosis was increased 2-4-fold for patients diagnosed in 1992, then declined and inverted, showing 40-70% lower mortality risk in patients diagnosed 2004, as compared to controls
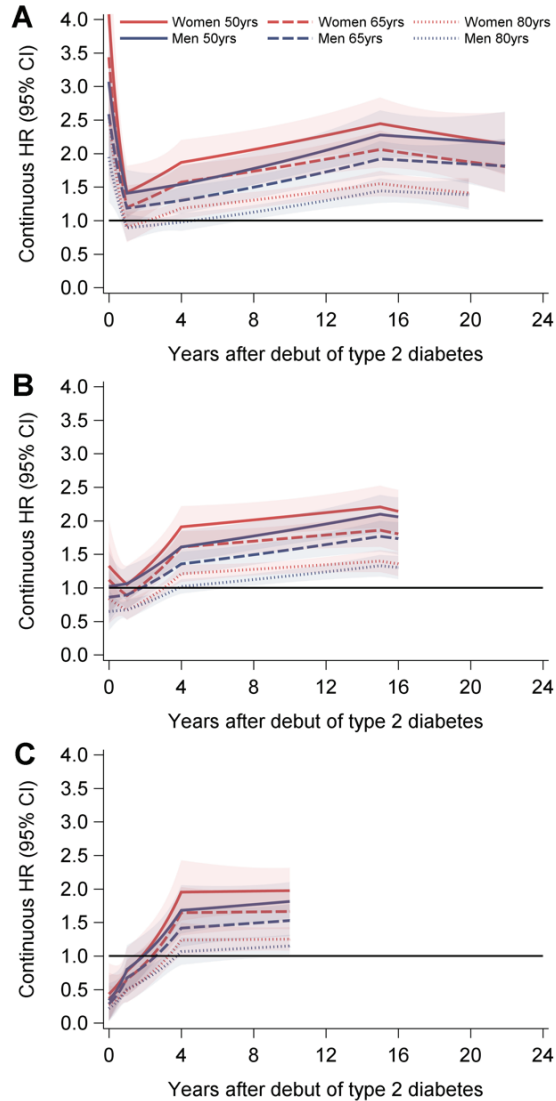
Figure 9. Continuous mortality HR, compared to population controls, for women and men aged 50, 65, and 80 years old at diagnosis of new-onset type 2 diabetes in 1992 (A), 1998 (B), and 2004 (C). (With permission from the Publisher)

4.1.2 CAUSE SPECIFIC MORTALITY

Cumulative mortality incidences per cause of death subcategory are plotted in Figure 10. Cardiovascular disease (ICD 9: 390–459, ICD 10: I) was the most common cause of death among patients in men (1127 deaths) and women (1066 deaths). The IRR for cardiovascular cause of death was 1.22 (95% CI 1.14–1.30) in men and 1.29 (95% CI 1.21–1.38) in women. The second most common cause of death was tumors (ICD 9: 140–239, ICD 10: C00-D48) with IRR 1.15 (95% CI 1.02–1.28) in women, and a non-significant increased IRR in men (1.08, 95% CI 0.98–1.19). Neither sex showed a significantly increased IRR regarding tumors after Bonferroni correction or after taking competing risks into account. The third most common cause of death was endocrine, nutritional and metabolic disease (ICD 9: 240–278, ICD 10: E) with IRR 5.29 (95% CI 4.35–6.43) in men, and 5.19 (95% CI 4.23–6.38) in women.

Figure 10. Stacked cumulative mortality incidences per cause of death subcategory, estimated by competing risk regression modeling. The Kaplan-Meier curve on top is depicting all-cause mortality. (With permission from the Publisher)

4.2 STUDY II

In total, 398 individuals with type 2 diabetes clinically diagnosed at age < 65 years were included and followed in the study (see flowchart Figure 11). Of the individuals included, 386 had no previous history of myocardial infarction or ischemic stroke.

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┌─────────────────────────────────────────────────────────────────────┐
│ 15 905 individuals registered in the Skaraborg Diabetes Register 1991-2004 │
└─────────────────────────────────────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────┐
│ 459 individuals < 65 years old with new-onset type 2 diabetes 1996-1998 │
└─────────────────────────────────────────────────────────────────────┘

                    ┌──────────────────────────────────────────────┐
                    │ - 61 individuals without analyzed C-peptide   │
                    └──────────────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────┐
│ 398 individuals with analyzed C-peptide: main analysis               │
│  • 266 individuals with complete data: Cox regression model 3        │
│  • 398 individuals, 132 with missing data: Cox regression imputed data model 4 │
└─────────────────────────────────────────────────────────────────────┘

                    ┌──────────────────────────────────────────────┐
                    │ - 12 individuals with myocardial infarction or │
                    │ ischemic stroke prior debut of type 2 diabetes │
                    └──────────────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────┐
│ 386 individuals without previous myocardial infarction or ischemic stroke: subgroup analysis │
│  • 258 individuals with complete data: Cox regression model 3        │
│  • 386 individuals, 128 with missing data: Cox regression imputed data model 4 │
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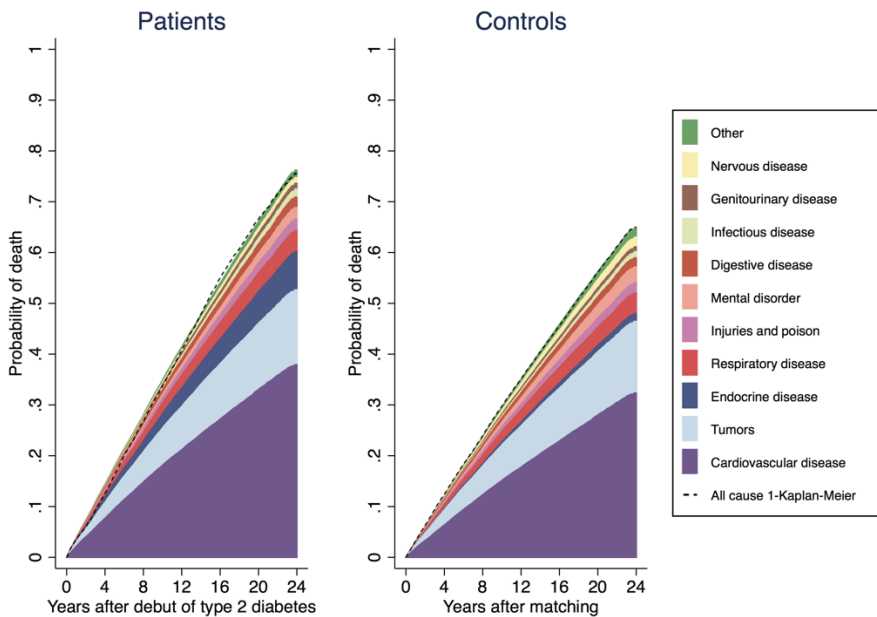
Figure 11. Flowchart of individuals included in the study for main and subgroup analyses. (With permission from the Publisher)

Baseline characteristics of the included individuals are presented in Table 6. Mean age at diagnosis was 52.4 years and almost 60% were men. C-peptide concentration measured at diagnosis or soon thereafter ranged between 0.1 and 4, with median value 0.88.

The median follow-up in the study was 17.0 years. The number of study outcomes, and outcome incidences are presented in Table 7. In total, 104 individuals died during follow up, 51 had a myocardial infarction, and 40 had an ischemic stroke. Similar outcome incidences were seen in the subgroup of individuals without previous myocardial infarction or ischemic stroke (data not shown).

Table 6. Baseline characteristics of study II.

Number of individuals	398
Male sex	238 (59.8%)
Age at diagnosis, years	52.4 ± 8.7
Current smoking, yes	102 (25.6%)
Body mass index, kg/m^2	31.3 ± 5.6
Systolic blood pressure, mmHg	140.6 ± 19.7
Diastolic blood pressure, mmHg	83.1 ± 9.7
Antihypertensive treatment	119 (29.9%)
HbA1c, IFCC mmol/mol	61.6 ± 19.1
C-peptide[1], nmol/l	0.88 (0.62–1.16)
Minimum	0.1
Maximum	4.0
eGFR, ml/min/1.73 m^2	103.9 ± 38.2
C-reactive protein[1], mg/l	3.4 (1.7–6.6)
Total cholesterol, mmol/l	5.8 ± 1.4
Previous myocardial infarction or ischemic stroke	12 (3%)

Numbers are expressed as mean ± standard deviation, or frequencies (%) if not otherwise specified. HbA1c: hemoglobin A1c. IFCC: International federation of clinical chemistry. eGFR: estimated glomerular filtration rate.
[1] median (interquartile range).
(With permission from the Publisher)

Table 7. Study outcomes and outcome incidence rates per 1000 person-years.

	Number of events	Incidence rate	95% CI
All-cause death	104	16.9	14.0–20.5
Cardiovascular underlying death	35	5.7	4.1–7.9
Cardiovascular contributing death	58	9.5	7.3–12.2
Cancer death	32	5.2	3.7–7.4
Cancer contributing death	36	5.9	4.2–8.1
Non-cardiovascular non-cancer death	37	6.0	4.4–8.3
Myocardial infarction	51	8.7	6.6–11.4
Ischemic stroke	40	6.8	5.0–9.2
Cardiovascular death, myocardial infarction, or ischemic stroke	90	14.8	12.0–18.1

CI: confidence interval. (With permission from the Publisher)

The association between C-peptide concentration at diagnosis of type 2 diabetes or soon thereafter, and the study outcomes are presented as adjusted hazard ratios in Table 8. In the fully adjusted imputed model 4 including all individuals, an increase of 1 ng/l of C-peptide concentration was associated with increased risk of the primary study outcome all-cause death (HR 2.20, 95% CI 1.49–3.25). There were also positive associations between increased C-peptide concentration and the secondary study outcomes: underlying (HR 2.69, 95% CI 1.49–4.85) and contributing (HR 2.31, 95% CI 1.43–3.72) cardiovascular cause of death, and the composite outcome of cardiovascular death, myocardial infarction, or ischemic stroke (HR 1.61, 95% CI 1.06–2.45). Similar associations were seen in the complete cases model 3, and in the crude, and sex and age adjusted models (data not shown).

Table 8. Association between 1 ng/l increase of C-peptide concentration and study outcomes.

	Model 3: Fully adjusted, complete cases (n=266)			Model 4: Fully adjusted, imputed cases (n=398)		
	HR	95% CI	p	HR	95% CI	p
All-cause death	2.90	1.81–4.66	<0.001	2.20	1.49–3.25	<0.001
CV underlying death	4.26	2.00–9.04	<0.001	2.69	1.49–4.85	0.001
CV contributing death	3.30	1.76–6.21	<0.001	2.31	1.43–3.72	0.001
Cancer underlying death	2.19	0.76–6.27	0.14	1.90	0.88–4.12	0.10
Cancer contributing death	2.45	0.93–6.48	0.071	1.98	0.95–4.13	0.069
Non-CV non-cancer death	3.32	1.30–8.48	0.012	1.94	0.92–4.08	0.081
Myocardial infarction	1.27	0.62–2.62	0.51	1.47	0.84–2.58	0.17
Ischemic stroke	1.36	0.60–3.06	0.46	1.22	0.62–2.39	0.56
CV death, myocardial infarction, or ischemic stroke	1.96	1.23–3.12	0.005	1.61	1.06–2.45	0.027

HR: hazard ratio. CI: confidence interval. CV: cardiovascular. The hazard ratios are adjusted for age, sex, smoking, systolic blood pressure, hemoglobin A1c, antihypertensive treatment, body mass index, c-reactive protein, estimated glomerular filtration rate, total cholesterol, and previous myocardial infarction or ischemic stroke.
(With permission from the Publisher)

4.3 STUDY III

In total, 62 557 individuals were included in the study (see flowchart Figure 12). The mean age at study entry was 65.0 ± 12.6 years, 42% of the individuals were men, and 16% were diagnosed with diabetes during follow-up.

Individuals diagnosed with diabetes during follow-up were more frequently men (48.7 vs 41.0%), had higher BMI (30.2 vs 28.2 kg/m^2), lower educational level (46.6 vs 38.2% with ≤ 9 years of school), lower income (16.2 vs 21.3% with income in the highest fifth), and were more often born outside of Europe (6.6 vs 4.2%), as compared to individuals without diabetes.

Individuals in the highest income group were younger (56.5 vs 70.4 years), had lower systolic blood pressure (154.1 vs 161.3 mmHg), less cardiovascular comorbidities (8.2 vs 15.7%), and were more frequently born in Sweden (86.9 vs 71.5%), as compared to those with the lowest income.

A similar pattern was seen for individuals with the highest versus lowest educational level regarding age, systolic blood pressure and cardiovascular comorbidities. However, the proportion of individuals born in Sweden was comparable (80.2 vs 81.2%), and the proportion born outside of Europe was higher (7.4 vs 4.0%).
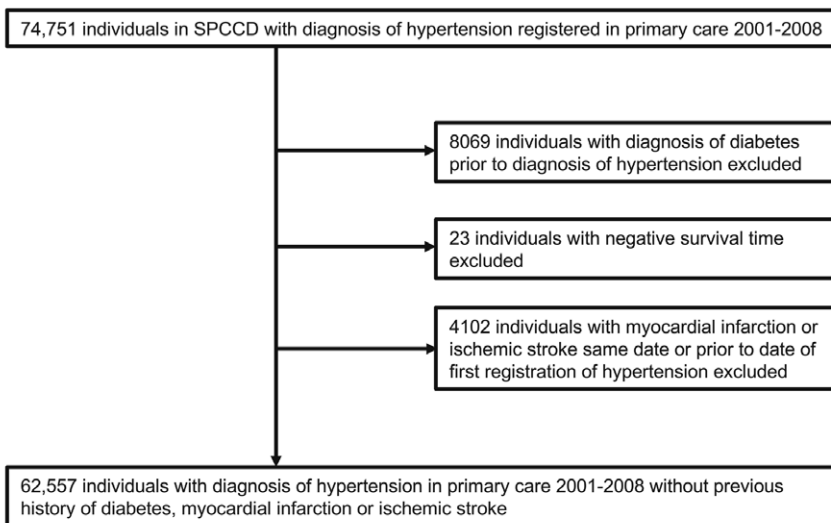

Figure 12. Flowchart of individuals included in the study. Negative survival times could be due to erroneous or reused personal identification numbers.

4.3.1 UNADJUSTED OUTCOMES

The median follow-up was 8.2 years regarding all-cause mortality, and 7.9 years regarding myocardial infarction and ischemic stroke. In total 13 231 deaths, 4321 myocardial infarctions and 4433 ischemic strokes occurred during follow up. Unadjusted event rates stratified for diabetes status, educational level and income are presented in Table 9. In general, the event rates were higher with diabetes versus without diabetes, and higher for individuals with low versus high educational level and income.

Table 9. Unadjusted study outcome rates per 1000 person-years.

	All-cause mortality		Myocardial infarction		Ischemic stroke	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Diabetes status						
No diabetes	24.4	23.9–24.9	8.3	8.0–8.6	8.8	8.5–9.0
Diabetes	41.0	39.5–42.6	13.2	12.3–14.1	12.1	11.2–12.9
Educational level						
No diabetes						
> 12 years	11.6	10.7–12.6	5.3	4.8–5.9	4.9	4.4–5.4
10–12 years	18.9	18.1–19.7	7.1	6.7–7.6	7.5	7.1–7.9
≤ 9 years	35.6	34.6–36.6	10.8	10.3–11.4	11.8	11.3–12.4
Diabetes						
> 12 years	22.9	19.3–27.2	8.4	6.5–10.9	8.9	6.8–11.5
10–12 years	33.1	30.5–36.1	10.4	9.0–11.9	10.7	9.4–12.3
≤ 9 years	51.5	48.8–54.3	16.6	15.1–18.2	13.8	12.5–15.3
Income						
No diabetes						
Highest fifth	6.7	6.1–7.3	4.5	4.1–5.0	3.8	3.4–4.2
Lowest fifth	49.5	47.9–51.1	12.5	11.7–13.3	14.0	13.2–14.9
Diabetes						
Highest fifth	15.6	13.2–18.3	7.4	5.8–9.3	5.3	4.0–7.0
Lowest fifth	66.5	62.3–70.9	18.1	16.0–20.6	17.8	15.7–20.2

CI: confidence interval.

4.3.2 ADJUSTED OUTCOMES

Adjusted hazard ratios of mortality, myocardial infarction, and ischemic stroke according to diabetes status, educational level, and income are presented in the forest plots in Figure 13–15.

Mortality

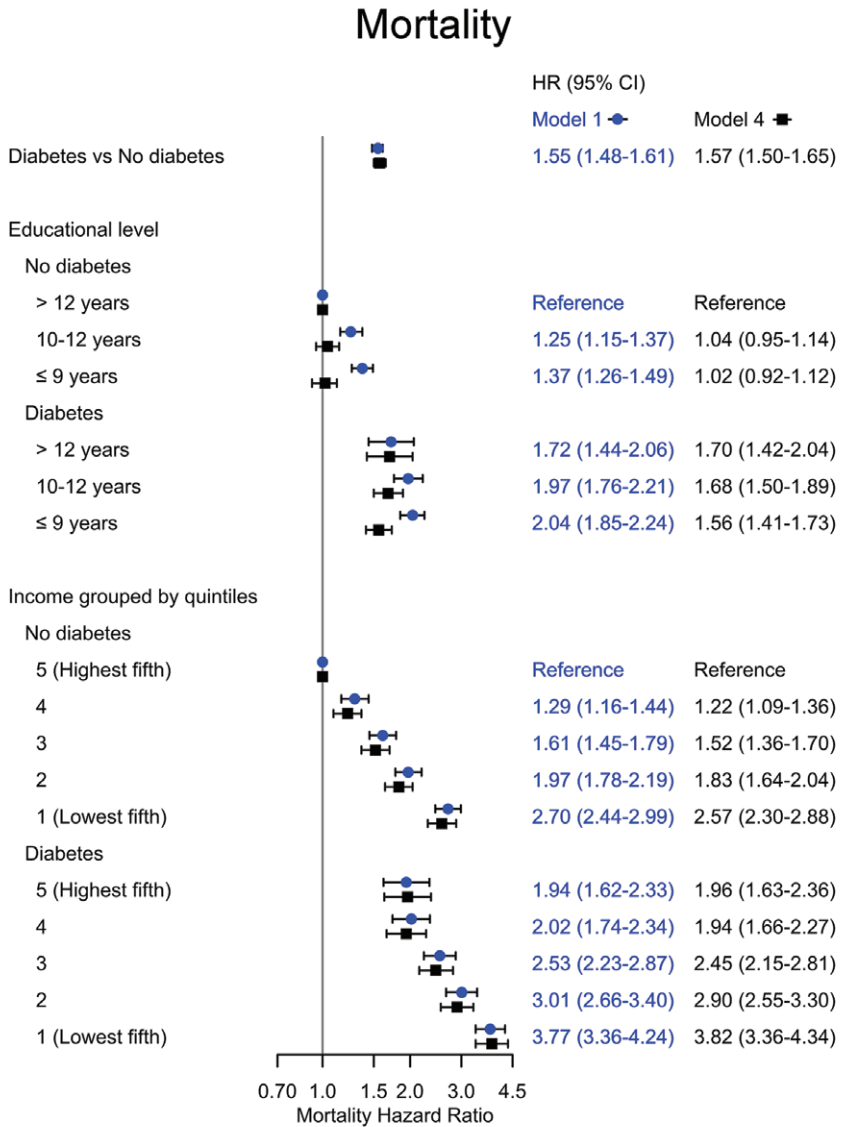|	HR (95% CI)	
	Model 1	Model 4
Diabetes vs No diabetes	1.55 (1.48-1.61)	1.57 (1.50-1.65)
Educational level		
No diabetes		
> 12 years	Reference	Reference
10-12 years	1.25 (1.15-1.37)	1.04 (0.95-1.14)
≤ 9 years	1.37 (1.26-1.49)	1.02 (0.92-1.12)
Diabetes		
> 12 years	1.72 (1.44-2.06)	1.70 (1.42-2.04)
10-12 years	1.97 (1.76-2.21)	1.68 (1.50-1.89)
≤ 9 years	2.04 (1.85-2.24)	1.56 (1.41-1.73)
Income grouped by quintiles		
No diabetes		
5 (Highest fifth)	Reference	Reference
4	1.29 (1.16-1.44)	1.22 (1.09-1.36)
3	1.61 (1.45-1.79)	1.52 (1.36-1.70)
2	1.97 (1.78-2.19)	1.83 (1.64-2.04)
1 (Lowest fifth)	2.70 (2.44-2.99)	2.57 (2.30-2.88)
Diabetes		
5 (Highest fifth)	1.94 (1.62-2.33)	1.96 (1.63-2.36)
4	2.02 (1.74-2.34)	1.94 (1.66-2.27)
3	2.53 (2.23-2.87)	2.45 (2.15-2.81)
2	3.01 (2.66-3.40)	2.90 (2.55-3.30)
1 (Lowest fifth)	3.77 (3.36-4.24)	3.82 (3.36-4.34)

0.70 1.0 1.5 2.0 3.0 4.5
Mortality Hazard Ratio

Figure 13. Forest plot showing hazard ratios (HR) with 95% confidence intervals (CI) regarding the association between mortality risk and diabetes status, educational level and income. Model 1 was adjusted for sex, age, and calendar year of study entry. The full model 4 was additionally adjusted for educational level, income, country of birth, pre-existing conditions at baseline, systolic and diastolic blood pressure, creatinine, smoking, body mass index, cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides.
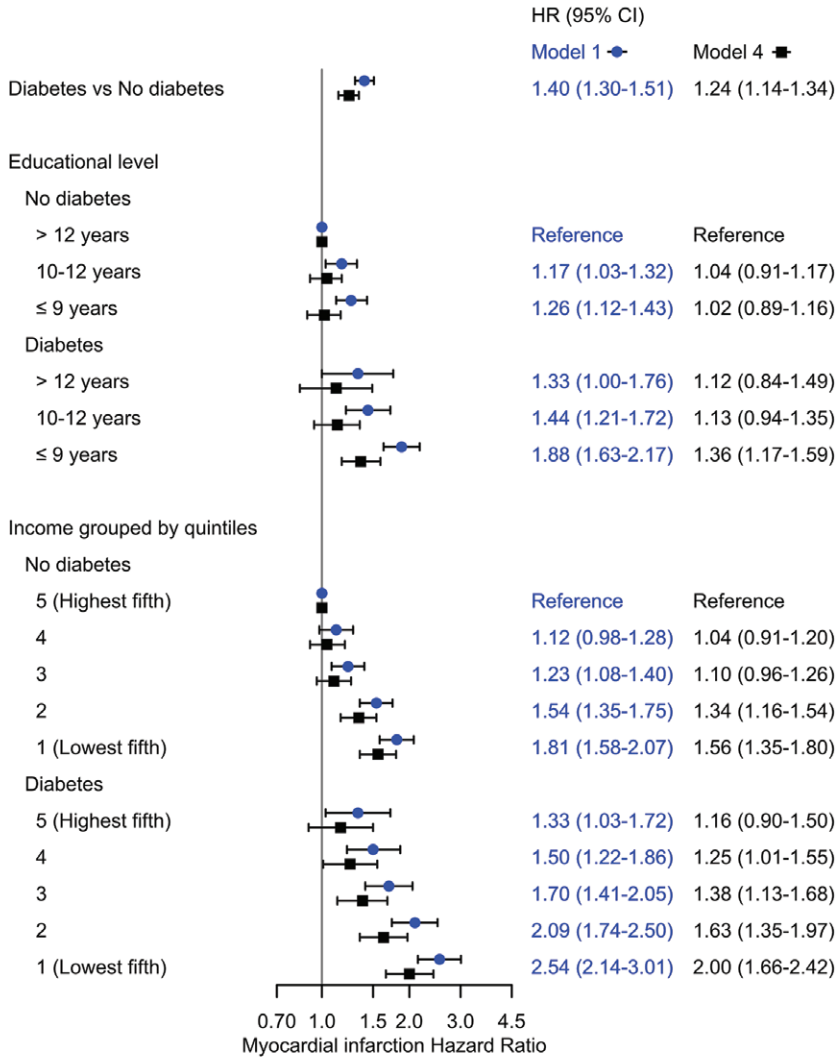
Myocardial infarction

Figure 14. Forest plot showing hazard ratios (HR) with 95% confidence intervals (CI) regarding the association between risk of myocardial infarction and diabetes status, educational level and income. Model 1 was adjusted for sex, age, and calendar year of study entry. The full model 4 was additionally adjusted for educational level, income, country of birth, pre-existing conditions at baseline, systolic and diastolic blood pressure, creatinine, smoking, body mass index, cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides.
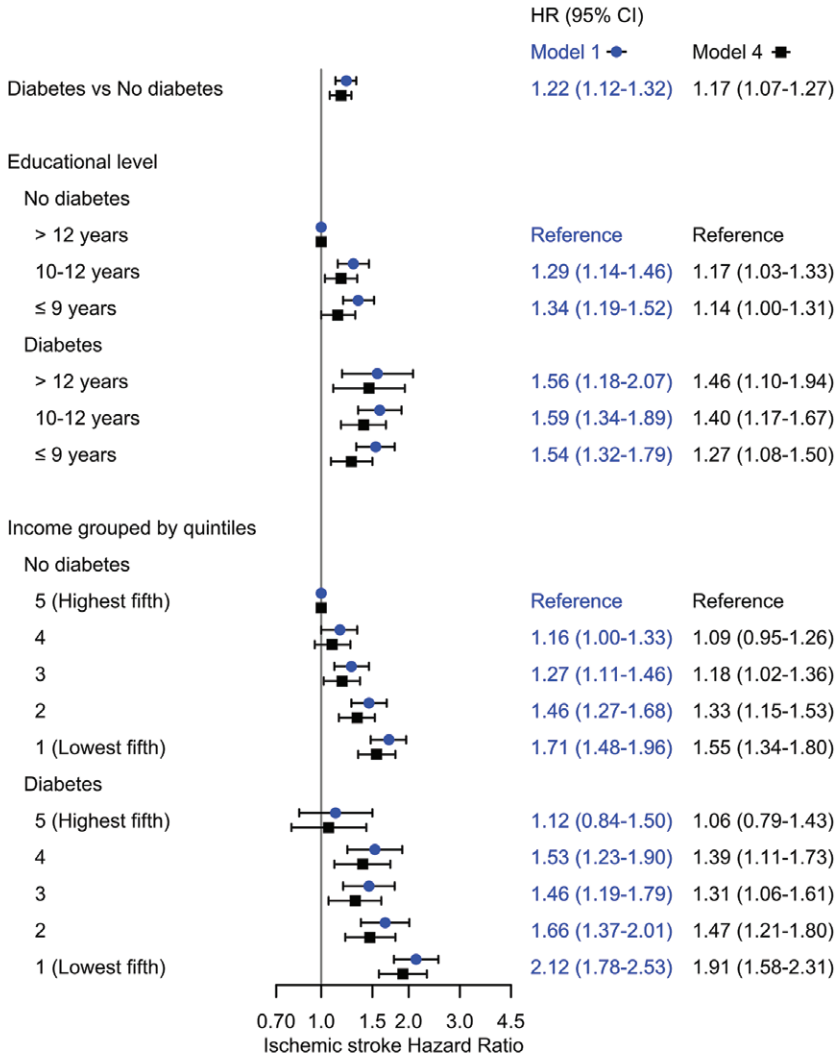
Figure 15. Forest plot showing hazard ratios (HR) with 95% confidence intervals (CI) regarding the association between risk of ischemic stroke and diabetes status, educational level and income. Model 1 was adjusted for sex, age, and calendar year of study entry. The full model 4 was additionally adjusted for educational level, income, country of birth, pre-existing conditions at baseline, systolic and diastolic blood pressure, creatinine, smoking, body mass index, cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides.

In the fully adjusted model 4, adding diabetes to hypertension was associated with elevated risk of mortality (HR 1.57, 95% CI 1.50–1.65), myocardial infarction (HR 1.24, 95% CI 1.14–1.34), and ischemic stroke (HR 1.17, 95% CI 1.07–1.27).

Low versus high educational level was associated with elevated risk of mortality and myocardial infarction in model 1 which was only adjusted for sex, age, and calendar year of study entry. For ischemic stroke, an increased risk was only seen for individuals without diabetes. After adjusting for income and other possible confounders in model 4, weaker or no associations were seen between low educational level and increased risk of study outcomes.

Low versus high income was strongly associated with increased risk of mortality, myocardial infarction, and ischemic stroke for individuals both without and with diabetes in all models. In model 4, using the combination of income in the highest fifth and no diabetes as reference, the mortality HR for income in the lowest fifth was 2.57 (95% CI 2.30–2.88) without diabetes, and 3.82 (95% CI 3.36–4.34) with diabetes. For myocardial infarction the corresponding HRs were 1.56 (95% CI 1.35–1.80), and 2.00 (95% CI 1.66–2.42), respectively. Regarding ischemic stroke, the corresponding HRs were 1.55 (95% CI 1.34–1.80), and 1.91 (95% CI 1.58– 2.31), respectively.

4.4 STUDY IV

As in study III, 62 557 individuals were included in the study (see flowchart Figure 12). The majority were born in Sweden (81%). The two largest immigrant groups were born in Finland (6.9%) and in a non-European country (4.6%). The country of birth subgroups were heterogenous. Non-Europeans were younger, had higher educational level but lower income, and less comorbidities, as compared to individuals born in Sweden.

4.4.1 UNADJUSTED OUTCOMES

The median follow-up was 8.2 years regarding mortality, and 7.9 years regarding myocardial infarction and ischemic stroke. In total 13 231 deaths, 4321 myocardial infarctions and 4433 ischemic strokes occurred during follow up. Diabetes was recorded among 15.2% of Swedish-born and among 22.7% of those born outside of Europe. The unadjusted outcome rates differed among the country of birth categories. For example, the mortality rate among Swedish born was 28.5 deaths/1000 person-years (95% CI 28.0–29.1), whereas the mortality rate was 11.7 deaths/1000 person-years (95% CI 10.4–13.2) among those born outside of Europe. In general, the outcome rates were higher during follow up with diabetes than without diabetes.

4.4.2 OUTCOMES WHEN ADDING DIABETES

In the fully adjusted model 4 (Table 10), increased mortality risk was seen in all country of birth categories when adding diabetes to hypertension. For myocardial infarction and ischemic stroke, a significantly increased risk was only seen in Swedish born.

Table 10. Cox regression models of fully adjusted study outcome hazard ratios when adding diabetes to hypertension.

	Mortality		MI		Ischemic stroke	
	HR	95% CI	HR	95% CI	HR	95% CI
Country of birth						
Sweden	1.59	1.51–1.68	1.25	1.14–1.37	1.16	1.06–1.28
Finland	1.49	1.21–1.83	1.20	0.86–1.67	1.26	0.89–1.78
Other Nordic countries	1.73	1.06–2.82	1.73	0.66–4.53	1.41	0.58–3.42
High-income Europe	1.50	1.13–1.99	1.31	0.87–1.98	0.97	0.62–1.52
Low-income Europe	1.61	1.14–2.30	1.35	0.80–2.29	0.94	0.52–1.70
Non-European	1.46	1.07–1.98	0.99	0.64–1.52	1.23	0.79–1.90

MI: myocardial infarction. HR: hazard ratio. CI: confidence interval.
(Modified with permission from the Publisher)

4.4.3 OUTCOMES IN FOREIGN BORN VERSUS SWEDISH BORN

Mortality HR for foreign born versus Swedish born are presented in Table 11.

Table 11. Cox regression models of adjusted mortality hazard ratios for foreign born versus Swedish born.

	Model 1		Model 4	
	HR	95% CI	HR	95% CI
Total cohort				
Country of birth				
Sweden	Reference		Reference	
Finland	1.28	1.18 – 1.38	1.21	1.11–1.31
Other Nordic countries	1.10	0.95–1.27	1.03	0.88–1.20
High-income Europe	0.88	0.79–0.97	0.82	0.74–0.92
Low-income Europe	1.14	0.99–1.30	0.80	0.70–0.92
Non-European	0.92	0.81–1.04	0.62	0.55–0.71
Follow-up time without diabetes				
Country of birth				
Sweden	Reference		Reference	
Finland	1.31	1.20–1.43	1.26	1.15–1.38
Other Nordic countries	1.09	0.92–1.28	1.01	0.86–1.20
High-income Europe	0.86	0.77–0.97	0.84	0.74–0.95
Low-income Europe	1.13	0.96–1.33	0.84	0.71–1.00
Non-European	0.89	0.76–1.03	0.65	0.56–0.76
Follow-up time with diabetes				
Country of birth				
Sweden	Reference		Reference	
Finland	1.10	0.93–1.30	1.05	0.88–1.26
Other Nordic countries	1.19	0.84–1.68	1.14	0.80–1.63
High-income Europe	0.87	0.70–1.07	0.78	0.63–0.98
Low-income Europe	0.97	0.75–1.25	0.74	0.57–0.96
Non-European	0.80	0.64–1.00	0.56	0.44–0.71

HR: hazard ratio. CI: confidence interval.
Age was used as time scale in both models. Model 1 was adjusted for sex and calendar year of study entry. Model 4 was additionally adjusted for educational level, income, comorbidities at baseline, creatinine, systolic and diastolic blood pressure, smoking, total cholesterol, low- and high-density lipoprotein, triglycerides and body mass index.
(Modified with permission from the Publisher)

In the fully adjusted model 4, increased mortality risk was seen in Finnish born during total follow-up and during follow-up without diabetes. Further, decreased mortality risk was most noticeable seen for non-European country of birth, and also for country of birth in low- and high-income Europe.

The risk of myocardial infarction was increased for Finnish born in all models during total follow-up (model 4: HR 1.17, 95% CI 1.03–1.33) and during follow-up without diabetes (model 4: HR 1.16, 95% CI 1.01–1.34). The results for ischemic stroke were non-conclusive.

5 DISCUSSION

The aim of this thesis was to study different epidemiological aspects regarding risk of mortality and cardiovascular complications among individuals with diabetes, hypertension, and hypertension with concomitant diabetes in primary care. Study I-II of this thesis used data from the Skaraborgs Diabetes Register, and study III-IV used data from the Swedish Primary Care Cardiovascular Database. Mortality and cardiovascular complications were assessed by high quality national registers – the Cause of Death Register and the National Patient Register.

The main findings of Study I were that excess mortality decreased over time and was driven by cardiovascular- and endocrine disease in patients in former Skaraborg County with type 2 diabetes clinically diagnosed between 1991 and 2004. In Study II, elevated level of the biomarker C-peptide was associated with increased risk of all-cause and cardiovascular mortality in patients < 65 years old at clinical diagnosis of type 2 diabetes between 1996 and 1998. In Study III, coexisting diabetes in patients in primary care with registered diagnosis of hypertension between 2001 and 2008 was associated with increased risk of mortality, myocardial infarction, and ischemic stroke. Low income in combination with hypertension and diabetes, as compared to high income in combination with hypertension without diabetes was associated with near 4-fold increased risk of mortality and 2-fold risk of myocardial infarction and stroke. In Study IV, non-European country of birth was associated with decreased mortality risk in hypertensive patients with and without diabetes, as compared to being born in Sweden. In contrast, being born in Finland was associated with increased mortality risk in hypertensive patients without diabetes.

5.1 GENERAL STRENGTHS AND LIMITATIONS

The studies in this thesis share some common strengths and limitations. In the early 1990s, the Skaraborg Diabetes Register prospectively registered 88% of the patients with diabetes in Skaraborg County. This high capture rate limits the risk of selection bias among the patients with clinically new-onset type 2 diabetes included in Study I–II, and increases the chance that patients included in the study are representative of patients met in everyday practice. Further, including only patients with new-onset type 2 diabetes, and not prevalent cases limits the risk of survival bias. Study III–IV from the Swedish Primary Care Cardiovascular Database include a large number of patients with hypertension in a mixed urban and rural primary care setting. This broad inclusion limits the

risk of patient selection bias that could arise in a secondary or tertiary care setting. Also, data from routine medical records were used reflecting the conditions in everyday clinical practice. By combining register-based data on comorbidity and socioeconomic status with individual clinical data derived from medical records it has been possible to adjust the study outcomes for many potential confounders. The study outcomes in all four studies were assessed by high-quality national registers using the unique personal identifier number. In particular, mortality data has very high validity and virtually complete coverage.

A general limitation of all four studies is the observational design. This design allows us to study associations between exposures and outcomes, but we cannot prove causality i.e., that the outcome is a direct effect of the exposure. Although the study outcomes have been adjusted for a variety of potential confounders, residual confounding is still possible. Further, the results could differ in other study settings e.g., in other countries with different health care systems or ethnic mixes. The results in Study I–II from the SDR are from a Swedish rural setting with patients mainly of European descent and might not be representative for Swedish urban populations with more diverse ethnic backgrounds. As is common in observational studies using real-world clinical data, missing data is present in Study II-IV. To reduce the loss of statistical power, and more importantly to reduce the risk of bias, the method of multiple imputation by chained equations was used to handle missing data.

5.2   MORTALITY IN TYPE 2 DIABETES

Study I explored mortality trends during 24 years in patients prospectively registered in the Skaraborg Diabetes Register with clinically new-onset type 2 diabetes debuted between 1991 and 2004. The excess mortality was 47% for patients with debut of type 2 diabetes in 1991, as compared to age- and sex matched individuals from the background population in Skaraborg. For each year between 1991 and 2004 the mortality risk decreased by 4% among patients and 2% among controls, leading to a net decrease in excess mortality by 2% per year. The most common cause of death was cardiovascular disease followed by cancer and endocrine disease. The excess mortality was mainly driven by 25% excess cardiovascular mortality and roughly five-fold risk of mortality due to endocrine diseases of which diabetes constituted over 85%. Patients < 55 years at debut of type 2 diabetes had around 2-fold increased mortality risk compared to controls and in the oldest patients no, or only small excess mortality was seen.

The results in Study I is mainly in line with findings from previous studies. The study adds knowledge about relatively low excess mortality in patients with prospectively registered clinically new-onset type 2 diabetes in 1991–2004 – a time period in which the coverage in the NDR was still low.

One specific strength of the study is the use of individual controls from the general population in Skaraborg instead of aggregated population statistics. Another strength is the methodologic approach which permits visualization of continuous HR during follow-up. One specific limitation includes the possibility that individuals with type 2 diabetes could have been selected as controls if they were not captured in the SDR.

5.2.1 MORTALITY TRENDS

The 32% overall excess mortality during follow up in Study I is low compared to some previous studies. Approximately doubled excess mortality was seen in another Swedish study including patients 1980–2004 [190], and 2–4-fold excess mortality was seen in a Danish national study including patients 1995–2006 [191]. In Finland, 68% excess mortality was seen in a study including patients on antidiabetic drug treatment in 2010–2017 [192]. In this study excess mortality decreased over time, in particular for coronary heart disease mortality and stroke mortality where excess mortality vanished during the later study period. However, the above-mentioned studies included patients with prevalent as well as incident type 1 and type 2 diabetes.

Results on excess mortality in type 2 diabetes are heterogenous. A systematic review and meta-analysis of studies in Latin America on the risk of all-cause mortality in patients with type 2 diabetes as compared to controls reported a relative risk of 2.49 [193]. In an Iranian 18-year follow up of patients 1992–2010, type 2 diabetes conferred 1.04 to 4.13 times higher mortality risk depending on age and sex, as compared to the general population [194]. In Denmark, a 16-year follow-up study of patients with newly diagnosed type 2 diabetes 1989–1992 revealed 1.5–2.5 fold higher mortality risk compared to the general population [195]. Lower excess mortality comparable to the findings in Study I was seen in a Lithuanian study showing 35% excess mortality in patients with prevalent type 2 diabetes 2010–2017 [196]. Similar findings in patients with new-onset type 2 diabetes 1993–2004 have been reported in an observational study from Scotland [72]. Also, in a Swedish nationwide observational study from the NDR including patients 1998–2011, the excess mortality was 27% adjusted for age and sex, and 15% after additional adjustments with a slight decrease in excess mortality over time [70]. Decreasing excess mortality in patients with diabetes has also been

reported from Canada and the United Kingdom [65], Denmark [191], the United States [64], and Australia [69]. In contrast, excess mortality in type 2 diabetes remained constant over time in another Scottish observational study including patients 2004–2013, with 38% excess mortality in men and 49% in women after adjusting for age and socioeconomic group [197]. Although most Western studies have reported declining mortality rates in patients with diabetes as well as in the general population, a Hungarian study reported slow or no decrease in mortality rates in patients with type 2 diabetes resulting in increasing excess mortality over time, especially in younger patients [198].

5.2.2 MECHANISMS OF DECREASED EXCESS MORTALITY

There are several potential mechanisms behind the closing mortality gap seen in Study I. First, a temporal trend is noted with falling early excess mortality as the calendar year of diagnosis increases. A possible explanation of this phenomena could be that patients during the early 1990s were diagnosed with type 2 diabetes in conjunction with the presentation of a serious diabetic complication that later led to death. Second, lower excess mortality could be due to selection of individuals with lower cardiovascular risk following the WHO lowering of the diagnostic cut off for diabetes in 1999 [12]. Third, the study includes patients with *clinically* new-onset type 2 diabetes. Bearing in mind that patients are likely to have been living with undiagnosed diabetes for several years before detection, it is conceivable that less delay and better prognosis during the latter study period following more extensive opportunistic screening of diabetes [199] plays a role. Fourth, decreasing excess mortality could be due to improved medical treatment of type 2 diabetes during the study period. Intensified blood glucose control with metformin was introduced as first-line treatment during the study period following the United Kingdom Prospective Diabetes Study (UKPDS) in 1998 where 39% decreased risk of myocardial infarction and 36% decreased risk of all-cause mortality was found in overweight patients [200]. Treatment with metformin was further emphasized after a 10-year UKPDS post-trial follow-up in 2008 where between-group differences in HbA1c levels were lost, but 33% reduced risk of myocardial infarction and 27% reduced risk of all-cause mortality persisted [201]. Also, beneficial effects of tight BP control in type 2 diabetes were reported from the UKPDS in 1998 [202]. This study aimed to compare tight BP control (< 150/85 mm Hg) versus less tight BP control (< 180/105 mm Hg). During follow-up the mean BP levels were 144/82 mm Hg and 154/87 mm Hg, respectively, resulting in 32% reduced risk of deaths related to diabetes as well as reduced risk of stroke and microvascular complications. Further, beneficial effects of lipid lowering treatment with simvastatin on mortality and

cardiovascular events in patients with coronary heart disease was reported in 1994 in the Scandinavian Simvastatin Survival Study [203]. Beneficial effects on cardiovascular events were also seen later in a post-hoc subgroup analysis of patients with diabetes [204]. Substantial beneficial effects of intensive multifactorial intervention of hyperglycemia, hypertension and dyslipidemia in patients with type 2 diabetes and microalbuminuria were reported in the Danish Steno-2 randomized study which allocated 80 patients to standard treatment and 80 patients to intensive treatment. Reduced risk of microvascular complications in the intensive treatment group were reported in 1999 [205]. In addition, 53% reduced risk of cardiovascular disease was reported in 2003 [206], and 46% reduced risk of mortality was reported in 2008 [207].

5.2.3   CAUSES OF DEATH

In Study I, cardiovascular disease was the most common cause of death constituting approximately 50% of all deaths in both patients with type 2 diabetes and controls. The second most common cause of death was tumours, representing 20% of all deaths in patients and 22% in controls. The third most common cause of death in patients was endocrine diseases (9.2%), and in controls respiratory diseases (6.5%). This hierarchy of causes of deaths in diabetes is in line with US data from 1998–2015 [208] and with data from Australia 1997–2010 [69]. Temporal shifts in causes of death were seen in these studies, with declining cardiovascular and diabetes related mortality in both absolute and relative terms, whereas cancer related mortality increased in Australia and remained fairly stable in the US. A similar shift was also reported in a Swedish nationwide study from the NDR regarding causes of death 1998–2012 in patients with type 2 diabetes [209]. Here the proportion of cardiovascular and endocrine mortality fell from 62% in 1998 to 44% in 2012. Inversely, the proportion of cancer mortality increased and was projected to become the most common cause of death in patients with type 2 diabetes by 2030.

5.2.4   AGE AND EXCESS MORTALITY

Study I showed an inverse correlation between age at onset of type 2 diabetes and the severity of excess mortality i.e., younger age conferred higher excess mortality which gradually declined with increasing age at debut of type 2 diabetes. This vulnerability in younger patients with type 2 diabetes is in line with other reports. A recent systematic review and meta-analysis including data 26 observational studies from 30 countries found that each 1-year increase in age of debut of type 2 diabetes was associated with 4% decreased risk of all-cause mortality, 3% decreased risk of macrovascular disease, and 5% decreased risk of microvascular disease [210]. Several hypotheses explaining

the accelerated development of complications in younger patients with type 2 diabetes have been proposed, including complications due to longer duration with disease, ethnic differences, and a more aggressive form of type 2 diabetes in younger people. In Study I, excess mortality in younger patients was seen from start of follow-up and do not primarily seem to be a consequence of duration of disease.

5.3 C-PEPTIDE PREDICTS MORTALITY IN NEW-ONSET TYPE 2 DIABETES

In Study II, the association between C-peptide level and mortality and cardiovascular outcomes were examined during 18-years of follow-up. The study included prospectively registered patients in the Skaraborg Diabetes Register less than 65 years old at debut of type 2 diabetes between 1996 and 1998. After adjusting for multiple risk factors and potential confounders, the risk of all-cause mortality was 2.2-fold increased per 1 nmol/l increase in C-peptide concentration, measured at debut of type 2 diabetes or soon thereafter. The corresponding mortality risks due to underlying or contributing cardiovascular disease were 2.7 and 2.3-fold, respectively. Of those who died, approximately one third died of underlying cardiovascular disease and just over half of the patients had a contributing cardiovascular cause of death. A weaker 1.6-fold increased risk of the composite endpoint of ischemic stroke, myocardial infarction, and underlying cardiovascular death was also seen. No significant association could however be found between C-peptide and risk of ischemic stroke or myocardial infarction per se.

The findings in study II are mainly in line with results from some previous studies [40, 42, 43]. The novel finding of the study is that the increased mortality seen in patients with new-onset type 2 diabetes and elevated levels of C-peptide is driven by cardiovascular disease.

One specific strength of the study is the inclusion of patients with new-onset type 2 diabetes. It is appealing to identify patients at high risk of adverse outcome in their early course of disease, to offer intensified multifactorial medical treatment, as previously discussed, and clinical follow-ups to reduce the risk of complications. Measurement of C-peptide is also affordable and available in routine clinical practice. As the beta-cell function and insulin secretion often deteriorate over time in type 2 diabetes, the association between C-peptide and clinical outcomes could possibly differ in relation to the timepoint when it is measured during the course of disease. The small sample size of 398 patients is another limitation of the study as it is underpowered to

detect associations between C-peptide and clinical outcomes with smaller effect sizes, for example myocardial infarction or stroke. Further, many patients are older than 65 years at debut of type 2 diabetes, but those patients were excluded in this study. The long follow-up starting in 1996–1998 is a strength of the study but also entails that multifactorial treatment was just gradually introduced during follow-up.

5.3.1 MECHANISM OF C-PEPTIDE AND CARDIOVASCULAR MORTALITY

Various possible mechanisms have been proposed linking elevated level of C-peptide and risk of cardiovascular mortality. One explanation could be that elevated levels of C-peptide mirrors high insulin concentrations and insulin resistance which are part of the metabolic syndrome including several cardiovascular risk factors [37]. Of note, the association between elevated C-peptide and cardiovascular mortality in Study II persisted also after adjustment for BMI, systolic blood pressure and cholesterol. The complexity of C-peptide as a biomarker for diabetic complications is underscored as elevated C-peptide has been shown to be associated with reduced risk of microvascular complications in type 2 diabetes [39]. This has also been seen in type 1 diabetes, suggesting that preserved pancreatic beta-cell function might have a protective effect in the development of microvascular complications [211]. Based on these findings, C-peptide has been considered as a potential therapeutical agent in type 1 diabetes [212].

Further studies are needed to disentangle the associations and possible causal effects of C-peptide on mortality, microvascular, and macrovascular complications in diabetes.

5.4 EDUCATIONAL LEVEL AND INCOME

In Study III, the interplay of socioeconomic status and diabetes on mortality and cardiovascular complications was explored in a cohort of patients registered with hypertension in primary care between 2001 and 2008. In this observational study from the SPCCD, the addition of diabetes in patients with hypertension was associated with 57% excess risk of mortality, 24% excess risk of myocardial infarction, and 17% excess risk of ischemic stroke, adjusting for multiple potential confounders. Low income in combination with hypertension and diabetes, as compared to high income in combination with hypertension without diabetes was associated with near 4-fold increased risk of mortality and 2-fold risk of myocardial infarction and stroke.

The association between low socioeconomic status and increased risk of mortality and cardiovascular disease is well known in individuals with [128-131] as well as without diabetes [125, 126]. However, this association has not until now been explored in hypertensive patients in primary care in a high-income country with subsidized universal healthcare.

One specific strength of the study was that the effect of diabetes on study outcome was evaluated by allowing the presence of diabetes to be time-updated. This reduces the risk of immortal time bias which would otherwise have occurred since patients must be alive until the moment diabetes is added either through a registered diagnosis of diabetes or prescription of an antidiabetic drug. A specific limitation of the study was that type 1 diabetes could not be distinguished from type 2 diabetes due to inconsistency in the registration of specific ICD-10 diagnoses related to diabetes. However, the results in the study are in practical terms reflecting type 2 diabetes, as 85-90% of diabetes in Sweden is type 2 diabetes, and that the proportion most likely is even higher in primary care.

5.4.1 DISENTANGLING THE EFFECTS OF EDUCATIONAL LEVEL AND INCOME

Low income, as compared to high income was consistently associated with increased risk of mortality, myocardial infarction, and ischemic stroke. The effect sizes of low income on study outcomes also persisted after adjusting for educational level and other confounders and were larger than when adding diabetes to hypertension. The effect sizes of low educational level, as compared to high educational level were similar as when adding diabetes to hypertension. However, the effect sizes of educational level were reduced when also adjusting for income. This finding should be cautiously interpreted as income most likely is a mediator of educational level, meaning that the full effect of educational level cannot be estimated if the effect is adjusted for income.

The effects of educational level and income might vary with calendar year and patients' age. For example, the difference in income among high-income earners and others is less evident after retirement. Also, high educational level is more uncommon in elderly patients who grew up during an era with less opportunities and availability to proceed with higher education at secondary school or universities. The shift in educational level is still in motion. According to Statistics Sweden the proportion of 25–64-year-old people with ≥ 15 years of education was 16% in 2000 as compared to 28% in 2019. Inversely, the proportion with ≤ 9 years of education was 21% in 2000 and

11% in 2019. Possibly, educational level and income were less tightly correlated earlier when higher education was less available and not required to the same extent by employers as today. Thus, schooling might have had less impact on income in elderly individuals in the SPCCD who had their schooling during the 1940s to 1960s. Although educational level and income are correlated, it has been argued that they cannot be used interchangeably as they measure different aspects of socioeconomic status [213].

5.4.2 MECHANISM OF LOW SOCIOECONOMIC STATUS AND ADVERSE OUTCOMES

The healthcare system in Sweden is universally subsidized and funded by taxes, with only low additional individual costs for pharmaceutical drug treatment and visits to healthcare clinics [214]. Thus, the adverse outcomes associated with low socioeconomic status is less likely to be due to a health care access bias. Previous studies have linked low socioeconomic status to unhealthy behaviors such as poor nutrition, alcohol use, smoking, and sedentary lifestyle, as well as stress, inequality, lack of social support and lack of knowledge and access to information about health risks [215]. Financial stress has been associated with risk of myocardial infarction [216], and low income to non-adherence to antihypertensive treatment [217]. Further, an association has been seen between neighborhood deprivation and increased risk of cardiovascular risk factors [218], mortality [219], and stroke [127] even after adjusting for additional socioeconomic factors. Thus, the effect of socioeconomic status, represented in Study III as educational level and income, on mortality and cardiovascular events is multifactorial and complex and it is not possible to pinpoint a specific underlying mechanism of action.

5.5 COUNTRY OF BIRTH

In Study IV, the associations between country of birth and diabetes status and the study outcomes mortality, myocardial infarction and ischemic stroke were explored in the same cohort as in Study III i.e., patients in the SPCCD with hypertension registered in primary care between 2001 and 2008. Coexisting diabetes was associated with 46–73% increased mortality risk depending on country of birth. Non-European country of birth was associated with 44% decreased mortality risk in hypertensive patients with diabetes, and 35% decreased risk in hypertensive patients without diabetes, as compared to being born in Sweden. In contrast, being born in Finland was associated with 26% increased mortality risk and 16% increased risk of myocardial infarction in hypertensive patients without diabetes, as compared to Swedish born. No

significant associations were found between country of birth and risk of ischemic stroke, as compared to Swedish born.

This is to the best of my knowledge the first study exploring the interplay between country of birth and diabetes on mortality and cardiovascular complications in a hypertensive primary care setting, allowing for adjustment for socioeconomic variables and clinical data including blood pressure levels. The study confirms the findings from the Swedish National Diabetes Register of 45% decreased adjusted mortality risk in non-Western immigrants with type 2 diabetes [131]. The study also adds that this association is seen in hypertensive patients without diabetes.

One specific strength of the study is the use of time updated diabetes status as in Study III. Another strength is that the results have been adjusted for blood pressure levels. In analogy with Study III, type 1 and type 2 diabetes could not be distinguished with certainty due to possible misclassification of ICD diagnoses, but the results mainly reflect type 2 diabetes which constitutes 85–90% of diabetes in Sweden. Another limitation of the study is the lack of data on potential confounding variables that might be linked to country of birth, for example dietary regimens, alcohol use, marital- and occupational status, social and family support, physical activity, and neighborhood deprivation.

5.5.1   THE MIGRATION MORTALITY PARADOX

The findings in Study IV are mainly in line with previous studies where a general mortality advantage has been seen in non-Western immigrants as compared to the native population [132]. This phenomenon has been called the adult migration mortality paradox, as it contrasts to reports of increased prevalence of diabetes [136] and cardiovascular disease [138, 220, 221] in non-western immigrants.

Several hypotheses have been proposed to explain the migrant mortality paradox. The *healthy immigrant effect* [222] suggests the possibility of self-selection bias where the most motivated, wealthy and healthy individuals chose to migrate. Also, individuals migrating to work or for study could have been allowed immigration or been recruited to the new country based on skills and education. The *salmon effect* [223] which is also called the *unhealthy remigration effect* or *remigration bias* implies that immigrants remigrate to their country of origin to seek social support and care when end of life is approaching. *Cultural effects* [224] due to differences for example in alcohol consumption, diet, and family and social support have also been discussed to contribute to the mortality advantage. The *migration-as-rapid-health-*

transition hypothesis [225] states that individuals from less developed countries experience a shifting cause of death panorama from infectious diseases to chronic non-communicable diseases such as cardiovascular disease. This results in an initial decline in infectious diseases related mortality upon migration to a high-income country, and exposure to risk factors of non-communicable diseases which leads to convergence of mortality to host-country levels with length of stay. The phenomenon of converging mortality risks was recently noted in a Swedish nationwide study revealing an overall 45% reduced mortality risk in first generation immigrants with type 2 diabetes and ≤ 24 years of stay in Sweden, whereas the mortality risk was reduced by 8% among those with > 24 years in Sweden [226]. In addition, the mortality risk in second generation immigrants with both parents born abroad was 28% higher, as compared to native Swedes.

However, there is no consensus concerning the underlying mechanism of the immigrant mortality paradox, and several of the hypotheses described above have been challenged. Regarding the salmon effect, lower mortality was reported in an US study among Puerto Ricans and Cubans as compared to non-Latino whites, even though deaths after remigration to Puerto Rico were registered in US death statistics, and although Cubans were not allowed to remigrate to Cuba [227]. Also, the healthy immigrant effect was not supported in this study as the mortality risk was lower among US-born Latinos as well as foreign born Latinos as compared to US-born whites. Similarly, the salmon effect and the healthy immigrant effect were not supported in Danish register-based studies showing higher burden of disease in refugees and family-reunification immigrants as compared to native Danes [228], as well as fewer remigrations to the country of origin as severity of disease worsened [229].

5.5.2   COMPLEX SOCIOECONOMIC PATTERNS

The associations between country of birth and socioeconomic determinants such as educational level and income are complex. The underlying reasons forcing or pushing people to migrate to Sweden may vary greatly. Some of the people that have migrated to Sweden during the last decade are refugees escaping wars in some of the poorest countries in the world such as Somalia and Afghanistan, whereas others are refugees from Syria which was once a middle-income country before the Syrian war started. Other people migrate to study. Further, work laborers might be unqualified or educated and highly qualified, migrating or being actively recruited from low-income as well as high income countries.

The mix of immigrants and the reasons for migrating have changed over time. During the post-World War II era, people migrated from other Nordic countries, especially Finland to Sweden for work. People from Iran migrated to Sweden for studies during the 1970s, and later as refugees during the 1980s to escape the Iran-Iraq war. During the 1990s, people immigrated from Balkan following the war in former Yugoslavia.

In summary, immigrant groups and the underlying reasons for immigration to Sweden and elsewhere are highly heterogenous, and although not studied in this thesis it is reasonable to assume that mortality and morbidity and its link to other socioeconomic determinants differ between the groups.

6 CONCLUSION

In conclusion, the aim of this thesis was to study different epidemiological aspects regarding risk of mortality and cardiovascular complications among individuals with diabetes, hypertension, and hypertension with concomitant diabetes in primary care. The main findings of the four register-based cohort studies included in the thesis were as follows:

- Excess mortality decreased over time in patients in the Skaraborg Diabetes Register with clinically new-onset type 2 diabetes 1991–2004, as compared to matched control individuals in the general population. The excess mortality was driven by cardiovascular and endocrine mortality and was most pronounced in younger patients.

- Elevated C-peptide levels measured at clinical debut of type 2 diabetes in patients younger than 65 years predicted all-cause mortality and cardiovascular mortality.

- Coexisting diabetes in hypertensive patients in primary care was associated with 57% increased risk of mortality, 24% increased risk of myocardial infarction, and 17% increased risk of ischemic stroke. Low income in combination with hypertension and diabetes, as compared to high income in combination with hypertension without diabetes was associated with near 4-fold increased risk of mortality and 2-fold risk of myocardial infarction and stroke.

- Non-European country of birth was associated with decreased mortality risk in hypertensive patients with and without diabetes, as compared to being born in Sweden. In contrast, being born in Finland was associated with increased mortality risk in hypertensive patients without diabetes.

Clinical implications of the study findings include that in diabetes and hypertension, C-peptide and socioeconomic factors are associated with risk of mortality and cardiovascular complications and could potentially be used to identify patients at high risk of adverse outcomes, to allocate health care resources, and to strengthen individual risk factor control with the aim to improve prognosis.

7 FUTURE PERSPECTIVES

Lower than historically reported excess mortality in type 2 diabetes have been reported in this thesis and in other recent studies. The importance of multifactorial treatment to improve prognosis has been demonstrated in prospective [207] and observational studies [230].

Future register-based research using real world data can be used to evaluate whether excess mortality in type 2 diabetes will continue to decrease, as the therapeutical arsenal available for treatment of type 2 diabetes have expanded with the addition of sodium-glucose cotransporter-2 (SGLT-2) inhibitors [231] and glucagon-like peptide-1 (GLP-1) receptor agonists [232] – treatments that have showed positive effects on mortality and morbidity in RCTs. Similarly, register-based research can be used to evaluate the effects seen in RCTs of other pharmacological treatments in real-world settings.

Identification of individuals with cardiometabolic conditions such as hypertension and diabetes at high risk of complications and premature death is important to offer individual support and medical treatment to improve prognosis. Socioeconomic determinants and biomarkers could be valuable tools to identify those individuals. However, further studies are needed to evaluate the possible additional value of such predictors to already established predictors used in clinical practice.

The mechanisms underlying the immigrant mortality advantage are poorly understood. Further research in this area is warranted including studies on epigenetics, gene environment interactions, and ethnic variations according to the novel subgroups of type 2 diabetes [233]. Register-based research can potentially be used to follow immigrant populations over generations to evaluate temporal shifts in risk of mortality and cardiovascular disease, and to possibly disentangle the effects of socioeconomic position.

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