Socioeconomic Aspects of Diabetes and Cardiovascular Disease

Studies based on the Swedish National Diabetes Register

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To Shawbo Khani and Hojat Rawshani for their efforts.

ABSTRACT

Four hundred million people in the world have diabetes. The incidence of type 1 diabetes has increased steadily in the last few decades and it is now the second most common chronic disease of childhood. Type 2 diabetes develops in adults and older individuals with unhealthy dietary patterns, overweight and sedentary habits.

It is well known that socioeconomic status has a substantial impact on health and longevity. The effect of socioeconomic status has been examined thoroughly in cardiovascular medicine. When it comes to diabetes, however, there are important gaps in knowledge. Socioeconomic status includes primarily income, education, ethnicity and occupation. These variables may serve as easily accessible risk markers.

The present thesis is based on the Swedish National Diabetes Register (NDR). The NDR includes the majority of all individuals (aged 18 years and older) with diabetes. We examined how socioeconomic status affects survival, risk factor control and the risk of developing heart failure. We also examined the incidence of type 1 diabetes in people aged 34 and younger.

We show that the incidence of type 1 diabetes in 15–34 year-olds is two to three times as high as previously reported. Our analyses show that the Prescribed Drug Register is probably the gold standard for monitoring the incidence of type 1 diabetes.

Low income and educational level was associated with two to three times as great a risk of serious cardiovascular events and death in type 1 diabetes. Being male, divorced, single or widowed was also associated with substantially higher risk of adverse outcomes. Controlling for conventional risk factors and confounders did not eliminate the disparities.

Risk factor control in type 1 diabetes has improved in the last two decades. However, the improvements have been less pronounced among individuals with low socioeconomic status. Some of the socioeconomic gaps have widened over time. For example, individuals with low education have not improved their glycaemic control (HbA1c) during the period 1996 to 2014, whereas those with high educational level lowered their HbA1c by 4.0 mmol/mol.

Non-Western immigrants to Sweden develop type 2 diabetes a decade earlier than native Swedes. Immigrants have higher HbA1c, greater risk of therapy failure and higher probability of developing albuminuria than native Swedes. Ethnicity has a greater impact on glycaemic control than income or educational level.

There are ethnic differences in the risk of developing heart failure among individuals with type 2 diabetes. Individuals from South Asia appear to be at greater risk of developing heart failure, whereas those from Latin America are at lower risk, than native Swedes. Individuals with low income had 70% higher risk of developing heart failure, as compared with individuals with high income.

Ethnicity and socioeconomic status should be routinely considered in clinical management if diabetes care is to improve. These variables are easily accessible risk markers. Stringent risk factor control may be the most effective means of reducing these disparities.

SAMMANFATTNING

Fyra hundra tusen svenskar har diabetes. Sjukdomen förekommer huvudsakligen som typ 1 och typ 2 diabetes. Typ 1 diabetes är den näst vanligaste kroniska sjukdomen hos barn och ungdomar. Typ 2 diabetes drabbar vuxna och äldre, huvudsakligen som en följd av vår nutida livsstil.

Att studera socioekonomiska aspekter av diabetes är viktigt eftersom det föreligger kunskapsluckor på området samtidigt som befolkningen blir allt mer nyanserad ur ett socioekonomiskt perspektiv. Med socioekonomiska aspekter avses i fösta hand etnicitet, inkomst och utbildning. Dessa faktorers betydelse för diabetessjukdomen är viktiga att kartlägga. Det är tänkbart att socioekonomiska faktorer kan utgöra ett större hinder för hälsa än traditionella riskfaktorer.

Denna avhandling är baserad på Nationella Diabetesregistret (NDR). I NDR är majoriteten av alla svenskar (18 år eller äldre) som har diabetes inkluderade. Syftet med NDR är att förbättra diabetesvården och som en del av detta ingår forskning. Vi undersökte hur socioekonomisk status påverkar riskfaktorkontroll och överlevnad vid typ 1 diabetes samt hur socioekonomisk status påverkar metabol kontroll och risken för hjärtsvikt vid typ 2 diabetes. Därutöver undersökte vi insjuknandet i typ 1 diabetes i åldrarna 0 till 34 år.

Vi fann att tidigare studier som hävdat att insjuknandet i typ 1 diabetes minskar bland yngre har varit bristfälliga; våra resultat visar att insjuknandet är två till tre gånger högre än tidigare beräknat. Vi fastställde också att det svenska Läkemedelsregistret utgör den bästa databasen för att övervaka insjuknandet i typ 1 diabetes.

Vi visade att låg inkomst och låg utbildning (jämfört med hög inkomst och hög utbildning) var associerade med nästan tre gånger högre risk för hjärtinfarkt, stroke och död bland individer med typ 1 diabetes. Detta förklarades inte av skillnader i kliniska (exempelvis riskfaktorer) eller demografiska variabler.

Under de senaste två decennierna har riskfaktorkontroll förbättrats bland personer med typ 1 diabetes. Förbättringarna har dock varit mindre uttalade bland personer med låg socioekonomisk status. Exempelvis har personer med låg utbildning inte förbättrat sin metabola kontroll (mätt som HbA1c) under de senaste tjugo åren.

Utomeuropeiska invandrare utvecklar typ 2 diabetes ett decennium tidigare i livet. De har sämre metabol kontroll, högre risk att missa behandlingsmålen liksom att utveckla njurskador. Detta trots att dessa grupper fick behandling för sin diabetes tidigare och hade fler besök hos sin vårdgivare.

Det finns etniska skillnader avseende risken att utveckla hjärtsvikt. Individer från Sydasien förefaller ha ökad risk att utveckla hjärtsvikt, medan individer från Latinamerika har lägre risk, jämfört med svenskfödda. Individer med låg inkomst har 70% högre risk att utveckla hjärtsvikt, jämfört med individer med hög inkomst.

Socioekonomisk status och härkomst bör beaktas vid omhändertagandet av personer med diabetes. Behandling och uppföljning bör individanpassas för att reducera risken för komplikationer bland de högriskgrupper som identifieras i denna avhandling.

LIST OF PAPERS

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

I. A Rawshani, M Landin-Olsson, A-M Svensson, L Nyström, H J Arnqvist, J Bolinder, S Gudbjörnsdottir. **The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods**. *Diabetologia. 2014 Jul;57(7):1375-81.*

II. A Rawshani, A-M Svensson, A Rosengren, B Eliasson, S Gudbjornsdottir. **Impact of socioeconomic status on cardiovascular disease and mortality in 24,947 individuals with type 1 diabetes**. *Accepted in Diabetes Care.*

III. A Rawshani, A-M Svensson, A Rosengren, S Franzén, B Eliasson, S Gudbjornsdottir. **Long-term trends in cardiovascular risk factors in type 1 diabetes: nationwide monitoring of 38,169 individuals from 1996 to 2014**. *Submitted*.

IV. A Rawshani, A-M Svensson, A Rosengren, B Zethelius, B Eliasson, S Gudbjornsdottir. **Impact of ethnicity on progress of glycaemic control: a study of 131,935 newly diagnosed patients with type 2 diabetes**. *Accepted in BMJ Open.*

V. A Rawshani, A-M Svensson, A Rosengren, B Zethelius, B Eliasson, S Gudbjornsdottir. **Ethnicity and development of heart failure: a study of 215,138 patients with type 2 diabetes**. *Manuscript*.

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This thesis deals with the impact of socioeconomic status and ethnicity on the characteristics and outcomes of diabetes. It also touches on another important topic: the incidence of type 1 diabetes. The studies were conducted in Sweden based on the National Diabetes Register. Several interesting findings are reported.

Uninitiated readers may miss some interesting perspectives and reflections. This chapter consists of five sections, which should avert that risk. In the first section, relevant historical aspects are reviewed. The many faces of diabetes and its implications for this thesis are discussed in the second section. In the third section, the relationships between socioeconomic status and health are discussed. Ethnicity is a complicated concept to which section four is devoted. In the fifth and final section, the Swedish healthcare system, equality and access to care are discussed.

1
PERSPECTIVES

A BITTERSWEET TALE OF SUGAR

The saga of diabetes is one of the most extraordinary examples of translational research. At the beginning of the twentieth century, diabetes was a rare but rapidly fatal childhood disease. Revolutionary discoveries during the first half of the century transformed it into a condition with which people could live for many years. By the end of the century, childhood diabetes was the second most common chronic disease of childhood but it would represent less than 10% of all cases of diabetes. Instead, the adult form of diabetes emerged as one of the most common and most serious diseases mankind has ever faced. A brief review of the history of diabetes is warranted, particularly as some facts are relevant to this thesis.

The term diabetes mellitus was coined by the Greek physician Aretaeus (80-138 C.E.) to describe a rare condition characterized by sweet tasting and excessive urine accompanied by weight loss and fatigue. In 1776, Matthew Dobson confirmed elevated glucose levels in the urine of individuals with diabetes. Little did either of them know that the sweetness would bring about a very bitter taste for mankind in the twentieth century.

Dramatic advances in the understanding of diabetes followed. Researchers deciphered gluconeogenesis,[1] glycogenesis, glycogenolysis,[2] hormones and enzymes involved in glucose metabolism.[3,4] In 1889, Oskar Minkowski and Joseph von Merring performed pancreatectomies on dogs and observed that it caused fatal diabetes. They suspected that the pancreas was essential to glucose metabolism.[5] Fredrick Banting and Charles Best discovered insulin in 1921 after treating diabetic dogs with an extract from the pancreas of healthy ones.[6] They succeeded in purifying insulin from bovine pancreases the following year and thus created a life-saving treatment.[7] A few decades later, the insulin gene was cloned and recombinant DNA technology made unlimited supply of insulin available.[8] As outlined by Polonsky, the saga of diabetes is extraordinary and overflowing with discoveries, many of which have extended beyond diabetes. Female researchers – Dorothy Hodgkin, Rosalyn Yalow and others – have played an essential role.[9]

Diabetes has changed a great deal since the endeavours of Banting and his colleagues. They recognized diabetes as a rare disease that develops primarily in thin children and adolescents; a phenotype commonly referred to as type 1 diabetes. This form of the disease is the result of an autoimmune destruction of the insulin-producing pancreatic beta cells (Figure 1A). Nowadays, type 1 diabetes is fairly common in children and adolescents. But the great majority of individuals with diabetes have developed the disease during or after adulthood;

this form is called type 2 diabetes and it coincides with overweight, a sedentary lifestyle and high calorie diets.

The ensuing metabolic disturbances in diabetes damage the circulatory system.[10,11] Diabetes doubles or triples the risk of macrovascular complications (coronary heart disease, stroke and peripheral artery disease). The risk of microvascular complications (neuropathy, nephropathy and retinopathy) is 5 to 10 times as high.[12-17]

TYPE 1 DIABETES AND THE ENIGMA

Type 1 diabetes represents an epidemiological conundrum. Although early health statistics are scarce, available data suggest that the disease was very rare at the beginning of the twentieth century. Its incidence appears to have been stable until the 1950s, when an increase was documented in several countries.[18] This trend prompted researchers to launch international multicentre studies. These efforts took off in 1980 and included subjects aged 14 and younger.[19] The Diabetes Epidemiology Research International (DERI) study group,[20] the World Health Organization's Diabetes Mondiale (DIAMOND) project,[21] and the EURODIAB are among the studies.[22] These sources have reported an annual 3% increase in the incidence of type 1 diabetes since the 1980s.[21,23,24] The steepest increase has been noted in the 0-4 age group, and the mean age at onset has decreased. The incidence in Europe is predicted to rise by 70% between 2005 and 2020 (Figure 1B).[25]

The explanation for the increase remains elusive. One hypothesis is that improved survival has increased the pool of susceptible genes. However, the rapid increase in the incidence and the striking spatiotemporal variations cannot be explained by genetic changes alone.[26-29] It follows that environmental factors are making a major contribution. Something has changed in the environment, causing more children and adolescents to develop type 1 diabetes, at a younger age and with less genetic predisposition.[26,30] The trigger that elicits the autoimmune process is totally unknown.[31]

It is believed that the increase in individuals aged 14 and younger represents a left shift in the age of onset as mirrored by a corresponding decrease in the remaining population. It implies that the cumulative incidence has not changed; individuals simply develop the disease earlier in life, which is why some refer to it as the *spring harvest theory*.[18,19,32] Epidemiological studies have been contradictory in this regard. Two out of three noteworthy studies that support the spring harvest theory originate from Sweden.[33-35] Reports from Finland,[36]

Italy,[37] and the UK,[38] however, have showed stable or increasing incidence up to the age of 39. It is imperative to resolve the conflicting findings, as they have implications for both research and clinical practice.

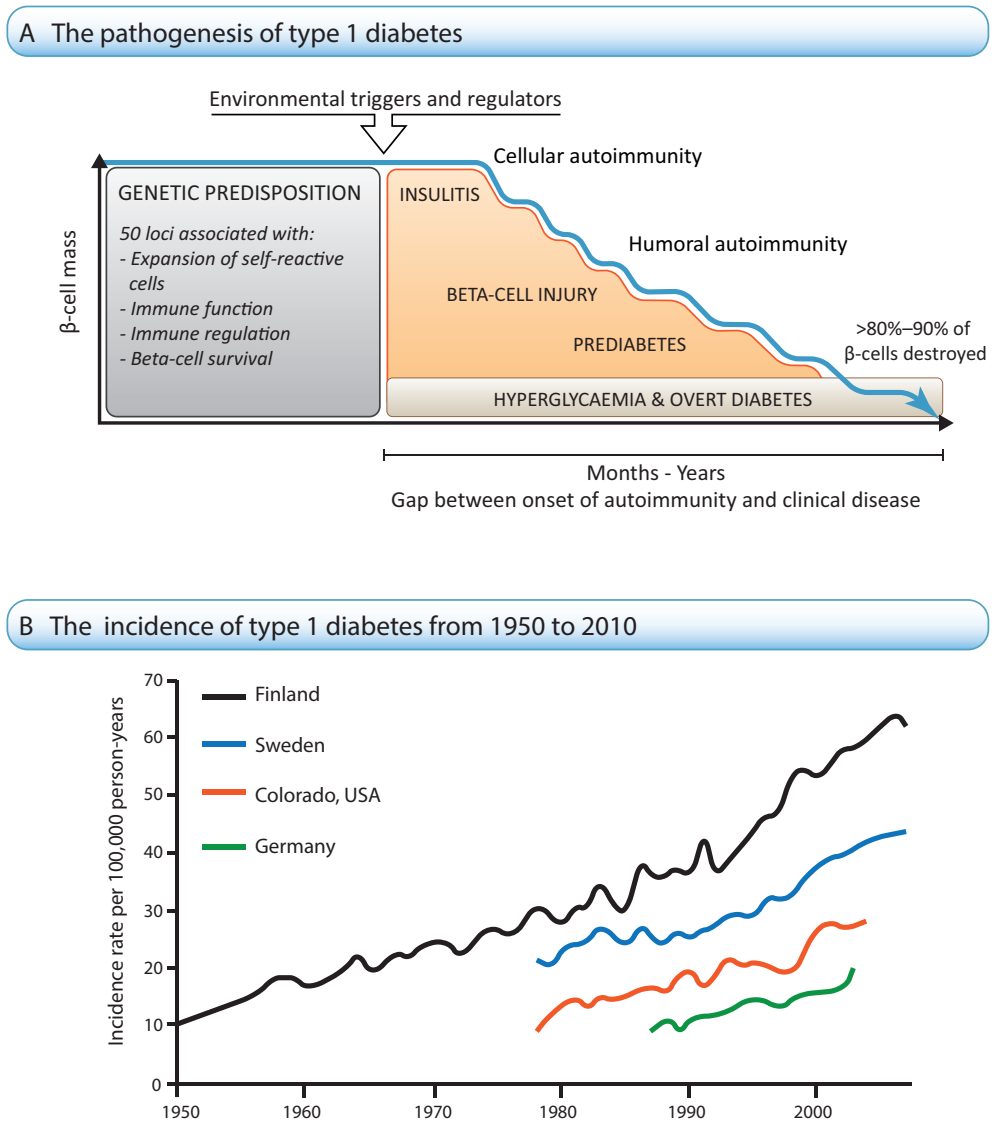


Figure 1 | **(A)** Pathogenesis of type 1 diabetes, as proposed by *Eisenbarth et al.*[39] **(B)** The Incidence of type 1 diabetes has increased 3% annually in the last few decades. Finland and Sweden exhibit the highest incidence rates in the world. Adapted from *Atkinson*.[31]

ADVANCES AND CHALLENGES

Management of type 1 diabetes has progressed in the last few decades. The cornerstone of management is intensive insulin therapy to maintain low blood glucose without provoking hypoglycaemia.[40] This task has been facilitated by improved insulin preparations and methods for insulin delivery,[41] as well as self-monitoring and real-time continuous monitoring of glucose levels.[42] The future holds additional promising solutions.[43]

It is likely that the risk of diabetes-related complications and mortality has decreased in the last decades. Yet individuals with type 1 diabetes still have 2 to 3 times as great a risk of death and their life expectancy is reduced by more than a decade.[13,44]

In summary, what was once a rare and rapidly fatal condition is now the second most common chronic childhood disease. Despite great strides in knowledge and management, people with type 1 diabetes still face a markedly elevated risk of cardiovascular disease and death. It has been suggested that the cumulative incidence is stable and that the spring harvest theory explains the increase among children. Continued epidemiological surveillance, along with basic science research, will be crucial to discovering the trigger of this autoimmune response.

TYPE 2 DIABETES AND THE WORLDWIDE EXPLOSION OF OBESITY

Type 2 diabetes is a different story altogether. In 2013, the International Diabetes Federation called diabetes a worldwide health crisis and one of the most serious diseases humankind has had to face. Approximately 400 million individuals are living with diabetes and another 300 million have impaired glucose tolerance, a precursor to diabetes. The pandemic is engulfing the world. Diabetes caused 5 million deaths in 2013, a figure that is predicted to increase by 50% over the next few decades. The crisis is escalating even though most cases of type 2 diabetes are preventable.[45] Developing countries are experiencing the greatest increase in the burden of the disease. It is important to understand just how the pandemic emerged.

Gaziano et al discuss the process of epidemiological transition.[46] The concept suggests that all societies pass through different epidemiological stages that imprint health and disease. These epidemiological stages are denoted in Figure 2.

All societies go through these stages, although at different times and at varying progression rates. The main causes of morbidity and mortality varies between

these stages. High-income countries (HICs) started the transition in the early twentieth century and have arrived in stage V. Low- and middle-income countries (LMICs) emerged from stages I and II decades after HICs and progressed rapidly; roughly 80% of people with diabetes today live in LMICs.

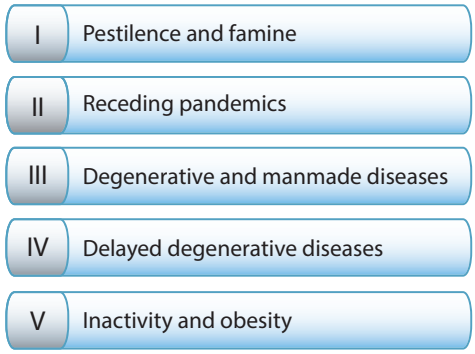


Figure 2 | Stages of the epidemiological transition.

THE STAGES

Most of human history has been characterised by *pestilence and famine*. Infections and malnutrition were the principal causes of disease and death throughout the world until 1900. Improved nutrition, cleaner water, increased food production and distribution, rising income and public health measures led to declining rates of infections and malnutrition. Life expectancy increased and agrarian societies industrialised. The age of *receding pandemics* had ended around 1950.

Urbanization and industrialization led to radical lifestyle changes. Diets high in saturated fats and carbohydrates, increased smoking and reduced physical activity led to the advent of hypertension and atherosclerosis. Life expectancy increased further due to medical progress and cardiovascular risk factors manifested in coronary heart disease and stroke (collectively referred to as cardiovascular disease). These conditions accounted for 35% to 65% of all deaths during the period of *degenerative and manmade disease*, which culminated between the 1960s and 1970s.[47]

As life expectancy continued to increase, the age of *delayed degenerative diseases* emerged. Cardiovascular disease and cancer were the predominant causes of disease and death, but age-adjusted cardiovascular death rates

declined by almost 50%. The reduction was due to aggressive treatment of hypertension, as well as public health campaigns that targeted smoking and consumption of atherogenic diets.

The encouraging decline in cardiovascular disease is now up against an unabated increase in overweight, which marks the age of *inactivity and obesity*. The explosion of overweight and obesity has caused a pandemic in both HICs and LMICs that affects all age groups. It is plausible that the increasing obesity explains the fact that age-adjusted cardiovascular mortality rates have levelled out for young women in the United States.[48] One in three Americans are obese,[49] and one in five Chinese are overweight or obese.[50] Almost 1.5 billion adults were overweight in 2008. The increase is particularly pronounced in LMICs.[51-54] Low-income groups in LMICs are experiencing the greatest increase in overweight and obesity.[55] It appears that poor people in LMICs are most susceptibility to developing obesity and diabetes.[55,56]

It should also be mentioned that beta cell function declines with age and the increased longevity has certainly reflected this on the diabetes prevalence.[57]

THE CAUSES

Our way of life has changed much in the last century. Urbanization and automation have evolved in tandem since the beginning of the twentieth century. Mass-production of automobiles began in 1910. Cars enabled long distance travel, reduced the need to walk or ride a bicycle and, along with automation, made work and daily life increasingly sedentary. Energy expenditure has declined steadily ever since Henry Ford introduced Model T.

Diet in the twenty-first century is characterized by large portions, processed foods, beverages high in sugar, an abundance of saturated animal fats, hydrogenated vegetable fats (containing atherogenic trans fatty acids) and simple carbohydrates. Consumption of plant-based foods is decreasing. Increased dietary fats – particularly saturated fats and trans fats – are promoting obesity, insulin resistance, beta cell dysfunction and glucose intolerance.[58] Soft drinks and other beverages high in sugar cause weight gain while increasing the risk of type 2 diabetes and coronary heart disease.[59] Maternal overweight during pregnancy can induce epigenetic and gene expression changes *in utero* that increases the risk of developing type 2 diabetes.[60]

Industrial production of tobacco started in the 1920s, when cigarette machines were invented. Evidence of the harmful effects of tobacco emerged in the 1960s.[61,62] Despite growing evidence, the consumption of tobacco continued to increase for several decades. Only in recent years has the increase plateaued out in HICs, whereas LMICs are experiencing increasing tobacco use.[63-65] Tobacco attracts unhealthy habits such as excess consumption of alcohol, soft drinks and processed foods. Smoking *per se* is associated with insulin resistance and increased risk of type 2 diabetes; a recent study showed that nicotine increases lipolysis, which results in body weight reduction, but this increase also elevates the levels of circulating free fatty acids and thus causes insulin resistance in insulin-sensitive tissues. [66-68]

Thus, urbanization, automation, automobiles, calorie dense foods, soft drinks, processed foods, tobacco – and habits associated with these phenomena – are the underlying causes of the cardiovascular and diabetes pandemic. These factors can be controlled primarily through legislation.

THE IRONY OF CUBA

Advances in the understanding and treatment of type 2 diabetes over the last two centuries have been extraordinary. In terms of disease, however, no progress has been made since Dobson's discovery in 1812. The situation is worse than ever and the most worrisome trend is in LMICs, from where migration to HICs is increasing.

Given the experience of the tobacco epidemic, it is unlikely that the obesity trend can be reversed in the near future. However, there is evidence that the pandemic can be halted. Shortly after the fall of the Soviet Union in 1989, Cuba suffered an economic crisis due to the loss of its main trading partner. Cubans could no longer enjoy the same level of produce and other amenities. Shortage of food, lack of public transportation and economic hardship reduced food, alcohol and tobacco consumption while people walked or rode their bicycles more. The proportion of physically active Cubans doubled in the first 5 years and average body mass index dropped 1.5 kg/m^2, while deaths from diabetes, coronary heart disease and stroke declined by 51%, 35% and 20%, respectively.[69] Thus, there is hope but tackling the diabetes pandemic will necessitate legislative actions.

In summary, type 2 diabetes has emerged as one of the most common and most serious diseases humanity has faced. The greatest burden of disease and the most adverse trend in risk factors take place in LMICs, from where migration to HICs is accelerating.

PATHOGENESIS OF TYPE 2 DIABETES

Blood glucose is regulated by a feedback loop between beta cells and insulin sensitive tissues (hepatic, skeletal muscle and adipose tissue). Insulin sensitivity in these tissues regulates the beta cell response via a feedback signal that is yet to be discovered. What is clear, however, is that the feedback increases as insulin sensitivity diminishes, stimulating beta cells to secrete more insulin in order to maintain glucose metabolism (Figure 3). The longstanding notion that beta cell failure is a late manifestation that is preceded by insulin resistance has been revised. Beta cell function is reduced for years or decades before the onset of diabetes. By the time type 2 diabetes is clinically manifest, more than 80% of beta cell function has been lost.[10,70] Genetic predisposition, ethnicity and the environment all govern beta cell function.[71-73]

Despite scientific advances, the usefulness of genetic markers is very limited once clinical indicators such as obesity, hypertension, dyslipidaemia, blood glucose and family history have been assessed.[74,75]

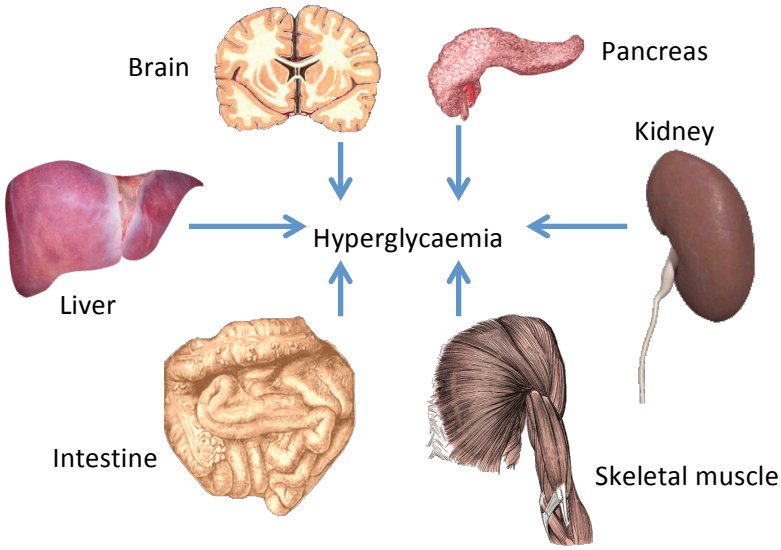


Figure 3 | Overview of organs that are involved in the pathogenesis of type 2 diabetes

SHADES OF HYPERGLYCAEMIA

Diabetes is the result of a clash between genes and the environment. The genes associated with diabetes are being rapidly discovered. More than 60 susceptibility loci have been associated with diabetes.[76-79] The environmental factors that cause type 2 diabetes are well known, as discussed previously. Those that trigger the autoimmune response in type 1 diabetes are a total mystery so far. Several potential triggers have been proposed but none has been proven.[39]

Clinicians typically distinguish between type 1 and type 2 diabetes based on age at onset, family history, presences of obesity, metabolic features, self-reactive antibodies and evidence of insulin deficiency. However, the traditional subdivision of diabetes into type 1 and type 2 is a gross oversimplification. Research over the past few decades has determined that diabetes is far more subtle. Moreover, the incursions of obesity into childhood and adolescence (which is pushing type 2 diabetes down the age span) and the improved ability to detect autoimmunity have blurred the picture. Studies II through V of the present thesis, as well as other studies from the Swedish National Diabetes Register, use epidemiological criteria to define this heterogeneous disorder. Thus, a brief discussion is warranted.

DIABETES IN CHILDHOOD AND ADOLESCENCE

Type 1 diabetes is the most common form of diabetes among children. The diagnosis is straightforward for an antibody-positive child aged 14 years or younger who is of normal weight, particularly if ketoacidosis is present. Most, but not all, persons with type 1 diabetes exhibit self-reactive antibodies.[31]

Twenty-first century children are increasingly overweight and obese.[80,81] In fact, type 2 diabetes is the most common form of diabetes among Americans younger than 20.[82] Non-Caucasians seem to be at the greatest risk of developing type 2 diabetes in adolescence.[83-85] The progress of beta cell failure is faster when type 2 diabetes manifests during adolescence than later in life. It appears that accumulation of ectopic fat in hepatic and skeletal muscle tissue is the main cause of diabetes in adolescence.[86-89]

Children and adolescents with type 2 diabetes are invariably obese and exhibit features of the metabolic syndrome. However, some of these may present with ketoacidosis,[90] and 10–40% may have detectable antibodies.[91,92] The picture is further blurred by the occurrence of monogenic forms of diabetes in children and adolescents. These forms of diabetes are characterized by onset before 25,

autosomal inheritance and evidence of insulin production. However, these features are also typical of type 2 diabetes.[93]

DIABETES WITH ONSET IN ADULTHOOD

Diabetes with onset in the 20–40 age group is particularly difficult to diagnose. Type 1 diabetes (including latent autoimmune diabetes in adults [LADA]), type 2 diabetes, and maturity-onset diabetes in the young (MODY) all occur in this group. Their distribution varies according to the country and setting. The incidence of LADA exceeds type 1 diabetes in some countries.[93]

Since obesity and metabolic disturbances are common in all age groups, their presence cannot rule out autoimmune diabetes. Absence of overweight or obesity, on the other hand, virtually excludes type 2 diabetes. Some adults without features of type 2 diabetes may have residual beta cell function, while others have a phenotype that suggests type 2 diabetes but still test positive for antibodies. The latter group is commonly designated as LADA. This form of diabetes shares genetic and phenotype features with both type 1 and type 2 diabetes. Individuals with LADA typically have obesity, dyslipidaemia, hypertension and antibodies. Onset of diabetes after 35 with antibodies against glutamic acid decarboxylase (GAD), along with residual beta cell function for 6 to 12 months strongly suggests LADA.[94-98]

DIABETES PHENOTYPES IN DEVELOPING COUNTRIES

Research in recent years has revealed that the fact of type 2 diabetes is changing in many parts of the world, particularly regions that are undergoing rapid economic development. The Middle East, South Asia and East Asia have the highest prevalence of diabetes. These populations are particularly susceptible to metabolic aberrations. Asians seem to be especially vulnerable in this regard. Diabetes develops a decade earlier in Asians than in Caucasian Europeans. Asians develop diabetes at a body mass index of around 26 kg/m^2, which is 4 kg/m^2 lower than Caucasian Europeans.[73,99,100] Moreover, Asians are more insulin resistant than other ethnic groups. Hyperinsulinaemia and type 2 diabetes are more common in Asian children.[73] This has prompted establishment of ethnicity-specific cut-offs for obesity.[101,102] It is believed that the thrifty genotype and thrifty phenotype hypotheses, discussed below, explains the susceptibility of Asian populations.

Thus, the phenotype of type 2 diabetes may vary considerably depending on the country of origin. This phenomenon has implications for the use of

epidemiological criteria to define types of diabetes. For example, since South Asians develop diabetes early in life, at low body mass index and rapidly progress to insulin dependency, they may be misclassified as having type 1 diabetes.

EPIDEMIOLOGICAL CRITERIA FOR DISTINGUISH TYPES OF DIABETES

The most frequently used definitions of type 1 and type 2 diabetes in the National Diabetes Register are based on epidemiological criteria. Type 1 diabetes is epidemiologically defined as treatment with insulin and onset at the age of 30 or younger. An assessment of this definition was performed among 7,000 patients; 97% of whom were treated in hospital clinics. Data were available concerning the clinical assessment of the type for 75% of the participants, 97% of whom had type 1 diabetes.[103] Type 2 diabetes is defined as treatment with diet only, oral hypoglycaemic agents only or onset at age 40 years or older and treatment with insulin only or combined with oral hypoglycaemic agents. For reasons discussed above, these criteria pose certain difficulties. We will emphasize the following issues.

– The epidemiological definitions do not consider body weight. Body mass index and waist circumference are available in the National Diabetes Register. Taking body mass index into consideration could increase the specificity, though at the expense of sensitivity. For example, considering type 1 diabetes, the presence of obesity could be used to rule out type 2 diabetes but it would inevitably exclude individuals with type 1 diabetes who are obese. As discussed above and shown in study III, individuals with type 1 diabetes are becoming increasingly overweight, which further reduces the usefulness of body weight as a criterion.

– Antibodies are not available in the National Diabetes Register. Islet antibodies have traditionally been the hallmark of type 1 diabetes but research over the last decade has revised this notion. Studies have generally reported that 90% of individuals with newly diagnosed type 1 diabetes have self-reactive antibodies.[104] Recent studies show that the proportion that does not display antibodies may be as high as 40% and this is more common among Hispanics and Africans.[91,92,105,106] Furthermore, 5–15% of adults diagnosed with type 2 diabetes exhibit antibodies and might actually have type 1 diabetes.[107,108] Thus, consideration of islet antibodies would not solve the puzzle either.

– Subjects are not necessarily included in the register at the time of diagnosis. Subjects are entered in the National Diabetes Register either at

the time of diagnosis or afterwards. Information that pertains to the period before entry in the National Diabetes Register is generally not accessible. A young person – for example a South Asian – with type 2 diabetes may have used oral hypoglycaemic agents before switching to insulin. If that person is 30 years or younger and enrolled in the register after switching to insulin therapy, a diagnosis of type 1 diabetes will be erroneously established.

– Ethnicity is not considered. As discussed above, and as is evident from study IV, diabetes phenotypes differ markedly in various populations. It follows that the risk of misclassification is much higher for non-Caucasians.

– Risk of informative missing. In the validation study described above,[103] 25% of the subjects had missing data regarding the clinician's classification, and it would not be justifiable to claim that data is missing completely at random. The large percentage of missing may reflect the difficulty in distinguishing types of diabetes. One may argue that the fact that 97% were treated in hospital clinics indicates that they had type 1 diabetes, but this could merely reflect the difficulty in managing these patients in primary care.

– Latent autoimmune diabetes in adults may be prevalent. The epidemiological definition of type 2 diabetes in the register is prone to include latent autoimmune diabetes in adults due to the similarities in phenotypes.

The consequences of misclassification depend on the research question and cohort. Consider a study examining the impact of age at onset (of diabetes) on survival in type 1 diabetes. If the epidemiological definition were to be used and a significant proportion of individuals older than 25 would actually have type 2 diabetes, the results would be seriously biased.

In summary, the epidemiological classifications of diabetes poses certain difficulties. We justify the use of the current epidemiological definitions as follows:

– The validation study showed satisfactory precision of the criteria.[103] This argument, however, assumes that missing data regarding the clinician's classification is missing at random.

– Study I of this thesis revisited the epidemiological definition of type 1 diabetes and reported that the epidemiological and clinical classification concurred in 94% of the cases.[109]

– The great majority of individuals in each epidemiologically defined group have the specified type of diabetes. The loopholes in the epidemiological criteria (e.g. onset of type 2 diabetes before 30 and treated only with insulin; adults with autoimmune diabetes who are initially treated with oral hypoglycaemic agents; autoimmune diabetes with onset at 40 or older etc.) present much less common incidences.

– Several internal assessments – *independent cohorts, separate time periods and for both types of diabetes* – have shown good concordance between clinical and epidemiological classifications; again assuming that data is missing at random.

– The criteria are pragmatic and they have so far been approved by several dozens of reviewers.[13]

Nevertheless, future validation studies (preferably by means of chart reviews) would be wise.

SOCIOECONOMIC STATUS AND HEALTH

People with greater privilege and wealth have always enjoyed better health. Socioeconomic status and health have had a relationship, referred to as *the gradient*, in all societies throughout history. The gradient poses a major public health challenge in all countries regardless of how the healthcare system is structured.[110]

The gradient was first studied in the nineteenth century to compare the longevity of the European elite to that of the working class. It has consistently been shown since then that socioeconomic status is related to self-reported health, morbidity and mortality. In 2006, the U.S Centers for Disease Control reported that a 25-year-old with a bachelor's degree lives 9 years longer than a comparable individual without a high school education. Low education at age 25 reduces the length of life more than does a lifetime of smoking.[111] Individuals with high socioeconomic status are simply less likely to die than their less affluent compatriots

Socioeconomic status is a multidimensional construct that describes the social standing and resources of an individual. It is commonly measured as a combination of education, income, occupation and ethnicity. The factors (domains) act both independently and jointly to exert a profound impact on health.[112]

Some researchers assert that the joint impact of all four domains – representing a broader underlying dimension of *social stratification* – is the effective agent. Less emphasis is placed on the independent effects of the various domains.[110,112,113] We will argue, however, that each domain should be studied separately to better delineate its effects. Such an approach facilitates identification of potential mediating factors and modifiable determinants of health.

Causality, association and reverse causation are central concerns. Researchers are typically interested in identifying causal mechanisms, an enterprise that can be difficult when studying the gradient. Reverse causation refers to the situation in which the outcome precedes the exposure, which is thought to be the cause, instead of the other way around. For example it may be difficult to determine whether low socioeconomic status causes heart attacks or vice versa. Cross-sectional studies are particularly vulnerable to reverse causation, but it may also appear – albeit less obviously – in cohort studies. Furthermore, socioeconomic status can consist of behavioural, environmental and psychosocial factors, that mediate or confound its effect. *Cutler et al* used data from the National Health Interview Surveys to illustrate that the effects of income, education, occupation

and ethnicity are independent of such confounders. The authors start off by examining the individual effect of income, education, ethnicity and occupation on mortality and self-reported health status after adjusting for demographic factors. They go on to simultaneously include all four domains of socioeconomic status in the same model and observe that income, education and ethnicity are still significantly associated with death, while occupation is not. They continue to adjust for health behaviours (smoking habits, alcohol consumption and physical activity), observing that the effect of income, education and ethnicity is weaker, though still significant. Nor did adjusting for health knowledge and stress invalidate the association between socioeconomic status and mortality.[114]

Thus, socioeconomic status acts primarily through income, education, ethnicity and occupation. These domains have both independent and joint effects on health. Behavioural and psychosocial factors mediate some of the differences in health outcomes. The extent to which the effect of socioeconomic status should be attributed to causality might ultimately be a philosophical question.

SOCIOECONOMIC DIFFERENCES IN HEALTH BEHAVIOURS

Socioeconomic disadvantage triggers a range of chronic stressors and health obstacles, such as unemployment and financial hardship. Longstanding socioeconomic disadvantage exhausts coping abilities and causes adverse health behaviours.[115,116] Having less education might make it hard to adopt healthy behaviours, partly due to lack of knowledge about their beneficial effects. Poor education may also aggravate attempts to adopt the control mechanisms required to lead a healthy lifestyle. Establishing healthy habits and avoiding unhealthy ones can be a never-ending battle. The ability to pay for fitness clubs, enrol in wellness programs, buy expensive produce, etc., improves health.[117]

Socioeconomically underprivileged individuals live in communities that often fail to motivate and facilitate healthy behaviours; their neighbourhoods abound with fast food restaurants and shops that sell cigarettes and alcohol. Lack of social support, cohesion and positive peer pressure make the situation even worse.[118]

SOCIOECONOMIC INEQUALITIES IN CARDIOVASCULAR DISEASE AND DIABETES

Socioeconomic disparities in cardiovascular disease and diabetes pose a major public health challenge. Numerous studies have shown that socioeconomic status is a powerful predictor of incident cardiovascular disease and diabetes. A small selection of studies is presented below.

Mackenbach et al examined 12 high-income Western countries and showed that individuals with low education had a 50% higher risk of developing cardiovascular disease, as compared with their better educated compatriots.[119] The effect of low education was fairly constant in all countries; i.e. there were no differences between market-based health care and tax-financed universal health care.

African Americans of every age experience higher mortality rates than their Caucasian counterparts. Blacks are less likely than Whites to undergo coronary revascularization and die considerably more often of coronary heart disease.[120] Unfortunately, disparities in control of blood pressure, cholesterol and glucose have not improved nationally for Blacks in the US.[121]

Alter et al studied 51,591 patients to determine whether Canada's universal healthcare system provides citizens with equal access to invasive cardiac procedures. They reported that the use of such procedures was 23% higher for individuals in the highest income quintile, than those in the lowest. For each $10,000 increase in neighbourhood income, the risk of death declined by 10%.[122,123]

Kanjilal et al examined long-term disparities in cardiovascular risk factors related to annual income and educational level. They reported that the decline in smoking rates has been less steep among socioeconomically disadvantaged groups, which also experienced a greater increase in diabetes incidence.[124]

Diabetes risk is unequally distributed among socioeconomic groups. The adjusted prevalence of type 2 diabetes is 50% higher in areas with low socioeconomic status.[125] *Harris et al* examined glycaemic control in a representative sample of American adults with type 2 diabetes and concluded that poor glycaemic control was more common in African Americans and Mexican-Americans than other groups. Interestingly, they found no relationship between glycaemic control and socioeconomic status or access to medical care.[126] Similar findings were reported in 2011 by *Egede et al*.[127]

South Asians appear to be particularly susceptible. Whereas cardiovascular death rates have declined markedly in HICs, death rates among South Asian immigrants to HICs have been stable, [128] or even increasing.[129,130] South Asians are at greater risk of cardiovascular disease.[131,132] They exhibit poor risk factor control and an especially high waist-hip-ratio.[133,134] South Asians are at greater risk of developing diabetes.[132,135] They develop diabetes earlier in life,[136,137] and they have poor glycaemic control.[138,139]

Among individuals with type 1 diabetes, low socioeconomic status increases the risk of coronary artery disease, end-stage renal disease and peripheral artery disease.[140] It has also been reported that low educational level is associated with increased mortality in type 1 diabetes.[140,141] A recent study from Sweden showed that exposure to low socioeconomic status during childhood increases mortality risk later in life among persons with type 1 diabetes.[142]

These are just for starters.

MIGRATION – A HARSH JOURNEY

Human beings have always migrated in search of better conditions. Natural disasters, poverty, war and persecution are strong incentives. More commonplace motives, such as the quest for jobs and educational opportunities, are also common. Migration is generally a complicated and tough process, which does not necessarily end after settling in a new host country.

Migration occurs on all scales and at all distances. People move to more developed regions, be it to urban areas in the same country or to another country. Global migration has increased substantially in the last few decades, partly due to greater mobility. HICs are becoming increasingly diverse due to accelerated migration from LMICs.[143] The ethnic admixture of Western societies is far more diverse than their healthcare systems are currently prepared to handle.

Migrants are heterogeneous. Their background varies from illiterate refuges to highly accomplished academics. Irrespective, for the great majority, migration is a difficult process. Immigrants bring their language, culture, habits, experiences, etc. However, they gradually adopt the lifestyle, culture and habits of the host country, a process termed *acculturation*. On the contrary to the expected, acculturation does not necessarily improve health. Immigrants to a Western country are exposed to a Western lifestyle, characterized by sedentary habits, calorie-dense and processed foods, lack of fruits and vegetables, sugar-rich beverages, automobiles and motorized transports. Immigrants may be at particular risk to these exposures due to genetic susceptibility,[73,100] rapid changes in diet and lifestyle,[144] difficult transitional phases as well as lingual, cultural and financial barriers to healthcare.[145,146]

Studies have examined the impact of migration on health by comparing the risk of disease in a migrant population to their non-emigrated compatriots. *Haenzel et al* showed that the incidence of colonic carcinoma among Japanese increased dramatically upon migration to the United States. The second generation Japanese immigrants had assumed incidence rates comparable to native United States citizens.[147] *Marmot et al* found that the age-adjusted prevalence of coronary heart disease among Japanese immigrants to California was twice as high as the prevalence in Japan and this was accompanied by a corresponding increase in blood cholesterol among Japanese in California.[148] *Alfredsson et al* reported that Finnish male immigrants to Sweden had 70% higher risk of developing acute myocardial infarction, as compared with Swedish natives.[149] Similar associations were found by *McKeigue et al* who examined South Asians living in the UK.[150]

As discussed above, the risk of developing diabetes is heavily affected by ethnicity and migration. Upon migration to HICs, Africans and Asians are at greater risk of developing diabetes than both natives in the HIC as well as their compatriots in their country of origin.[73,151,152]

Thus, immigrants who originate from regions with low disease rates will gradually acquire rates that resemble those of their new country. In many instances, as we have noted for cardiovascular disease and diabetes, immigrants will actually have higher risk than native people. Researchers have suggested some explanations for these observations. The *thrifty genotype hypothesis* suggests that evolutionary pressure selected individuals who could store nutrients efficiently (primarily as abdominal fat) and endure periods of starvation. These genes have become unfavourable in an era of food abundance and physical inactivity. It predisposes the individual to develop insulin resistance and metabolic aberrations.[73] The *thrifty phenotype hypothesis* states that an unfavourable intrauterine environment due to poor nutrition results in low birth weight and rapid postnatal growth. This is associated with increased risk of diabetes and cardiovascular disease.[153-155]

Thrifty genotypes and phenotypes may have offered a survival advantage during evolution, but the dramatic lifestyle changes in recent decades have rendered these characteristics hazardous. This is potentiated by the fact that migration to more developed areas leads to decreased levels of physical activity, increased body mass index and abdominal obesity.[156-159]

Many immigrants experience psychosocial and financial stress. Their transition might include a reduction in socioeconomic status, along with loss of social capital and social cohesion. Those who have fled from cruelty and deprivation might have difficult experiences to deal with. Furthermore, immigrants face lingual barriers, underemployment, unstable housing and poor working conditions. These factors are outlined in Figure 4.

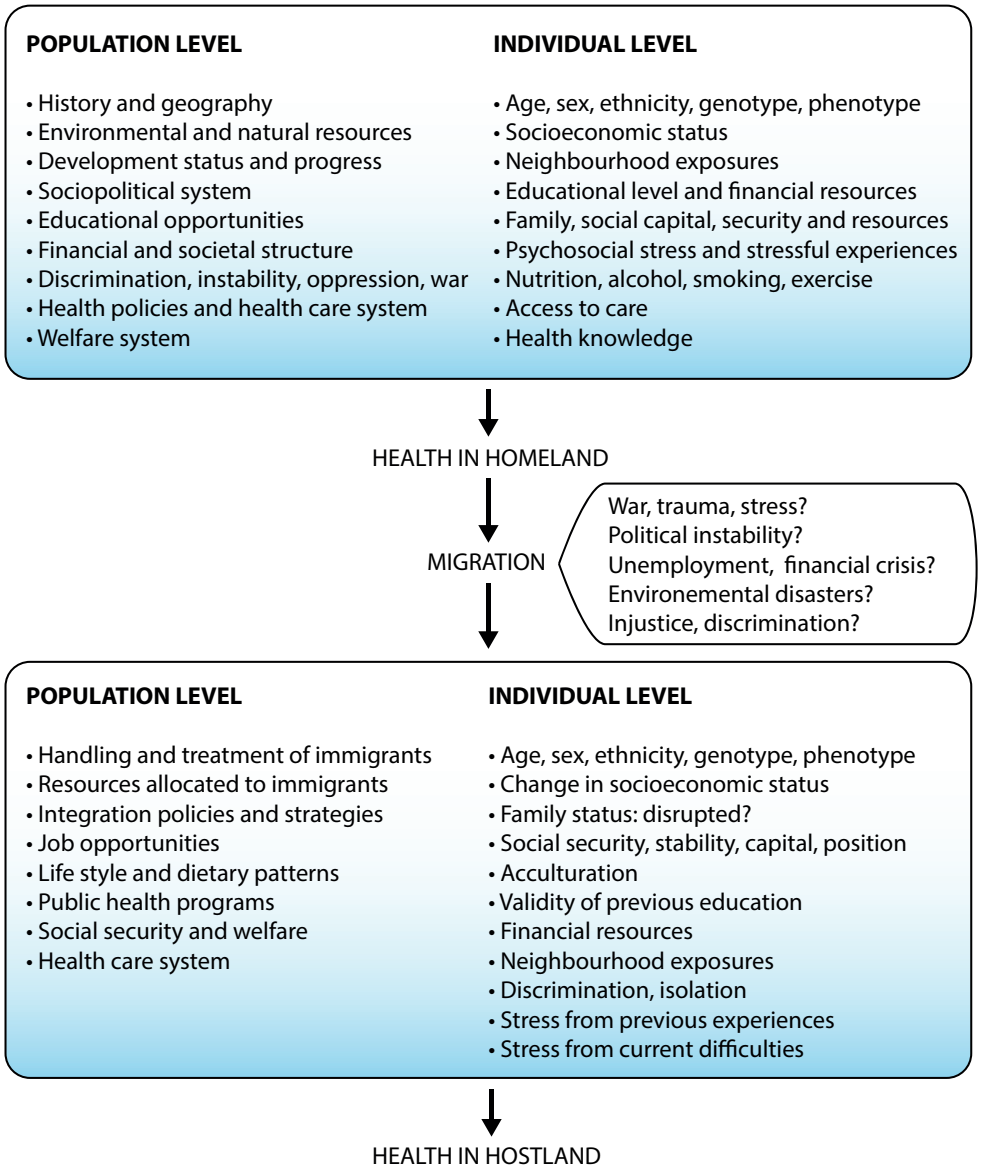


Figure 4 | Factors affecting health when migrating from less developed to more developed countries.

HEALTHY IMMIGRANT EFFECT

Several studies have reported that newly arrived immigrants have better health than native-borns. The observation that the risk of disease is lower among immigrants on arrival has been termed the *healthy immigrant effect*. Over time,

however, the health of immigrants converges to the native-borns. The explanation for this remains elusive, but it is believed that those who are able to migrate represent the healthier, wealthier and stronger subgroup of their population. Further, immigrants may have healthier behaviours prior to migration but they gradually adopt the unhealthy Western lifestyle, ultimately putting them similar or higher risk.[160]

ETHNICITY – A COMPLICATED MATTER

Ethnicity is arguably one of the most inflamed variables in medical research and a discussion regarding the nature of this variable is inevitable.

Ethnicity and race have been studied in various disciplines, such as medicine, epidemiology, genetics and anthropology. The use of ethnicity in medical research has provoked an intense debate. We will argue that such a debate is prudent as it may prevent inappropriate use of ethnicity as a variable [161-168]

Many consider ethnicity to be a rich variable that functions as a proxy for other characteristics. Ethnicity may reflect lifestyle, culture, religion, socioeconomic status and genetics. It is due to these nuances that ethnicity is both a rich and complicated variable. Unfortunately, there are numerous examples of inappropriate and unethical use of ethnicity in medical research. Controversies have followed and sullied this interesting variable.[161,162,168]

Most experts agree that ethnicity does affect disease prevalence, characteristics and outcomes. They also emphasize that socioeconomic status, health behaviours and lifestyle account for the majority of the ethnic differences. Thus, when studying the relationship between ethnicity and disease it is crucial to adjust for socioeconomic status and other potential confounders. Many studies fail to do so.[169]

There is disagreement about using ethnicity as a proxy for genetic variation. Opponents claim that ethnicity is a social and phenotype classification without biological significance. Proponents claim that ethnicity actually catches some genetic variation, which is of value.[75,170-173]

Another important issue is the lack of consensus regarding ethnic categories. Commonly used classifications are rudimentary and typically based on skin colour. This improved in 2011 due to recommendations issued by the U.S National Institute of Health. The following categories were advised: *American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White Hispanic/Latino, White not Hispanic/Latino*). All studies which are funded by the National Institute of Health must ensure adequate representation of ethnic minorities.[174] However, this classification is not suitable for the Swedish population due to differences in the ethnic composition. One may also argue that the classification of the National Institute of Health is somewhat blunt.[169,175]

From a political point of view, ethnicity is an intricate matter. The risk of prejudiced and biased interpretation of research results must be taken into consideration. Carelessness might lead to stigmatization and discrimination. One example at hand is study IV of the present thesis. In study IV it is reported that immigrants had worse glycaemic control than native Swedes, despite having more appointments and receiving treatment earlier. It could be interpreted as immigrants had more appointments due to difficulties controlling their disease or that Swedish natives are discriminated since they are offered less appointments to their clinic. A similar example was shown by *Exner et al*.[176] They reported that angiotensin-converting enzyme (ACE) inhibitors were less effective in African Americans. This could lead to less African Americans being offered ACE inhibitors, which are highly effective medications. A subsequent study confirmed that the blood pressure lowering effect was 4.6 mmHg lower in Blacks than Whites but additional analyses showed that many Blacks would actually benefit more from ACE inhibitors than would Whites.[177,178]

DEFINITION OF ETHNICITY

There is no consensus regarding the criteria for defining an ethnic group. Geographic, social, cultural and historical elements are important. An ethnic group is characterized by a high degree of mutual history, geographic location, language, lifestyle, family structure, religion, art and material culture.[173] Many ethnicities – both within and between countries – share these characteristics. It is difficult to draw distinct boundaries between neighbouring populations. Furthermore, ethnicity appears to be a changeable concept. Neighbouring ethnicities tend to adapt to and adopt from each other. It is also common that some individuals identify themselves with several ethnicities. Thus, defining an ethnic group and determining an individual's ethnicity can be difficult.

ETHNICITY AND GENETICS

The use of ethnicity as a proxy for genetic heterogeneity is one of the central and most controversial issues. Some believed that the Human Genome Project would show that mankind was genetically homogenous, but that was not the case. Little by little, an increasing number of genetic variants, with varying prevalence according to ethnicity, were discovered. Some of these were insignificant, while others appeared to affect disease and biology.[29,170,179,180]

The title of Francis Collins paper, *"What we do and don't know about race, ethnicity, genetics and health at the dawn of the genome area",*[181] insinuate that we are yet not capable of determining this. Although the human genome is being

unravelled at an astonishing pace, we are only in the beginning of this era. Most experts agree that ethnicity is a flawed proxy for genetic variation.[29,170-172,180,181] Some claim that ethnicity is biologically meaningless or lacks evidence,[171,182-185] while others state that ethnicity could be considered a surrogate for genetics.[172,186-189]

Shortly after celebrating the completion of the Human Genome Project, researchers reported ethnic and geographic differences in the prevalence of certain gene variants. This sparked enormous interest and projects like the *HapMap* and *1000 Genomes Project* were launched. This resulted in complete sequencing of thousands of individuals from all continents and the sequences are publicly available. Notably, these projects rely on ethnic phenotype to assure inclusion of a large genetic variation.[190-193]

The nucleotide sequence of any two individuals will differ on average once in every thousand base pairs, which yields a total of 3 million base pairs variation in the entire genome.[194] Genetic variation occurs predominantly as single nucleotide polymorphisms (SNPs) and copy number variants (CNVs). SNPs is the most common variation and occur as variations in base pairs, while CNVs generally includes more than 1000 base pairs. Researchers have so far identified millions of SNPs. The majority appears to be neutral but some are associated with diseases. The most frequent SNPs occur on all continents.[29,180] However, there are SNPs that appear to be more common in some populations. There are several possible explanations for this, the most likely being that the variant is new.[191,192]

Interestingly, the largest genetic variation has been found in Africa. It is believed that the genetic variation outside Africa is a subgroup of the African lines.[29,195-198] Approximately 85-90% of the genetic variation known today is represented on all continents. The remaining 10–15% are genetic variation between continents.[199,200] The significance of this variation is becoming elucidated but much work remains. Nevertheless, there is agreement that genetic variation exists between geographic areas.[191,192,199,201,202] It is actually possible to determine an individual's geographic origin solely by analysing SNPs.[188,203]

In summary, mankind is genetically homogenous but some variation exists and it is rather well represented by geographic origin. The clinical importance of this genetic variation remains to be clarified. More populations must be sequenced before the issue can be resolved. Meanwhile, ethnicity should not be considered a proxy for genetics; genotyping is the golden standard for determining genetic variation.[204] Researchers should, however, be aware that observed differences could be due to genetic variations.

ETHNIC CATEGORIES USED IN THIS THESIS

We created ethnic categories by grouping geographically adjacent countries. Our categories respected ethnical composition, economic development, language and religion.[205,206] Information on each participant's country of birth was obtained from Statistics Sweden. For simplicity, we did not assess parent's country of birth or number of years residing in Sweden. Figure 5 depicts the ethnic categories.

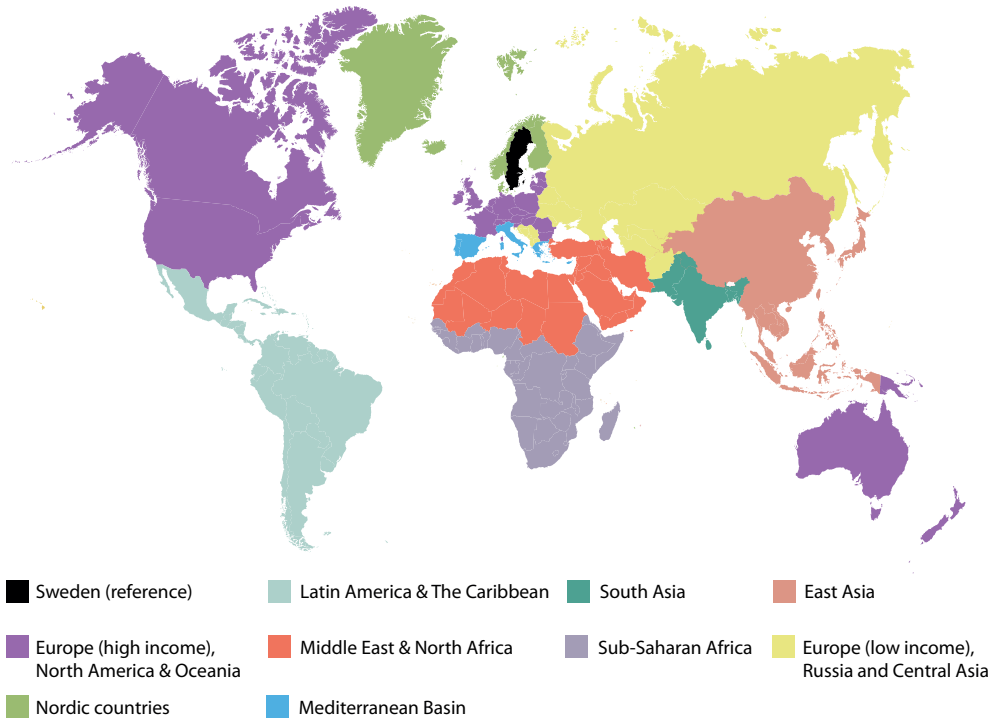


Figure 5 | Ethnic categories in studies IV and V.

EQUITABLE ACCESS TO CARE

The majority of studies on socioeconomic and ethnic disparities have been conducted in the United States. This has implications for the interpretation of such studies. Healthcare in the United States is market based, which engenders financial barriers to care. This should, however, not be interpreted as a confounder since access to care lies on the causal pathway between socioeconomic status or ethnicity and health. Nevertheless, studies from the United States will inevitably measure the effect of these exposures in a setting where healthcare is not available to everyone. This affects the generalizability and could introduce bias (discussed below).

Sweden, Norway and the United Kingdom stand out among the industrialized countries by having a public health care system. This ensures equitable access to care for the entire population. The patient shares no costs or pays a negligible part of it. According to a recent survey of adults in 11 high-income countries, Sweden and the United Kingdom ranked highest on measures of financial access to care and availability of care. The present thesis is based on studies conducted in Sweden, where barriers to health care are very low and disadvantaged groups are frequently targeted in ways to increase their use of health care. It follows that our studies should describe the intrinsic effect of socioeconomic status and ethnicity on health.

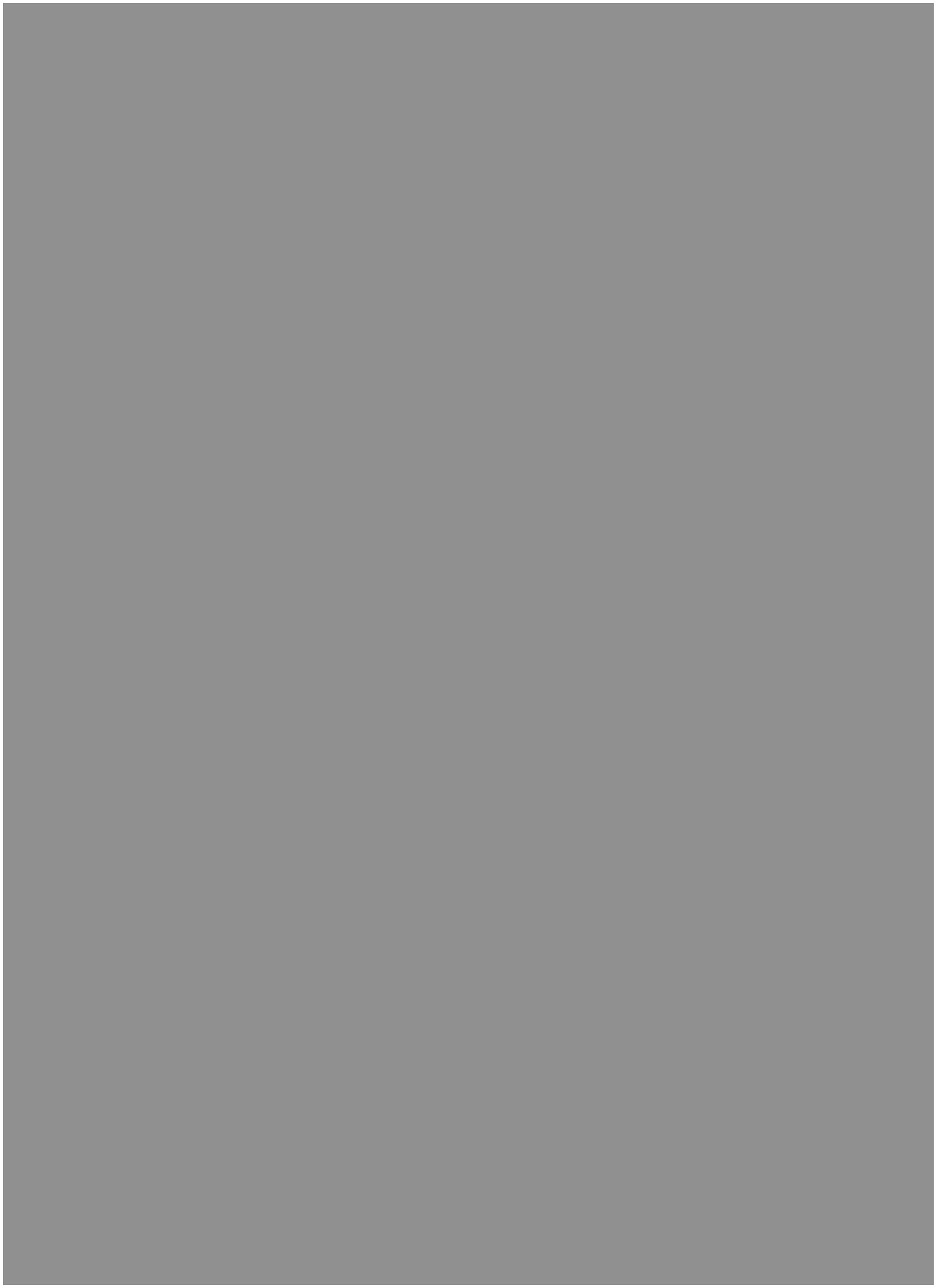
THE SWEDISH HEALTH CARE SYSTEM

The Swedish health care system is heavily subsidized by county and municipal taxes. The fees paid by patients for appointments, hospital stays, surgical and non-surgical procedures represents a fraction of the actual costs. Patients who are hospitalized are charged a daily fee of maximally 100 Swedish kronor (SEK, approximately 10 Euros or 11 US dollars on 21 April 2015), regardless of the cause of hospitalization, the type and number of procedures performed or the level of care. A visit to the doctor costs 100–300 SEK. If the doctor issues a referral, the patient is not charged any additional fee. The fee for an appointment with a nurse is 50-220 SEK.

The amount a patient pays for health care is subject to a ceiling, which is referred to as high-cost protection. This ensures that no citizen pays more than 1,100 SEK over a period of twelve months. Once a citizen has paid 1,100 SEK, the citizen receives a free pass that is valid for the remainder of the 12-month period. All prescriptions issued by physicians and nurses are subject to high-cost protection

of 2,200 SEK. Individuals below the age of 20 are seldom charged for any appointments.

In summary, there are fundamental differences between studies conducted in the United States and those conducted in Sweden. Access to and use of health care is a significant concern in studies from the United States. However, this does not invalidate or compromise the findings, it merely implies that American and Swedish studies are not measuring the same entities.



2 AIMS

The primary objective of this thesis was to investigate the impact of socioeconomic status and ethnicity on diabetes. The secondary objective was to reassess evidence in favour of the spring harvest theory and examine alternative methods to monitor the incidence of type 1 diabetes.

Specific aims:

- Examine the incidence of type 1 diabetes by means of capture-recapture; determine if previous studies are valid; examine if the Prescribed Drug Register can be used to monitor the incidence.

- Examine how income, education, marital status, immigrant status and sex relate to cardiovascular disease and death among individuals with type 1 diabetes.

- Examine trends in risk factors among individuals with type 1 diabetes from 1996 to 2014, in the overall cohort and in relation to sex, income and education.

- Examine the effect of ethnicity on glycaemic control in a cohort of patients with type 2 diabetes.

- Examine the impact of ethnicity on the risk of heart failure in diabetes.

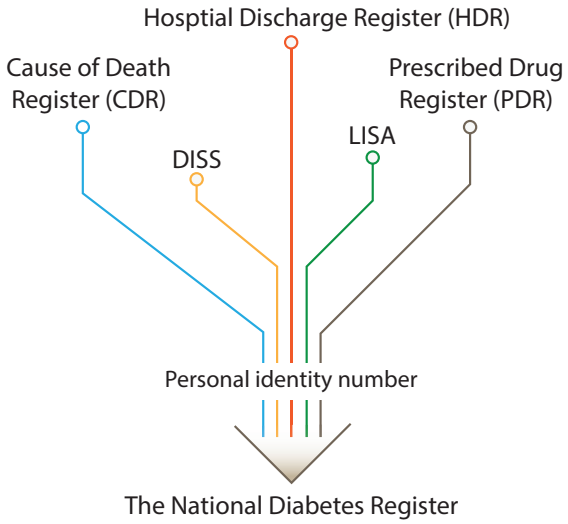
This chapter describes the data sources, methods and ethical considerations. The first section deals with the data sources. Ethical aspects are discussed in the second section. The final section describes statistical and epidemiological concepts relevant to the present thesis.

3

PATIENTS AND METHODS

DATA SOURCES

The Swedish National Diabetes Register (NDR) is the foundation of the present thesis. We linked the NDR to the Hospital Discharge Register, the Cause of Death Register and the Prescribed Drug Register, all of which are kept by the Swedish National Board of Health and Welfare (NBHW). To obtain data on socioeconomic variables and ethnicity we linked our data to the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) kept by Statistics Sweden. In study I we used the Diabetes Incidence Study in Sweden (DISS), which is operated by researchers from several counties.



Study	Sources
Study I	NDR, DISS, PDR
Study II	NDR, CDR, HDR, LISA
Study III	NDR, LISA
Study IV	NDR, LISA
Study V	NDR, LISA, CDR, HDR

Figure 6 | The present thesis is based on a fusion between the NDR and several databases, all but one (DISS) kept at the National Board of Health and Welfare and Statistics Sweden. Abbreviations: LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies; DISS: The Diabetes Incidence Study in Sweden.

THE SWEDISH NATIONAL DIABETES REGISTER

The Swedish Society for Diabetology initiated the NDR in 1996 as a tool for quality control of diabetes care and benchmarking against treatment guidelines. Physicians and nurses at participating primary healthcare centres and hospital outpatient clinics report patient data at least once a year, either online or by direct transfer of data from electronic medical records. The report includes information on clinical characteristics, results of laboratory analyses, medications

and presence of complications. Participation is optional but many counties encourage healthcare centres to do so and the level of ascertainment is high. Roughly 90% of all individuals with type 2 diabetes and 95% of individuals with type 1 diabetes are enrolled in the NDR.[109,207] The high participation is partly due to a long tradition of using quality registers in Sweden. Quality registers have become implemented as a routine part of clinical practice. A previous validation against patient charts showed that 94% of the entries in the NDR were valid.[208]

THE NDR FOR RESEARCH

Although the primary purpose of the NDR is quality assurance, it can be used for research. In June 2014 the NDR had enrolled 536,446 persons who contributed almost five million appointments. Clinical data from the NDR can be linked to any database that uses the unique 12-digit personal identification number. This identification number is virtually ubiquitous for all personal errands in Sweden.

Population databases are abundant in Sweden. For example, it is possible to obtain data on educational level, income, family and housing circumstances, drug prescriptions, hospital admissions, country of birth, birth data, mother's pregnancy data, social security, military enlistment etc., through linkage with databases at the National Board of Health and Welfare and Statistics Sweden. The government has operated some of these registries for more than half a century. Linkage with other registries is also a straightforward process.

Clearly, the NDR provides unique opportunities to study diabetes. It boasts with nationwide coverage, abundance of variables and vast data linkage possibilities. This provides an exceptional source to answer important research questions.[209]

REGISTERS KEPT BY THE NATIONAL BOARD OF HEALTH AND WELFARE AND STATISTICS SWEDEN

The Hospital Discharge Register, which is part of the National Patient Register, has complete nationwide coverage since 1987. It includes information about primary and secondary diagnoses (classified according to the International Classification of Disease [ICD] system) and surgical and non-surgical procedures. Validation studies, carried out by means of patient chart reviews, confirmed a high validity with positive predictive values of 85-95 % for most diagnoses.[210,211] The Cause of Death Register was established in 1961 and contains information about dates and causes of death for everyone in the population register.[212-214]

The Prescribed Drug Register, which was established in 2005, contains information about all prescriptions that have been filled.[215]

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) has kept annual registers since 1990 for everyone aged 16 or older who was in the population register each year. LISA includes information about socioeconomic variables, such as educational level, income, country of birth, occupation, etc., and is kept by Statistics Sweden.[100]

THE DIABETES INCIDENCE STUDY IN SWEDEN

The Diabetes Incidence Study in Sweden (DISS) was launched in 1983 and includes incident cases aged 15–34 years diagnosed at departments of paediatrics, internal medicine and endocrinology.[216,217] The patients are reported on a data entry form. Each clinic appoints a physician to serve as a contact, provide information about the DISS and make sure that new cases are reported. Classification of the diabetes type is based on a clinical assessment, as well as an analysis of islet cell antibodies since 1998. The DISS has long been the only source to estimate the incidence rate among individuals older than 14 years. However, the level of ascertainment in the DISS is uncertain. Previous checks have relied on data from 1983 to 1997, including roughly 15% of the at-risk population.[33,218] Swedish reports that have contributed substantially to the spring harvest theory are based on a fusion of the DISS and the Swedish Childhood Diabetes Register (SCDR). Started in 1977, the SCDR includes patients aged 14 and younger. The SCDR participates in international multicentre studies and has a level of ascertainment approaching 100% through stringent validation procedures and vigorous data collection.[219]

DIABETES DIAGNOSIS

In Sweden the WHO diagnostic criteria are used to diagnose diabetes. However, HbA1c has been accepted as a diagnostic criterion only since January 2014.[220,221]

ETHICAL CONSIDERATIONS

Studying the effect of ethnicity and socioeconomic status is a delicate matter. Careful formulation of hypotheses and reporting is crucial to avoid stigmatization and discrimination. The aim of the present thesis was to gain a greater understanding of socioeconomic and ethnic disparities in diabetes. We hypothesized that socioeconomically disadvantaged groups and immigrants would exhibit adverse characteristics and outcomes. Identifying and estimating

the excess risk among these groups would provide opportunities for reducing the disparities. Socioeconomic variables and ethnicity are easily accessible risk markers that could improve risk prediction. However, despite our motives there is an inevitable risk of violating the integrity of the participants. Immigrants and ethnic minorities are of particular concern, and these ethical issues have been discussed previously.

All patients have approved entry in the NDR and they have been informed that data could be used for research. They have not, however, provided consent to any specific study. It is likely that some patients would oppose being included in these studies. Obtaining written informed consent for the large number of patients included would have been unfeasible and compromised many aspects of the studies. We will argue that the following measures guarantees the participant's integrity:

– The NBHW and Statistics Sweden de-identified all participants before returning matched data to the NDR.

– The participant's geographic location in Sweden was not assessed.

– Analyses were conducted and reported at the group level.

– We did not study ethnic categories *per se*. We studied larger geographic groups, although this coincides with ethnicity.

– We did not highlight disparities that did not represent opportunities for improving diabetes care.

We obtained ethical approval to conduct our studies by the Regional Ethical Review Board in Gothenburg, Sweden.

STATISTICAL METHODS

The studies included in this thesis make use of conventional statistical and epidemiological methods to address bias, confounding, covariate adjustment and statistical inference. This section provides discussions regarding survival analysis, mixed-effects models, capture-recapture methods and implications of missing data. These topics are relevant to the present thesis as well as registry-based research in general.

SURVIVAL ANALYSIS

Survival analysis is applied when the time to an event is of interest. The purpose of survival analysis is to examine the nature of the survival distribution. The events of interest in the present thesis were typically death or cardiovascular events.

The survival distribution can be estimated with descriptive unconditional methods (e.g. the Kaplan-Meier method) or by means of regression models. Unconditional methods are appropriate when the groups that are being studied are directly comparable or when the analyst seeks to visualize the survival function. Regression models allow for modelling of the relationship between survival and a set of predictor variables, commonly referred to as *covariates*.

The survival function is based on two quantities for each patient; the time a patient was observed and an indicator denoting whether follow-up ended with an event or not. Patients that do not experience an event are *censored*. Three types of censoring occur. *Right-censoring* occurs when the observation time ends before the event has occurred. This can be due to emigration, loss of follow-up for other reasons or simply end of follow-up. *Left-censoring* occurs when the commencement of the exposure is unknown. When both censoring types occur, an individual is said to be *interval-censored*. Censoring complicates the likelihood function and hence the estimation of survival models. Careful consideration of the nature of the censoring is important. In some instances censoring can be informative and neglecting this may introduce bias. Regarding the studies in the present thesis, we cannot rule out that we have underestimated the hazard among immigrants in study II and study V, since immigrants are more likely than Swedish natives to stay abroad and experience an event. This is more likely among elderly immigrants who tend to return to their country of birth. This phenomenon is referred to as *salmon bias.*

The survival distribution is described in terms of two functions: the *survival function S(t),* defined as the probability that a person survives past time *t* and the *hazard function h(t)*, defined as the instantaneous failure rate:

$$h(t) = -\left\{\frac{\left[\frac{dS(t)}{d(t)}\right]}{S(t)}\right\}$$

Where *h(t)* denotes the probability that a patient will experience an event at the next instant, given that the patient survived until time *t*.

Descriptive statistics for survival analysis are based on an estimate of the survival function. It is important to get a sense of the survival distribution. The survival curve reveals timing and rate of events. The Kaplan-Meier method is the most commonly used technique for this purpose. It is used to display the proportion of patients that survive past a certain time point. The median survival time is of interest, as the mean cannot be estimated reliably. Kaplan-Meier curves start at 1.0, since the probability of surviving beyond time 0 is 1. For each event the line steps down until follow-up ends. Survival curves can be obtained and compared (with the log-rank test) for different groups. The Kaplan-Meier method has been used in studies IV and V.

It is not possible to control for covariates with the Kaplan-Meier method. To estimate the effect of socioeconomic status and ethnicity on outcomes, after controlling for covariates, we use regression models.

Recall that the hazard function *h(t)* for an event at time *t* is the instantaneous event rate among patients who have not yet experienced the event. It is related to the survivor function *S(t)*. The power horse of survival analysis, *Cox proportional Hazards model*, is derived from the hazard function. The model is defined as:

$$h(t) = h_0(t) \times e^{(b_1x_1 + \ldots + b_kx_k)}$$

$\mathbf{h_0(t)}$ is the baseline hazard at time t
$\mathbf{x_1, \ldots, x_k}$ are k independent covariates
the exponent gives the linear regression form of the predictors x_1, **…**, x_k.

Dividing through by the baseline hazard (h_0) and taking natural logarithms yields:

$$\ln\left[\frac{h(t)}{h_0(t)}\right] = b_1x_1 + \cdots + b_kx_k$$

The left-hand side is the log of the hazard ratio.
The right-hand side is an ordinary regression equation.

Cox's model implies that the ratio of the hazard functions for two patients is constant over time because the term $h_0(t)$ cancels from the ratio and the other terms are free of *t*. The model does not assume any distribution for the baseline hazard. The hazard ratio for a specific predictor is interpreted as if all other variables are held constant. It is, in terms of magnitude, similar to relative risk but less extreme than odds ratios. A Wald confidence interval is sufficiently precise.

Cox's model is, with few exceptions, always preferred when performing survival analysis on observational data. The model is semi-parametric. It makes parametric assumptions concerning the effect of the predictors on the hazard function, but makes no assumption regarding the nature of the hazard function $h(t)$ itself. The model has the advantage of not needing to specify the baseline hazard, which can take any form. It is assumed that predictors act multiplicatively on the hazard function and that the predictors are linearly related to log hazard or log cumulative hazard. Outliers have little effect on the model since it uses the rank ordering of the survival times.[222,223] The model is estimated by means of partial likelihood, which is less efficient than parametric methods, which use maximum likelihood. In the studies included in the present thesis, the assumption of linearity is tested by expanding continuous predictors into restricted cubic splines and then evaluating the spline terms.

The proportional hazards assumption, which must be fulfilled, states that there are no time by predictor interactions. In other words, the predictors must exert the same effect on the hazard function at all values of *t*. We examined this by assessing Schoenfeld residuals and plotting *log(-log S(t))* against *t*. Formal hypothesis tests (p values) were not used.

An exclusive feature of Cox's model is its ability to adjust for variables that are not modelled. This is done by stratification. It is prudent to stratify by variables that are difficult to model or do not satisfy the proportional hazards assumption. The underlying hazard function is allowed to vary across levels of the stratification variable. Survival times are ranked independently in each stratum. A mutual vector of model coefficients is then fitted in the entire data set. This can be viewed as pooling the estimates from the strata.

In study II we present Cox adjusted survival curves, which are also referred to as *Cox-Kalbfleish-Prentice* curves. These curves are derived by fitting a Cox model and then predicting survival conditional on a set of covariates.

In some situations there may be unmeasured factors that could affect the survival. Participants might be heterogeneous and represent different underlying survival distributions. *Cox frailty models* can handle such data by incorporating a random effect into the hazard function to account for this heterogeneity. Frailty models can also be used to analyse repeated events. A frailty term for ethnicity was tested in study V but this did not yield any difference in the estimates.

Cox's model can be generalized to include time-dependent covariates and thus take repeated measurements into account. We model virtually all covariates (except from sex, age at inclusion and duration of diabetes at inclusion) as time-dependent predictors. This is appropriate since we had access to updated information of the covariates that change during follow-up. The course of these covariates might be more informative of the survival experience than their baseline values. This is done by means of the counting process formulation of Andersen and Gill.[224]

We have also fit survival models by means of Poisson regression, under the framework of generalized linear models. Survival time was used as an offset in the model. Poisson regression is fully parametric and assumes that the hazard is both proportional and constant over time. Poisson regression yields incidence rates in absolute figures as well as incidence rate ratios. The latter is comparable to hazard ratios derived by means of Cox regression. Poisson regression was used in study V.

MIXED-EFFECTS MODELS

The National Diabetes Register is a large longitudinal database with repeated measurements, unbalanced and missing data. The latter two are inevitable in any large study. Participants enrolled in the National Diabetes Register are examined repeatedly, at different points in time and with varying time intervals. The longitudinal nature provides unique opportunities to study the changes in response variables over time but it also complicates the analyses. Statistical techniques that handle longitudinal and complex data structures have evolved remarkably in the last decades. Mixed-effects models stand out as the most versatile class of models to handle such data. Similar to traditional regression models, mixed-effects models examine the relationship between predictor variables (covariates) and a response variable. The ability of mixed-effects models

to account for correlation and dependency between observational units (i.e. individuals), as well as handling hierarchies, makes them suitable for longitudinal data. Correlation and dependency between observational units violates fundamental assumptions of ordinary least-squares regression.

A mixed-effects model is defined by the presence of a factor (categorical) variable that represents the dependency or hierarchy between observational units. In the studies included in the present thesis, the units are the patients and the factor variable is the patient's identity. The patient's identity may be specified with any labelling, since the labelling itself is irrelevant. The crucial step is to incorporate the dependency for observations from the same patient. We model patient as a random effect in the model, which means that the dependency between observations are accounted for, but we do not obtain coefficients for patient.

The concept of fixed effects and random effects is fundamental in mixed-effects models. The term *effect* refers to the estimated parameters (coefficients, standard errors etc.) for a covariate. *Fixed effects* are covariates that have fixed levels, they are reproducible and the levels by themselves are of interest. Sex (male vs. female) is a fixed effect: the patient's sex will (presumably) not change if it was to be re-measured and we are generally interested in differences between males and females. Ethnicity, from this point of view, is a fixed effect. The patient, however, is a *random effect*: patients are randomly drawn from the population; the patient identity in itself is of no interest; if we were to sample again from the population we would include a different set of patients and there is dependency among the observations from the same patient. Any model that incorporates random effects is referred to as a mixed model, as it must also include at least one fixed effect (the intercept in a null model).

Studies III and IV mainly handle repeated measurements over time. We incorporated random effects for patient (which yields a random intercept) and time (which yields a random slope).

Unbalanced design (which arise due to the fact that subjects are examined a varying number of times and at various occasions) and missing data is accommodated in mixed-effects models, which makes it unnecessary to impute missing data. Therefore we did not impute missing data in studies III and IV.

COVARIANCE

The correlation between measurements on the same individual implies that knowledge of the value of the response at one occasion provides a likely value of

the response on a future occasion. In other words, the values are *correlated*. Moreover, the variance of the response will change over time, a phenomenon called *heterogeneous variability*. Correlation and heterogeneous variability – collectively referred to as *covariance* – invalidates the use of traditional multiple regression. Covariance must not only be accounted for, it should also be modelled correctly to obtain reliable estimates of the fixed effects. Study IV was analysed in SAS (Statistical Analysis Software, SAS Institute Inc., version 9.3), which allows for explicit selection of covariance structure (e.g. autoregressive(1), compound symmetry, unstructured, Toeplitz). We noted that the difference in estimates were small but the models converged more easily with an autoregressive(1) structure. Study III was analysed in R (R Foundation For Statistical Computing) using lme4,[225] which do not provide an easy means for defining the covariance structure. lme4 constructs the covariance matrix depending on the structure and formulation of the random effects.

USE OF MIXED-EFFECTS MODELS

Studies III and IV include linear and generalized (binomial family) mixed-effects models. In the linear mixed-effects models we have attempted to describe the change in HbA1c and other continuous dependent variables over time. This is a common application of linear mixed-effects models. Consider the following situation:

$$E\left(Y_{ij}|Time_{ij}\right) = \beta_0 + \beta_1 \times Time_{ij}$$

$E\left(Y_{ij}|Time_{ij}\right)$ *is the mean response* $(HbA1c)$ *at time* j
β_0 *is the population intercept*
$\beta_1 \times Time_{ij}$ *is the population slope*

$Time_{ij}$ denotes the timing of the measure on the i_{th} patient at the j_{th} occasion. The population intercept β_0 is the mean HbA1c when $Time = 0$, which could be considered as baseline. β_1 is the coefficient for the rate of change in the response variable for one unit increase in time. This equation describes the average change in the entire population and thus fails to recognize that individuals in the population are heterogeneous. HbA1c at baseline may vary, as can the rate of change in HbA1c over time. Mixed-effects models overcomes this by incorporating the intercept and slope for each individual, in addition to the population parameters:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i}) \times Time_{ij} + e_{ij}$$

The left-hand side of the equation denotes the response for patient i at time j. $(\beta_0 + b_{0i})$ denotes the intercept for individual i. $(\beta_1 + b_{1i}) \times Time_{ij}$ denotes the slope for individual i. e_{ij} denotes the random error. The interpretation of β_0 and β_1 has not changed. Random effects are denoted by b_{01} and b_{1i}, *which* represents the difference between the population mean (intercept and slope) and individual i.

CAPTURE-RECAPTURE METHODS

Incidence and prevalence data exists for most diseases, typically through research databases or health registers. Obtaining unbiased estimates of incidence and prevalence requires data with high level of ascertainment and use of correct as well as consistent classifications. In order to reliably estimate incidence, the time of onset of the disease must be recorded. Furthermore, to address long-term trends it is crucial to maintain the high level of ascertainment over time. This can be a tremendous challenge.

The reliability of a register must not be judged by its methods or the organization operating it. Reliability can only be judged by using formal techniques to estimate the number of cases that are missed by a register. Missed cases will underestimate the incidence or prevalence while a varying level of ascertainment will lead to biased trends.

Capture-recapture methods can be used to estimate the completeness of any register. These methods are used widely in epidemiology to estimate prevalence of diseases.[226,227] Capture-recapture was originally developed to estimate the size of animal populations. It was carried out by sampling an animal population on two occasions. On each occasion the researchers captured, tagged and then released as many animals as possible. The total number of animals in each sample and the number of animals captured twice is used to calculate the true size of the population. This is an attractive method since it allows for use of incomplete registers to estimate the total number of units in the population.

Both simple equations and regression models can be used to obtain capture-recapture estimates. Regression models are more flexible and thus preferred. At least three registers should be included in the procedure and two assumptions should be respected:

– **Dependency**: capture in one register should not modify the risk of being captured in other registers.

– **Heterogeneity**: all individuals in the population should have equal risk of being captured.

Violation of these assumptions may lead to biased estimates of the true population size.

Consider the scenario where one attempts to estimate the prevalence of type 1 diabetes by using records from hospital outpatient clinics, hospital discharge records and a cause of death register. Capture-recapture estimates could be seriously biased due to potential dependence between the sources. For example, patients admitted to hospitals are likely to be referred to the outpatient clinic for follow-up after discharge. Being admitted to hospital will therefore modify the probability of being seen in the outpatient clinic. It is also likely that individuals with severe disease are more likely to be captured in the hospital discharge register, since the healthier individuals do not need in-hospital care. It follows that capture-recapture must be done carefully to avoid obtaining biased results.

Dependence and heterogeneity is best examined by log-linear regression models; the interactions between sources can be modelled by means of conventional regression approaches. We used log-linear models in study I and observed dependency between the sources. This was addressed by incorporating interaction terms in the models.

Capture-recapture methods may produce biased estimates of the population size if one source captures very few cases. The resulting estimates may range from heavily underestimated to implausibly large. We suspected that this was the case in study I, as discussed in the paper.[227]

For a comprehensive review on capture-recapture methods, we refer the reader to the references.[226-229]

MISSING DATA

This is an important topic throughout the present thesis. Missing data can seriously compromise the validity and inferences of any study. Awareness of the implications of missing data has increased in the last decades and methods to tackle the issue have evolved in parallel. Approaches to handle missing data depend on the cause leading to missing values. The definitions of missing data in Table 1 are cited from *Sterne et al.*[230]

TABLE 1. TYPES OF MISSING DATA

Missing completely at random (MCAR) There are no systematic differences between the missing values and the observed values. For example, blood pressure measurements may be missing because of breakdown of an automatic sphygmomanometer
Missing at random (MAR) Any systematic difference between the missing values and the observed values can be explained by differences in observed data. For example, missing blood pressure measurements may be lower than measured blood pressures but only because younger people may be more likely to have missing blood pressure measurements.
Missing not at random (MNAR) Even after the observed data is taken into account, systematic differences remain between the missing values and the observed values. For example, people with high blood pressure may be more likely to miss clinic appointments because they have headaches.

If data is MCAR it will not affect inferences or validity of the study (available data is unbiased) but it will reduce the power of the study. However, it is virtually impossible to verify that data is MCAR and most statistical techniques assume that data is MAR. Subject matter knowledge and data exploration must guide the decision about the mechanism leading to missing data.

HANDLING OF MISSING DATA

A brief description of the most common methods for handling missing data follows.

Complete case analysis, in which cases with missing data are excluded from the analysis, is discouraged. Valid estimates from complete case analyses require that data is MCAR, which is an unrealistic and unverifiable assumption. Complete case analysis leads to bias and reduced power. It is, however, acceptable to perform complete case analyses as sensitivity analyses.[231]

Simple imputation commonly involves replacing missing values with a single mean or using *last observation carried forward* (alternatively *first observation carried backward*) if the study is longitudinal. This method is preferred over complete case analysis, but still inferior to multiple imputation. The reason for this is that simple imputation do not account for the uncertainty of the imputation, which may lead to false narrow confidence intervals.[230]

Imputation by statistical models can be done by means of weighted estimating equations and multiple imputation. The latter has emerged as the preferred method to impute missing data in medical research. It uses model-based predictions, derived from the data itself, to generate multiple sets of plausible values for missing data. Regression models provide more reliable imputations since the uncertainty can be taken into account. Confidence intervals and p values are more conservative as compared with simple imputation. Multiple imputation generally assumes that data is MAR, which is more realistic than MNAR. However, as for MNAR, this assumption cannot be verified and additional sensitivity analyses are prudent.

MULTIPLE IMPUTATION AND MICE

Multiple imputation has emerged as the preferred means of handling missing data in medical research. It involves filling in missing data several times by creating multiple complete data sets. The missing values are filled in based on the observed data and the relations observed in the data for other participants. Each missing value is filled in several times to account for the uncertainty of the predictions.

We used Multivariate Imputation by Chained Equations (MICE) in study II. MICE is also referred to as *fully conditional specification (FCS)* or *sequential regression multiple imputation*. It is probable one of the best methods to fill in missing data. MICE handle continuous, binary and ordinal data in a robust fashion. It is used under the assumption of MAR and operates by generating a series of regression models whereby each variable with missing data is modelled conditional on the other variables in the data. Each variable is modelled according to its distribution. Interested users are referred to references.[230-232]

ROLE OF BIAS AND ERROR

Most discussions of bias and error fall under the headings of *selection* (of the study population), *information* (collection, analysis, interpretation) and *confounding*. These phenomena are unavoidable concerns of all epidemiological studies. A brief discussion is therefore warranted.

In planning, analysing and interpreting the studies included in the present thesis we have made an effort to minimize the role of error and bias. It is, however, unlikely that observational studies can eliminate bias and confounding. Indeed, even randomized trials may suffer from bias that invalidates the results. Proper handling of bias and error increases the internal and external validity of a study. It also allows for reliable estimates of the relation between exposure and outcome.

BIAS

Bias may be either negative (i.e. underestimate the effect of an exposure) or positive (i.e. overestimate the effect of an exposure).

The nature of the data in the National Diabetes Register and our sampling methods assure minimal *selection and sampling bias*. For example, 95% of all individuals with type 1 diabetes in Sweden are included in the National Diabetes Register and they are all eligible for inclusion in our studies. The subjects are not asked specifically for enrolment in the studies (ethical considerations have been discussed previously). Any sample drawn from the register is therefore likely to represent the target population. Moreover, we apply few exclusion criteria; in general we only exclude individuals that have already – at the time of their index observation – experienced the event of interest.

Healthcare access bias is, as discussed previously, very small in the studies included in the present thesis. Patients entered in the National Diabetes Register, as well as those admitted to hospitals and outpatient clinics, should represent a random sample from the population. In a market-based health care system this may be a substantial issue since the population presenting in hospitals and other clinics may not be representative of the background population. They may be more a more affluent subgroup or veterans that introduce *survival bias*.

We tackle the problem of *competing risks* by assessing several (competing) outcomes separately as well as performing formal competing risk analyses (study V). We have avoided outcomes that are specific causes of death, since such outcomes may lead to competing risk situation.

We cannot rule out *Neyman bias*, which could have been introduced if the exposure under study (income, education, ethnicity) is associated with very high risk of the outcome. It is possible that some socioeconomic or ethnic groups are at such high risk that they have developed the disease early, before start of inclusion, and thus fulfilled the exclusion criteria. It is possible that the findings in study II, regarding the risk of developing cardiovascular disease, is a reflection of Neyman bias. We observed that individuals in the lowest income quintile had somewhat lower risk of developing cardiovascular disease than participants in the second lowest income group.

Another concern is *spectrum bias*, which arise if the definition of cases is too narrow. This could happen with regards to definition of diabetes types. We believe that our epidemiological definitions of type 1 and type 2 diabetes are well-balanced, as discussed previously. If we had included islet antibodies and body mass index in our definitions, it is possible that the encircled population would not have been representative of the target population. Implications of the epidemiological classifications have been discussed previously.

We have prepared manuscripts for all the research questions originally formulated and therefore not succumbed to *publication bias.* The research philosophy at the National Diabetes Register is that every finding is interesting, regardless of the direction.

In study IV it is reported that immigrants had more appointments to their clinic than Swedish natives and that immigrants had a greater risk of developing albuminuria. This could be due to *detection bias*, which implies that an exposure (ethnicity) may influence the detection of disease by more intensive health care contact. We have not accounted for this in the study, since we did not adjust for number of appointments. We do, however, argue that the large difference in the risk of albuminuria will not be abolished by controlling for a covariate that differed little between the groups.

Loss to follow-up is a negligible problem in these studies, with a certain reservation for *salmon bias*, which was discussed previously. We studied hard endpoints that should be detected in the databases that were merged with

the National Diabetes Register. The Hospital Discharge Register, the Prescribed Drug Register and the Cause of Death Register are intensively regulated to avoid loss of data. Transfer of data is carried out electronically and data is matched through the personal identity number. With regard to longitudinal studies of risk factors (studies III and IV), the great majority of all participants have repeated measurements in the National Diabetes Register.

The precision of the classifications of ethnicity, income and educational level is robust. Data were obtained from the NBHW and Statistics Sweden. Swedish law governs the mandatory registration of all citizens' country of birth, income and educational level. Immigrants' country of birth is registered at arrival in Sweden. Immigrants may also apply for qualifying their earlier educational credits. It cannot, however, be guaranteed that foreign educations are fully credited in Sweden. It is likely that some immigrants may have a higher education than apparent. This would reduce the hazard associated with low education.

Random measurement errors occur in the National Diabetes Register as in any other database. When measurement errors are random, they vary unpredictably around their true values. It can be due to imprecision of measurement tools or biological variability. Systematic measurement errors occur when the errors have a particular direction, e.g. they tend to be higher than the true values.[233] Paradoxically, systematic measurement errors are often addressed by researchers, whereas random measurement errors are neglected due to a misunderstanding. It is true that the average error for a variable with random measurement error will be zero, but it is not certain that it will not affect the association between exposure and outcome. Random measurement error can cause attenuation or "flattening" of the slope of the line describing the relation between the independent variable and the dependent variable. This is known as *regression dilution bias*.[234] The regression slope is biased towards zero when random measurement error occur in an independent variable. Random measurement error in a dependent variable will inflate the standard error and widen the confidence interval.[235] The large sample sizes drawn from the NDR will not account for this; a large sample size will reduce the impact of measurement errors in the dependent variable, but it will have no effect on the bias for the independent variable. Studies that only assess covariates at baseline are at particular risk of regression dilution bias. The studies in the present thesis are longitudinal and participants are examined repeatedly, providing updated values of the majority of the predictor variables. We have not restricted any analyses to the baseline values, all observations have been used. We appreciate that the

course of the covariates might be more informative of their effect than their baseline values.

NON-OVERLAPPING DISTRIBUTIONS

Studies II through V of the present thesis include various forms of regression analyses for estimating the relationships among variables. The purpose was to compare outcomes between socioeconomic and ethnic categories after accounting for important covariates. As is evident from the descriptive tables of studies II through V, there are marked differences in the distributions of several important covariates, in particular age and duration of diabetes. Regression models have been shown to perform poorly in situations where there is insufficient overlap in the distribution of important covariates,[236,237] but their standard diagnostics do not involve checking this overlap. Furthermore, if differences in the covariate distribution are large, the individuals that are comparable (i.e. overlap) may not be representative of their populations. For example, Swedish natives that develop type 2 diabetes in the age-range where the disease commonly develops in South Asians, may not be representative of the average Swedish person with type 2 diabetes. With regard to survival analysis, if there is insufficient overlap and few or no events occur among individuals that are comparable, the estimates will be unreliable. This shortcoming may not be overcome by incorporating spline terms and interactions, although such means could be tempting.

Matching methods may have advantages over regression approaches; these methods highlight areas of the covariate distribution where there is not sufficient overlap between the groups. Matching also allow for assessing the quality of the inferences, by elucidating the overlap in the distribution and density of the covariates. There are several possibilities to perform matching. Matching on key covariates (age and sex) was attempted in study V, but the results remained unchanged. We did not, however, perform propensity score matching, which could have been used to compare immigrants with Swedish natives. These methodological difficulties will be examined in detail in future studies.

CONFOUNDING

Confounding is the distortion of an association by other factors that influence both the outcome and exposure under study. It arises when the groups that are being compared differ with respect to a risk factor that affects the outcome. Confounding mixes up causal and non-causal relationships. True causal risk factors and non-causally proven predictors of cardiovascular

disease are well known. We have adjusted for virtually all known and presumed predictors of the outcomes studied in the present thesis. Regression adjustment for these confounders should have, provided that misclassification is not a significant problem, eliminated the bias from confounding.

This chapter describes study design, participants and outcomes. Details are available in the attached documents.

4
STUDY DESIGN

STUDY I

BACKGROUND

The incidence of type 1 diabetes has increased 3% annually since the 1980s. The steepest increase has been noted in the age range 0–4 years and it appears that onset has shifted to younger age groups.[25] It has been suggested that the increase in persons aged 14 years and younger represents a left shift in the age of onset and that this increase is mirrored by a corresponding decrease in the remaining population. This idea has been referred to as the *spring harvest theory*. Two out of three noteworthy studies supporting the spring harvest theory originate from Sweden.[33-35] Studies from Finland, Italy and the United Kingdom reject the spring harvest theory by reporting stable or increasing incidence up to the age of 39.[36-38]

HYPOTHESIS

We hypothesized that previous Swedish studies were invalid due to diminishing level of ascertainment in the DISS register, which covers individuals aged 15-34 years.

AIMS

We reassessed the incidence of type 1 diabetes in the age-range 0–34 years in Sweden. We used three nationwide registers and capture-recapture methods to estimate new incidence rates. We also explored whether the incidence could be monitored by means of the Prescribed Drug Register (PDR) alone.

METHODS AND PARTICIPANTS

We used the NDR, the DISS and the PDR to calculate the incidence rates in each register separately and jointly by means of capture-recapture methods.[226,227]
Definition of type 1 diabetes in the PDR: Men receiving at least one prescription and women receiving at least three prescriptions (intending to exclude gestational diabetes) of insulin were classified as having type 1 diabetes if they had never been given oral glucose-lowering drugs. The date of receiving the first prescription was regarded as onset of the disease.
Definition of type 1 diabetes in the NDR: Ninety-five percent of the subjects of the study had been diagnosed with type 1 diabetes on the basis of a clinical assessment. The remaining 5% were classified as type 1 diabetes on the basis of

the epidemiological definition discussed previously. Year of disease onset is available in the NDR.
Definition of type 1 diabetes in the DISS: Classification of the diabetes type is based on a clinical assessment, as well as an analysis of islet cell antibodies.

We calculated incidence rates in the NDR (20–34 year olds for 2006–2011), the DISS (15–34 year olds for 2006–2009) and the PDR (0–34 year olds for 2007–2011) separately. We used a three-sample capture-recapture procedure to estimate the level of ascertainment in each register. For this we used a sample of all cases in the 20–34 age group with disease onset in 2009. Ascertainment for each register was calculated as the actual number of cases divided by the capture-recapture estimate. We also used the capture-recapture method to estimate new incidence rates by age group and sex in 2007–2009.

STUDY II

BACKGROUND

The impact of socioeconomic status on cardiovascular disease and mortality in type 1 diabetes has not been established. Previous studies, which are hampered by small samples and inadequate adjustment for confounders, suggest either a modest effect or no effect of socioeconomic status on death and cardiovascular disease.[140,141,238]

HYPOTHESIS

We hypothesized that income, educational level, marital status and immigrant status are independent predictors of cardiovascular disease and death in type 1 diabetes.

AIMS

We aimed to study the gradient in a large cohort of patients with type 1 diabetes.

METHODS AND PARTICIPANTS

We included 24,947 individuals (220,281 appointments) with type 1 diabetes, without a history of cardiovascular disease, who had at least one listing in the NDR between 2006 and 2008. Type 1 diabetes was defined on the basis of epidemiologic data. We retrieved data from the Cause of Death Registry, the Hospital Discharge Register and the LISA. Patients were followed until a first incident event, death or end of follow-up. The association between socioeconomic variables and the outcomes was modelled using Cox regression, with rigorous adjustment for known and presumed risk factors and confounders.

STUDY III

BACKGROUND

The last decades have witnessed many advances in the treatment of type 1 diabetes. Intensive insulin therapy, lowering of blood pressure and lipids,[40,239,240] as well as improved methods for insulin delivery and glucose monitoring should have improved risk factor control.[241,242] However, long-term trends in cardiovascular risk factors have not been studied in people with type 1 diabetes.

HYPOTHESIS

We hypothesized that risk factor control in type 1 diabetes has improved since 1996 but there are socioeconomic disparities in the improvements.

AIM

We used the NDR to investigate long-term trends in six cardiovascular risk factors, from 1996 to 2014. Trends were assessed in the overall cohort and in relation to sex, income and education.

METHODS AND PARTICIPANTS

We included all individuals with type 1 diabetes who had at least one listing in the NDR between January 1, 1996, and April 22, 2014. We used the epidemiological definition of type 1 diabetes. Trends in glycaemic control (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), smoking and physical activity were assessed. We used generalized mixed-effects models to perform the analyses.[225]

STUDY IV

BACKGROUND

Studies on ethnic disparities in glycaemic control have been contradictory and compromised by excessively broad categories of ethnicity and inadequate adjustment for socioeconomic differences.

AIM

We aimed to study the effect of ethnicity on glycaemic control in a large cohort of patients with type 2 diabetes.

HYPOTHESIS

We hypothesized that despite equitable access to care and adjustment for socioeconomic confounders, ethnicity would be an independent predictor of glycaemic control.

METHODS AND PARTICIPANTS

Patients with at least one entry in the NDR from 1 January 2002 to 31 December 2011 were included if they had been reported within 12 months of the date of diagnosis. Ninety-six per cent of the subjects had been diagnosed with type 2 diabetes on the basis of a clinical assessment. The remainder were included on the basis of the epidemiological definition discussed previously. Progress of HbA1c for up to 10 years was examined. Mixed models were used to correlate ethnicity with HbA1c (mmol/mol). The effect of differences in glycaemic control was examined by assessing the risk of developing albuminuria. To put it into perspective, we compared the effect of ethnicity to that of income, education and physical activity.

STUDY V

BACKGROUND

Socioeconomic status is a powerful predictor of cardiovascular disease in diabetes, but whether this association extends to heart failure (HF) is unknown.

HYPOTHESIS

We hypothesized that socioeconomic status and ethnicity would be independent predictors of HF in type 2 diabetes.

AIM

We used a large cohort of individuals with type 2 diabetes to examine the relation.

METHODS AND PARTICIPANTS

We included 215,138 patients with type 2 diabetes in the NDR during 2007–2012. Patients were followed up until hospital admission for HF, death, or end of follow-up on Dec 31, 2012. Poisson regression was used to calculate incidence rates of HF. Cox regression, with adjustments for known and presumed risk factors of HF, was used to assess the association between patients' characteristics and HF.

The main findings of the studies are presented and discussed in this chapter. Some reflections and clinical implications are also discussed.

This chapter is composed mostly of excerpts from the original manuscripts. To spare space some of the tables described in this chapter are only available in the attached manuscripts (references will be clear).

5
RESULTS AND DISCUSSION

STUDY I

We examined the incidence rates of type 1 diabetes in people aged 0–34 years. We hypothesized that the DISS, which had provided evidence in favour of the spring harvest theory, has inadequate level of ascertainment. We also explored whether incidence could be monitored by means of the Prescribed Drug Register (PDR) alone, using a proxy for diagnosis.

RESULTS

In terms of the proxy for diagnosis of type 1 diabetes, 91% of the cases identified in the PDR among the 18–34 age group could be matched in the NDR; ninety-one per cent of the cases were classified as type 1 diabetes in the NDR. When the analysis was restricted to patients aged 18–30, 94% of cases were classified as type 1 diabetes.

Regarding the level of ascertainment in 2009 for 20–34 year olds, 151 cases were reported in the DISS, 312 in the NDR, 406 in the PDR and 475 altogether. The best-fitting log-linear model, which included the interaction between the NDR and DISS, resulted in an estimate of 528 (95% CI 508, 554) patients in the population. Thus, the level of ascertainment was 29% in the DISS, 59% in the NDR and 77% in the PDR. The level of ascertainment was also calculated for 2007 and 2008 – the results were very similar.

Table 1 (in the attached publication) and Figure 7 (below) present incidence rates obtained in separate registers and by means of capture–recapture. For patients aged 14 and younger, the incidence rates obtained in the PDR were very similar to those reported by the SCDR in 2005–2007.[219] For the 15–19 age group, we had data from the PDR and DISS only, the results showing that incidence rates are two to three times higher in the PDR than in the DISS. For the 20–34 age group, we compared all three registers separately, as well as their combined capture–recapture estimates (2007–2009). In terms of the separate registers, the DISS had the lowest incidence and the PDR had the highest (generally twice as high). The highest incidence rates were obtained by means of the capture–recapture method.

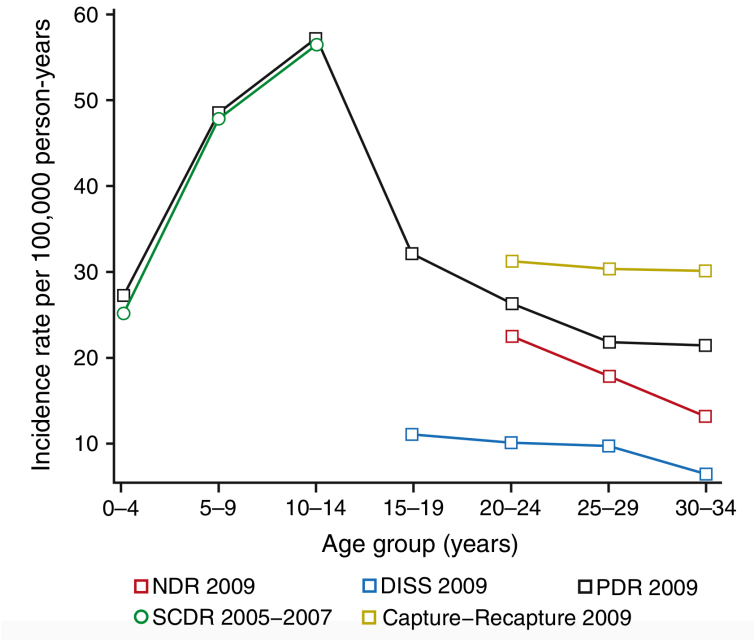


Figure 7 | Incidence rates per 100,000 person-years by age group and register in 2009 (men and women). Data from the NDR, DISS, PDR and the capture–recapture method included all three sources. Data from the SCDR (2005–2007) are also presented for comparison purposes.[219]

DISCUSSION

Sweden and Finland manage some of the largest registers for monitoring diabetes incidence. Given that the two countries also have the highest incidence rate of type 1 diabetes in the world, their reports are important.[25] Two out of three noteworthy studies supporting the spring harvest theory originate from Sweden. These studies were based on the DISS, which includes 15–34 year olds, and the SCDR, which includes patients aged 14 and younger.[33,34] The third study is from Belgium, a country with rather a low incidence.[35] Reports from Finland, Italy and the UK, on the other hand, indicate increasing or stable incidence in patients aged 39 and younger.[36-38]

Our analysis showed that the DISS had a level of ascertainment of 29% during 2007–2009. This should seriously call into question previous Swedish reports on the subject. It also suggests that evidence supporting the spring harvest theory have to be discarded. However, it does not negate the theory per se.[32]

We hypothesised that incidence rates could be monitored solely via a proxy for diagnosis of type 1 diabetes in the PDR. Using the PDR, we found that the incidence rate in the 15–34 age group was 2–3 times higher than in the DISS. The PDR showed that incidence rates in young people were equal to those in children aged 0–4 years. The proxy for diagnosis was scrutinised and appeared to be reliable. The method's ascertainment capability was assessed by comparing incidence rates in patients aged 14 and younger with figures from the SCDR (2007–2009), which has virtually 100% level of ascertainment – the results were very similar.[219] We showed that the risk of including other types of diabetes was very small: 91% of cases identified in the PDR for the 18–34 age group could be recaptured in the NDR, where 91% were classified as type 1 diabetes. When only 18–30 year olds were considered, 94% were classified as having type 1 diabetes.

Incidence rates estimated by means of capture–recapture was higher than in the PDR. We remark on the difference in the nature of the three registers. All three registers are nationwide. Data entry in the NDR and DISS depends on the active participation of clinics, as well as patient consent. Our analysis showed dependence with regard to entry in the NDR and DISS, perhaps reflecting patterns of clinical practice (i.e. differing proclivities to engage in research and conduct quality assurance projects). However, entry in the PDR is a passive and inevitable consequence of the disease. All individuals with type 1 diabetes must receive insulin and it is impossible to do so in Sweden without having been entered in the PDR. Regardless of entry in the other registers, all patients will be referred to the PDR, but the PDR does not issue referrals. The delay from disease onset to receipt of the first prescription for insulin should be no more than 2–10 days. Thus, the PDR should include every Swede with type 1 diabetes at the time of diagnosis. Plausible explanations for the fact that estimates from the PDR were lower than those obtained by means of capture-recapture are as follows:

> *Classification of the type of diabetes differs* in the three registers. Misclassification leads to inclusion of other types of diabetes, which inflates the estimated population size, particularly if the NDR and DISS have low levels of ascertainment.
>
> *The ascertainment in the DISS was very low*. As discussed previously, a low ascertainment level may bias the capture-recapture estimates.[227]

Given the nature of the disease and inevitable entry in the PDR, we believe that our proxy for diagnosis in the PDR (particularly for patients aged 30 and younger) is a reliable and feasible approach to future monitoring. The PDR is arguably the gold standard for monitoring the incidence of type 1 diabetes.

IMPLICATIONS AND FUTURE PERSPECTIVES

The results from this study were quite dramatic, which might explain why it received mass media attention. It was covered in all major Swedish newspapers as well as public television.[243]

The main result of the study was that substantial evidence in favour of the spring harvest theory is discarded. The notion that the incidence is decreasing among persons older than 14 years is questioned. This has important implications for health care planning and research.

The study also established a cost-effective and reliable method to monitor the incidence of type 1 diabetes. We are planning to use this method to examine trends in the incidence.

STUDY II

This study examined whether income, educational level, marital status and immigrant status are independent predictors of cardiovascular disease (CVD) and death in type 1 diabetes. A total of 24,947 individuals (220,281 appointments, mean follow-up 6 years), without a history of CVD, were included. Patients were followed until a first incident event, death or end of follow-up. We computed two Cox models for each outcome. The first model, referred to as the *minimally adjusted model*, was adjusted for socioeconomic, demographic and diabetes-related variables. The second model, referred to as the *maximally adjusted model*, was adjusted for other risk factors and confounders.

RESULTS

Immigrants and native Swedes were comparable at baseline in terms of age and sex (Table 1 in the attached manuscript). Immigrants had lower income, were twice as likely to be smokers, were less physically active and tended more to be married. Individuals who were married were fairly comparable to those who were divorced with regard to age and sex. Individuals who were divorced were more often women, had higher HbA1c, were twice as likely to be smokers *etc*.

Individuals with a college/university degree had higher income, 5 mmol/mol lower HbA1c, were more likely to be married, used insulin pump more frequently, smoked less and had less albuminuria, compared with their less educated compatriots. Income quintiles 2, 3 and 4 were approximately of the same age; those with high income were more likely to be married, had lower HbA1c, lower rates of smoking as well as albuminuria (Table 2 in the attached document).

Age and sex adjusted survival curves

Cox adjusted survival curves for death (Figure 8, below) indicated that income, education, marital status and immigrant status were significantly (all $p < 0.05$) associated with survival.

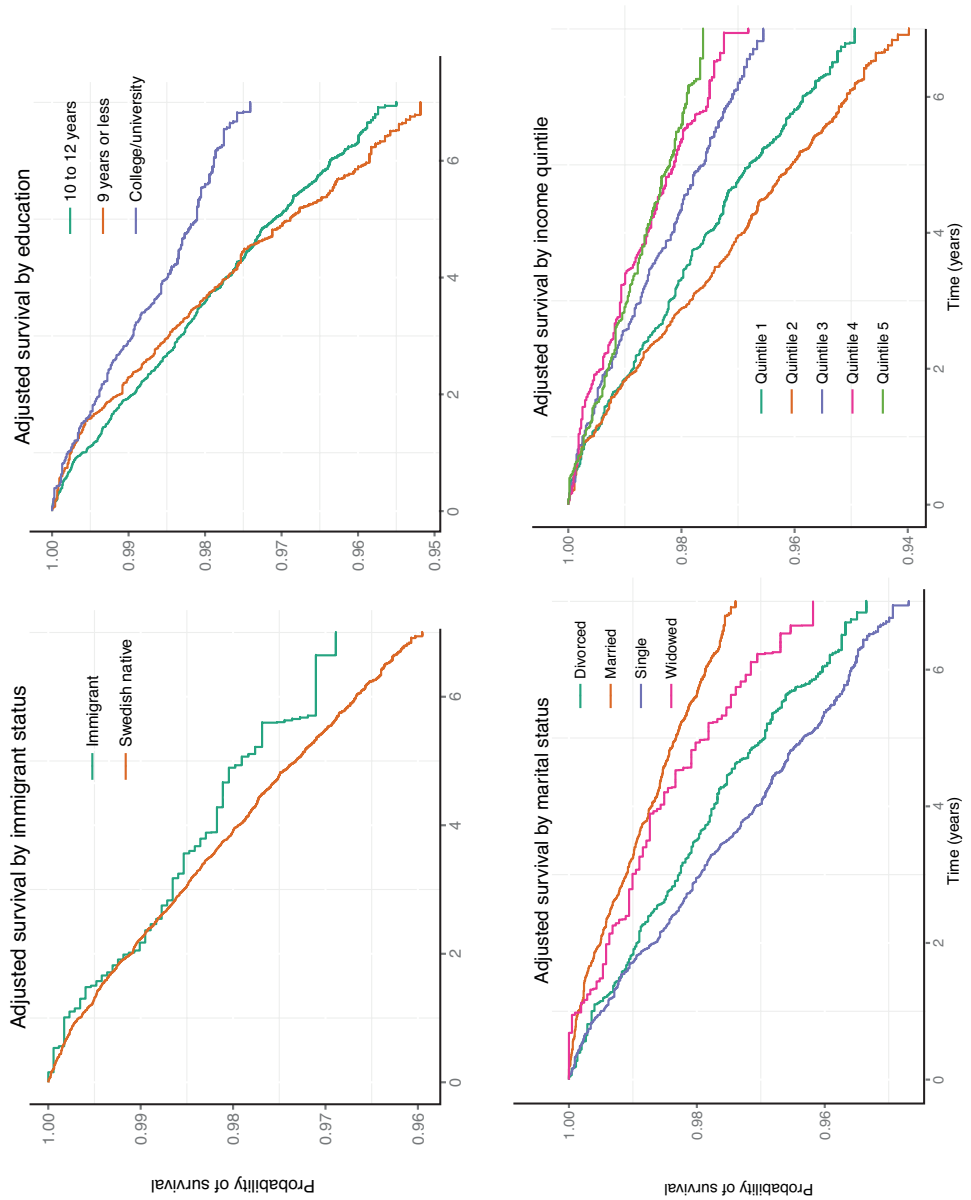


Figure 8 | Adjusted survival curves for death according to income, education, marital status and immigrant status.

Adjusted hazard ratios for cardiovascular events and death

Marital status

As compared with being single (the reference category for marital status), being married did not affect the risk of fatal/nonfatal CVD, fatal/nonfatal CHD or

fatal/nonfatal stroke (Figure 1 in the attached manuscript). Being married was associated with 50% to 64% lower risk of all cause death, CV death and diabetes-related death (Figure 2 in the attached manuscript). Being divorced increased the risk of fatal/nonfatal CVD by 32%. The same tendency was noted for fatal/nonfatal CHD and stroke but without statistical significance (Figure 1 in the attached manuscript). Being divorced was associated with 40% lower risk of CV death, as compared with being single (Figure 2 in the attached manuscript). Being widowed was associated with 56% greater risk of fatal/nonfatal CVD and more than twice the risk of fatal/nonfatal CHD (HR 2.12, 95% CI 1.59–2.82) (Figure 1 in the attached manuscript).

Income

As compared with the highest income quintile, individuals in the two lowest income quintiles had roughly twice the risk of fatal/nonfatal CVD, fatal/nonfatal CHD and fatal/nonfatal stroke in the minimally adjusted model. This was somewhat attenuated in the maximally adjusted model (Figure 1 in the attached manuscript). As compared with the highest income quintile, the two lowest quintiles had roughly three times as great a risk of death, diabetes-related death and CV death in the minimally adjusted model. The risk of all-cause death was still twice as much in the maximally adjusted model; the risk of CV death was three times as much and the risk of diabetes-related death was twice as much (Figure 2 in the attached manuscript).

Educational level

As compared with having 9 years or less education, individuals with a college/university degree had 31%, 26% and 45% lower risk of fatal/nonfatal CVD, fatal/nonfatal CHD and fatal/nonfatal stroke, respectively, in the minimally adjusted model. These differences were attenuated in the maximally adjusted model and remained statistically significant only for fatal/nonfatal stroke (HR 0.55, 95% CI 0.40–0.75) (Figure 1 in the attached manuscript). Likewise, for all cause death, CV death and diabetes death, a college/university degree was protective in the minimally adjusted model but the effect was invalidated in the maximally adjusted model (Figure 2 in the attached manuscript). Having 10–12 years of education was associated with 48% higher risk of CV death, as compared with those having 9 years or less education (Figure 2 in the attached manuscript).

Immigrant status

The point estimates in all models indicated that immigrants had 10–40% lower risk of the outcomes, as compared with native Swedes (Figures 1 and 2 in the attached manuscript). This was statistically significant (in the maximally adjusted model) for fatal/nonfatal CVD, all-cause death and diabetes-related death.

DISCUSSION

This study shows that socioeconomic status is a powerful predictor of cardiovascular morbidity and mortality in type 1 diabetes. The effect of socioeconomic status was striking despite rigorous adjustments for covariates. Individuals in the two lowest income quintiles had 2–3 times higher risk of cardiovascular events and death than those in the highest income quintile. As compared with low educational level, having high education was associated with approximately 30% lower risk of stroke. As compared with being single, individuals who were married had more than 50% lower risk of death, CV death and diabetes-related death. Immigrants had 20–40% lower risk of fatal/nonfatal CVD, all-cause death and diabetes-related death. Additionally, we show that males had 44%, 63% and 29% higher risk of all-cause death, CV death and diabetes-related death, respectively.

Despite rigorous adjustments for covariates and equitable access to health care at a negligible cost,[244,245] socioeconomic status and sex are robust predictors of cardiovascular disease and mortality in type 1 diabetes; their effect was comparable to that of smoking, which represented a hazard ratio of 1.56 (95% CI 1.29–1.91) for all-cause death.

Previous studies have shown that socioeconomic status is associated with glycaemic control and risk factors in type 1 diabetes,[246-251] but few studies have examined how socioeconomic status relates to cardiovascular disease and death. Available studies reported either a modest effect or no significant effect of socioeconomic status, or they were inadequately adjusted to allow for reliable inferences.[140,141,238,252] Furthermore, on the contrary to these studies, our study shows that the effect of education is much weaker after controlling for income.

Immigrants had lower risk of CVD and death. This contrasts to findings for type 2 diabetes, where immigrants are at higher risk of death.[253,254] This might be explained by the *healthy immigrant effect,* which was discussed in Chapter 1.[160]

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The fact that the excess risk was not mediated by known risk factors does not imply that risk factor control is less important. On the contrary, stringent risk factor control will be crucial to reducing morbidity and mortality among disadvantaged groups. The final solution to these disparities is, however, unlikely to emerge from conventional risk factor control. More individualized management and allocation of resources to clinics and clinicians are important

measures but neither can such actions eliminate the gaps. These socioeconomic disparities can only be overcome with health policy and societal reforms.

STUDY III

In this study we examined long-term trends in risk factors from 1996 to 2014, in the overall cohort and in relation to sex, income and education. We calculated adjusted estimates of HbA1c, systolic blood pressure (SBP), LDL cholesterol (LDL-C), body mass index (BMI), physical activity and smoking. We included all patients with type 1 diabetes entered in the Swedish National Diabetes Register from 1996 to 2014 (n=38,169 contributing 457,577 appointments).

We computed two separate models for each response variable. The first model, suitable for determining long-term trends, was stratified by the categories of the variable of interest; i.e. trends for males and females were fitted in separate models and the same was done for educational and income categories. This approach provides reliable trends for each category but comparing categories (e.g. males vs. females) could be biased since the estimates for males and females were derived from separate models. Therefore, we also fitted models stratified by calendar year, which allows for direct comparison between categories. The two types of models yielded very similar results, which is why only the first type is presented here. Refer to the attached manuscript for details.

RESULTS

HbA1c (Figure 11, below) – Overall, HbA1c declined from 68.1 mmol/mol to 64.0 mmol/mol from 1996 to 2007 and then reversed to 66.8 in 2012, declining slightly in the remaining two years. By the end of the study period there was no noteworthy improvement in HbA1c since the turn of the millennium. Education was inversely associated with HbA1c, with a constant gap. Individuals with a college/university degree lowered their HbA1c with 4.1 mmol/mol, whereas those with 9 years or less education did not lower their HbA1c during the 19 years follow-up. Considering income, trends evolved similarly in all groups and those in the two highest income quintiles had lower HbA1c, as compared with individuals in lower income quintiles.

Body mass index (Figure 12, below) – Overall BMI increased linearly, from 24.7 kg/m^2 to 26.1 kg/m^2 from 1996 to 2014. Females had somewhat higher BMI throughout (Supplemental Figure 1D in the attached manuscript). BMI increased with a similar slope for all income and educational categories. Individuals with less than a college/university degree had higher BMI throughout. Income quintiles 2, 3, 4 and 5 differed little regarding BMI, whereas quintile 1 had significantly lower BMI throughout.

Systolic blood pressure (Figure 13, below) – Overall SBP decreased from 131.2 mmHg in 1996 to 125.9 mmHg. We noted a tendency for increasing SBP the last two years of the study. SBP declined faster for those with less education and lower income. The gaps were virtually abolished by the end of the study period.

LDL cholesterol (Figure 14, below) – Overall LDL-C declined from 2.85 in 2002 to 2.59 in 2014, which was, however, not significantly lower than LDL-C in 2006. Higher education, but not higher income, was associated with lower LDL-cholesterol.

Smoking (Figure 15, below) – The overall prevalence of smoking was 13.8% in 1999, which decreased to 10.8% in 2014. Odds ratio for being a smoker in 2014, compared with 1999, was 0.75 (95% CI 0.69 to 0.82). Corresponding odds ratio for men was 0.73 (95% CI 0.65 to 0.83) and 0.77 (95% CI 0.69 to 0.87) for women. There were staggering differences in relation income and education, with no tendencies towards reduced gaps. Smoking rates among persons with 9 years or less education was three times higher than among those with a college/university degree. In relation to income, the highest rates of smoking occurred in the two lowest income quintiles.

Physical activity (Figure 16, below) – Although we observed a drop in physical activity during 2007 and 2008, the overall pattern showed no change in physical activity. In 2004, 53.7% were physically active, which was no different from 53.6% in 2014. There were no differences in rates of physical activity in relation to gender, but large and constant differences in relation to income and education. High income and high education was associated with higher levels of physical activity.

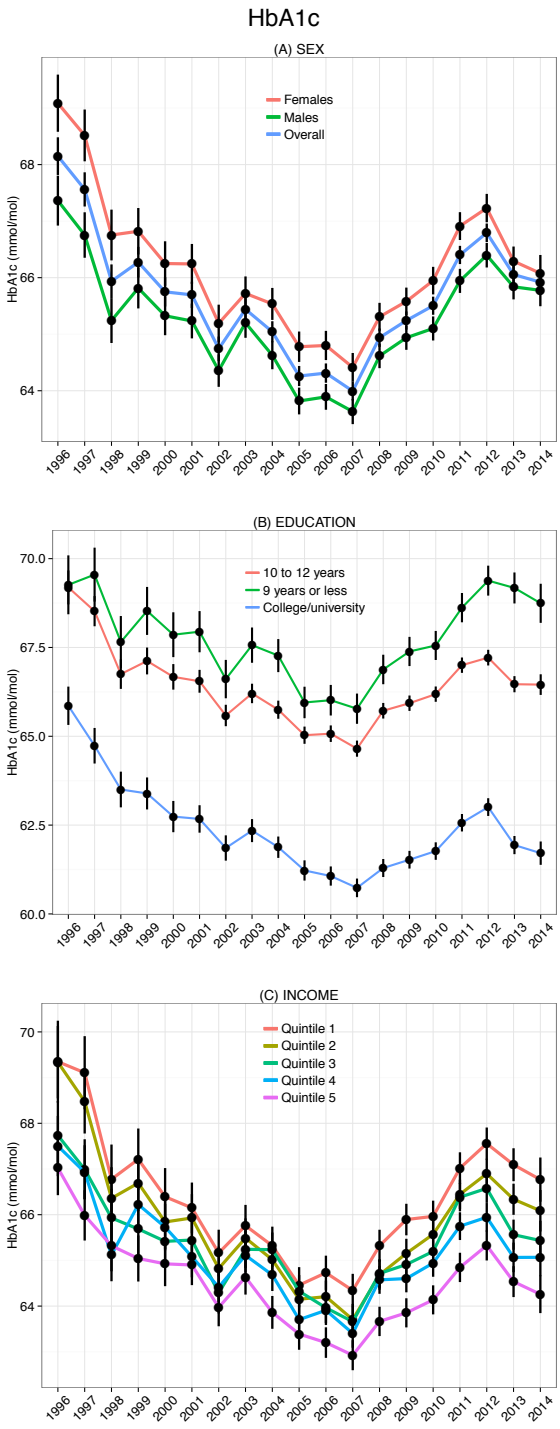


Figure 11 | Long-term trends in HbA1c, stratified by sex, income and education.

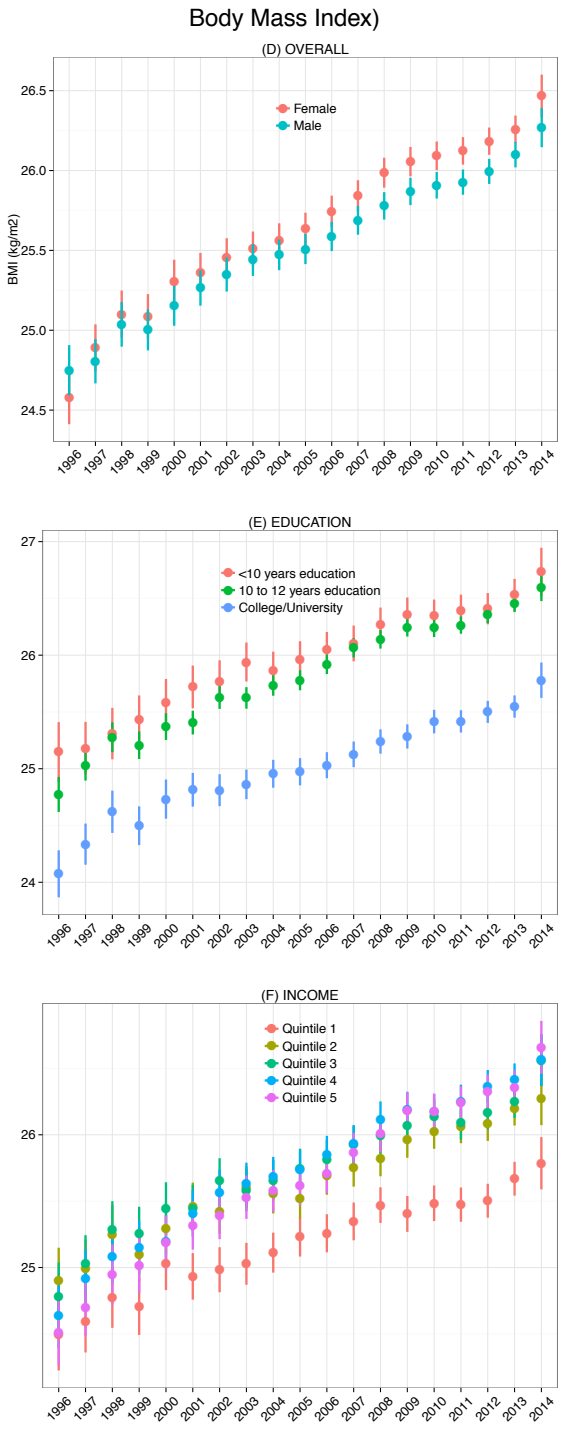


Figure 12 | Long-term trends in BMI, stratified by sex, income and education

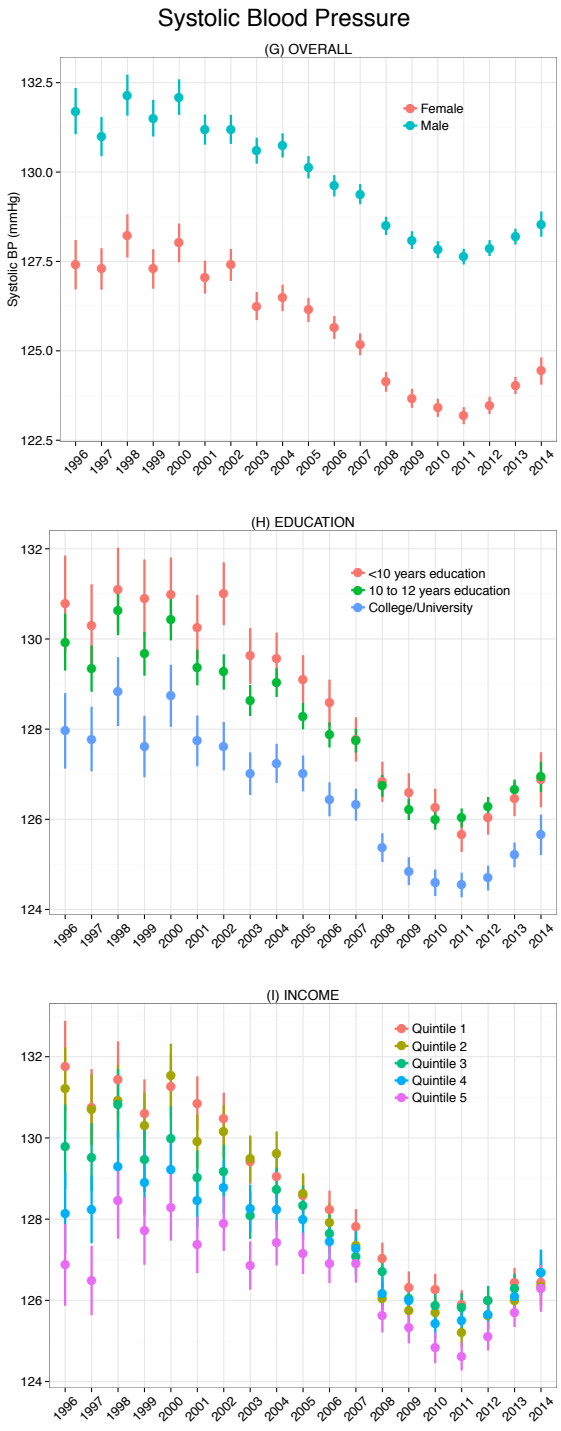


Figure 13 | Long-term trends in SBP, stratified by sex, income and education

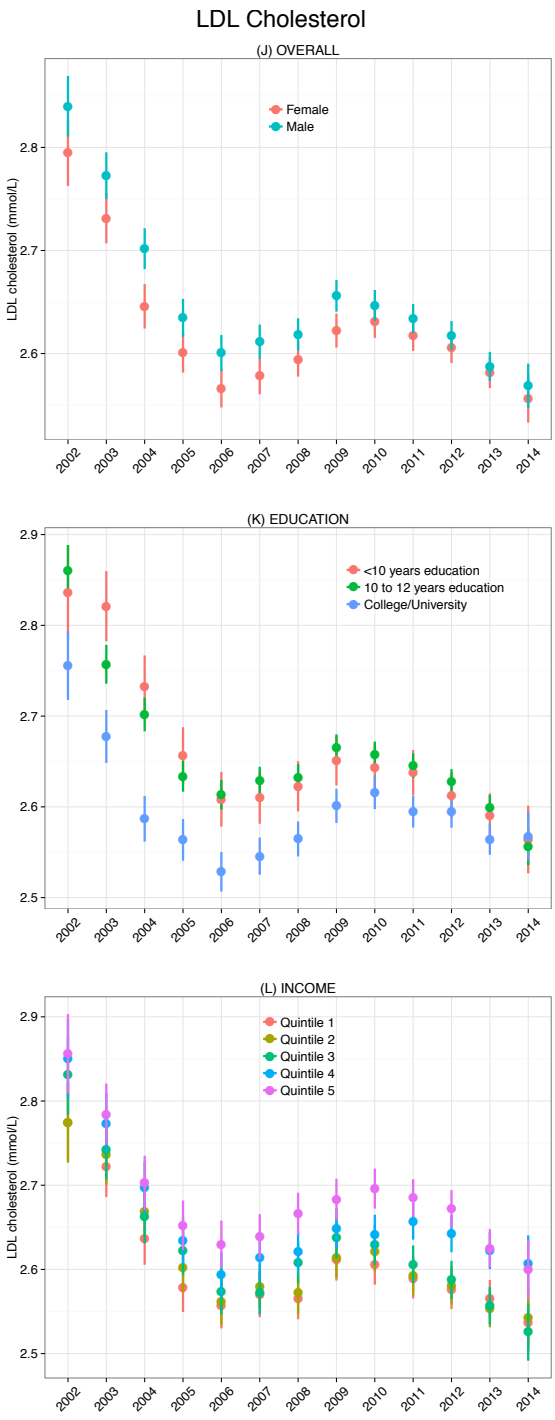


Figure 14 | Long-term trends in LDL cholesterol, stratified by sex and education.

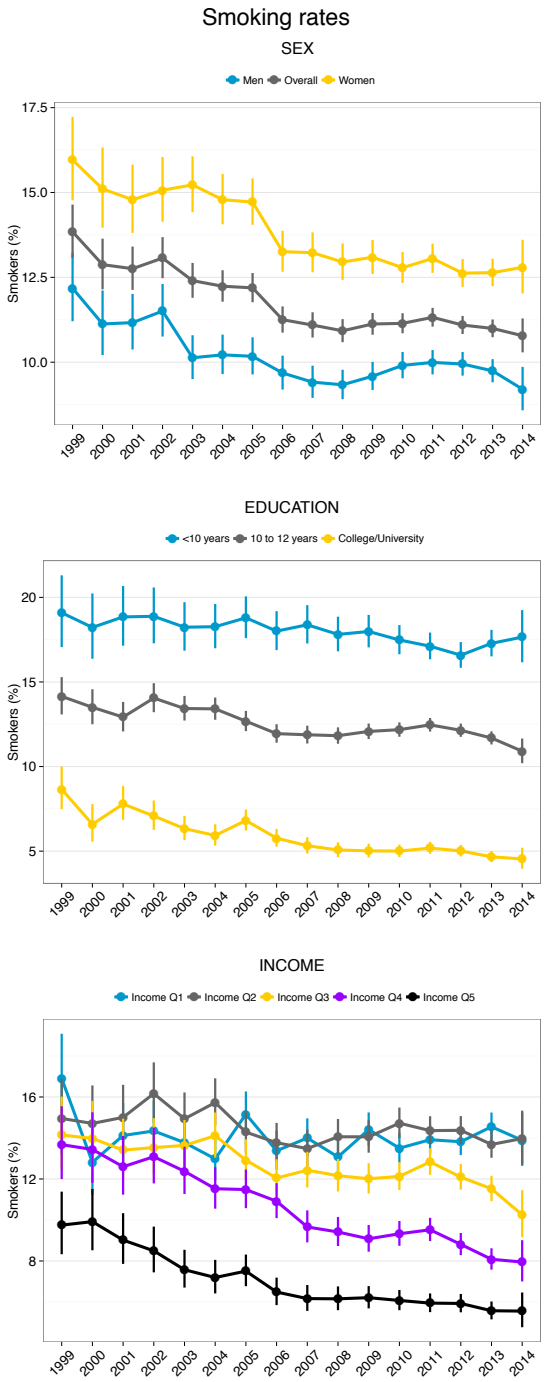


Figure 15 | Long-term trends in smoking, stratified by sex, education and income.

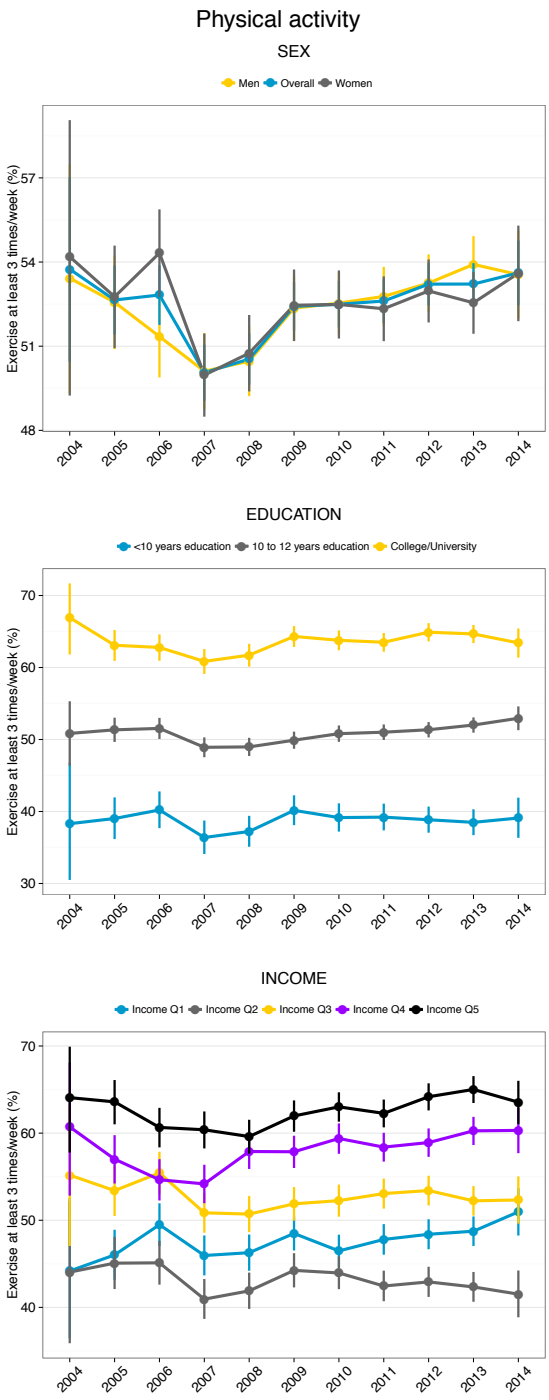


Figure 16 | Long-term trends in physical activity, stratified by sex, income and education.

DISCUSSION

Favourable trends for glycaemic control and serum cholesterol were interrupted starting from 2007, and have only recently started to improve again. Ultimately, HbA1c has not improved since the turn of the millennium. BMI increased markedly and consistently. Individuals with type 1 diabetes are now on average overweight. Systolic blood pressure declined steadily for 16 years but has started to increase in the final years. Odds of being a smoker declined 25%, whereas rates of physical activity have not changed. Socioeconomic disparities were marked throughout but some gaps were reduced over time.

HbA1c started to increase in 2007 after a decade of improvement and then decreased again in the final two years. By the end of the study period there had been no improvement in HbA1c for a decade. Evidence from the Diabetes Control and Complications Trial (DCCT), indicates that the temporary increase in HbA1c can be costly in the years to come, despite improved glycaemic presently.[255] The increase in HbA1c could be explained by less intensive treatment, dietary changes or a combination of both. Since management of type 1 diabetes have often been extrapolated from type 2 diabetes, it is possible that the Action to Control Cardiovascular Risk in Diabetes (ACCORD, published in 2008) – which reported increased mortality in type 2 diabetes when aiming for intensive glycaemic control – had an influence on type 1 diabetes as well.[256] There are other plausible explanations, such as changes in diet patterns (discussed below). Regardless, the recent decline in HbA1c could – at least to some extent – be attributed to campaigns and improvement programs aiming at reversing the adverse trend. Such incentives were launched at the time of noticing the adverse trend.

Type 1 diabetes has traditionally been a disease of lean individuals, but this is changing.[257] The linear increase in BMI, which we note over a period of almost two decades followed the trend in the overall population.[258-261] However, overweight in type 1 diabetes does not necessarily represent an increased risk. The Pittsburgh EDC study showed that optimal BMI for patients with T1DM appears to be between 25 and 30 kg/m^2.[262] However, this trend should also be monitored, since obesity is strongly associated with hospitalization for heart failure in patients with type 1 diabetes.[263]

The paradoxical findings that low income (compared to high income) and high education (compared to low education) were associated with lower BMI are difficult to disentangle based on our analysis. In the light of the other findings, it suggests that income and education act through different mechanisms.[110] There

are many possible explanations. For example, individuals with low income displayed worse glycaemic control, which could be due to less intensive treatment (weight gain is a common consequence of intensive treatment of type 1 diabetes). Furthermore, individuals in the lowest income quintile were often smokers; smokers tend to have lower body weight than do non-smokers and smoking cessation is frequently followed by weight gain.[264] However, this does not explain why individuals with a college/university degree had lower BMI than their compatriots.

We report that 16 years of steady reductions in blood pressure were interrupted in 2012, whereupon an increase in blood pressure was noted. The reason for the reduction is likely to be multifactorial. We believe that increased use of antihypertensive medications is the main reason for this. The use of antihypertensives increased from 24% in the beginning to 40% by the end of the study period. The increasing blood pressure in the last years could to some extent be explained by increasing BMI.

The trend in LDL-C were similar to that of HbA1c. The trend in our cohort is concordant with that of the general population, which displayed a similar increase from 2007.[265] One speculative explanation for this phenomenon is the emergence of the LCHF (Low Carbohydrate High Fat) movement in Sweden. The LCHF diet, in many aspects similar to the Atkins diet, proposes a high intake of saturated fats. The LCHF diet was popularized through blogs, recipe books, TV appearances and newspapers articles. It gained wide public attention and particularly among persons with diabetes.[266] Scientific evidence for the LCHF diet is scarce, in particular for persons with type 1 diabetes.[267-269] The LCHF trend coincides with the increase in LDL-C and HbA1c in our study population, as well as in the general population.[270] Studies have shown that saturated fats increase insulin resistance, total cholesterol and LDL-C.[268,271-275] Enthusiasm for the diet has levelled off in recent years, probably due to opposition from the scientific community and officials.[276]

Roughly half of the patients were physically active and there was no change in this proportion over a decade. We hypothesized that the increased awareness of the beneficial effects of exercise, along with improved treatment and glucose monitoring methods, would pave the way for increasing physical activity.[277] However, our findings still contrast against the trend in the general population, which displayed a decline in physical activity during the same period.[278] All levels of physical activity, including leisure activities, recreational sports, and competitive professional performance, can be performed by people with type 1 diabetes who do not have complications and are in good blood glucose control.

Clinicians and patients should take advantage of available methods and equipment to facilitate exercising.

In 2001, roughly 19% of all Swedes aged 16–84 years were smokers. The corresponding figure in our cohort was 12.8%. Smoking rates declined 30% between 2001 and 2012 in Sweden; the corresponding figure in our cohort was 15%.[279] It follows that persons with diabetes smoke less than the general population but smoking cessation has been less successful among persons with type 1 diabetes.

We note marked socioeconomic disparities. Low income and low educational level was associated with higher HbA1c throughout the study period, without any tendency to reduced gaps. It is of outmost importance to note that those with 9 years or less education have not improved their HbA1c over a period of almost two decades. The gap in SBP between men and women was also constant throughout the whole period. On the other hand, we noted encouraging trends towards reduced gaps in SBP in relation to education and, in particularly, income. Furthermore, individuals in the lowest income quintiles and those with 9 years or less education have not managed to reduce their smoking rates for almost two decades. Clinicians should pay attention to underprivileged individuals and make an effort to reduce these disparities. They should also note that the income and education appears to act differently on risk factor control and the disparities appear to be larger in relation to education.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Improvement in risk factor control over the last two decades has neither been uniform nor universal. Clinicians should pay attention to underprivileged groups and make an effort to reduce socioeconomic disparities. They should also note that the income and education appears to act differently on risk factor control and the disparities appear to be larger in relation to education.

STUDY IV

Tight glucose control in type 2 diabetes has shown long-term beneficial effects on microvascular complications, cardiovascular disease and mortality.[12,280-283] In this study we examined ethnic differences in glycaemic control. Previous studies on this matter have been contradictory.[126,284,285] We examined this association in a large cohort of patients with type 2 diabetes. The NDR was used to identify patients with newly diagnosed (within 12 months) type 2 diabetes. A total of 131,935 patients (with 713,495 appointments), representing 10 ethnic groups, were followed up to 10 years. The progress of HbA1c for up to 10 years was examined. The effect of glycaemic disparities was examined by assessing the risk of developing albuminuria.

RESULTS

Roughly 80% of the study population were Swedish natives. Immigrants had more appointments per year. Non-Western immigrants in particular had almost 30% more appointments (Table 1 in the attached document). The proportion of males varied from 37% (East Asia) to 70% (Mediterranean Basin). Patients from high-income Western countries were as much as 18 years older at the time of diagnosis. Particularly low age at the time of diagnosis was found for South Asia (46.0), East Asia (50.0) and Sub-Saharan Africa (47.3). BMI was 2–3 kg/m^2 lower among non-Western groups. Native Swedish patients had the lowest mean HbA1c (51.9 mmol/mol) of all groups. Low-income and non-Western groups had HbA1c ranging from 54 to 58 mmol/mol. Systolic blood pressure was lower among non-Western groups. Lipid profiles were less favourable among non-Western groups. There were no major ethnic differences in terms of physical activity. Smoking rates were higher among patients from the Middle East, North Africa and low-income Europe. A history of CVD was more common among Western groups, but non-Western groups were 10–12 years younger at the onset of CVD. The overall prevalence of albuminuria was approximately 14%, and there were no noteworthy ethnic differences. College or university education was more common among non-Western populations, but they were generally in lower income quintiles.

GLYCAEMIC CONTROL – CRUDE FIGURES

HbA1c declined during the first 1–3 years of follow-up and then increased for all ethnic groups (Figure 17, below). However, there were conspicuous and consistent ethnic differences in HbA1c levels throughout the study. Swedish patients (the reference category) had the lowest mean HbA1c at every point in

time while patients from high-income Western countries had only slightly higher levels. Patients from low-income Europe, Russia and Central Asia, as well as all non-Western populations, had substantially higher HbA1c levels throughout the study. On average, Swedish and other Nordic populations remained below the target level until the fifth year. Mediterranean Basin, high-income European, North American and Oceanic populations remained below the target level until the fourth year, whereas low-income European, Russian and Central Asian populations remained below only until the second year. The remaining five ethnic groups did not reach the target level at any point.

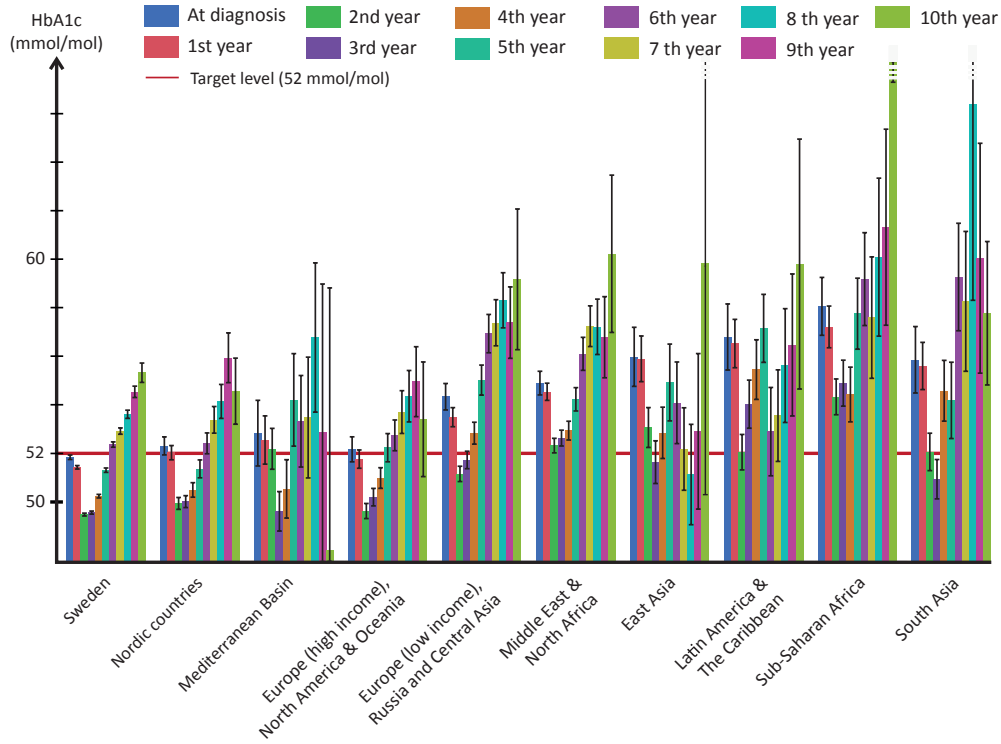


Figure 17 | Progress of glycaemic control from time of diagnosis by ethnicity/race. Values are annual mean HbA1c from time of diagnosis by ethnicity/race. The red horizontal line in the background depicts the national target level (52 mmol/mol) set for type 2 diabetes

GLYCAEMIC CONTROL – ADJUSTED FIGURES

Because there was an interaction ($p < 0.0001$) between ethnicity and glucose-lowering treatment, we stratified the analysis by type of treatment. Table 2 (below) presents β coefficients (i.e. predicted difference in mmol/mol HbA1c) by ethnicity. To convey a sense of the impact of ethnicity as compared to other

factors, coefficients for physical activity are also presented. Being from Sub-Saharan Africa, South Asia, East Asia, the Middle East and North Africa, Latin America or low-income Europe, Russia and Central Asia predicted substantially higher HbA1c. East Asian ethnicity predicted 1.8–3.8 mmol/mol higher HbA1c, depending on the stratum. Similarly, low-income Europe, Russia and Central Asia predicted 1.2–1.9 mmol/mol higher HbA1c. Latin America and the Caribbean predicted 1.9–4.8 mmol/mol higher HbA1c. South Asian origin predicted 1.9–4.2 mmol/mol higher HbA1c. Sub-Saharan Africa predicted 1.6–3.6 mmol/mol higher HbA1c. In comparison, no physical activity predicted 0.8–1.3 mmol/mol higher HbA1c, as compared to daily physical activity.

TABLE 2. PREDICTION OF HBA1C (MMOL/MOL) BY TYPE OF GLUCOSE-LOWERING TREATMENT

	DIET & LIFESTYLE	OHA	INSULIN (±OHA)
ETHNICITY/RACE			
Sweden	reference	reference	reference
East Asia	3.79 (2.59, 5)	1.84 (0.7, 2.97)	2.13 (-0.36, 4.62)
Europe (HI) & North America	0.14 (-0.37, 0.65)	0.19 (-0.41, 0.79)	1.86 (0.42, 3.3)
Europe (LI), Russia and Central Asia	1.58 (1.05, 2.11)	1.2 (0.66, 1.74)	1.89 (0.63, 3.16)
Latin America & The Caribbean	1.89 (0.76, 3.02)	2.42 (1.3, 3.54)	4.84 (2.6, 7.07)
Mediterranean Basin	0.57 (-0.74, 1.88)	0.61 (-0.84, 2.05)	1.17 (-2.7, 5.04)
Middle East & North Africa	1.85 (1.37, 2.34)	0.93 (0.46, 1.41)	2.79 (1.58, 4.01)
Nordic countries	-0.01 (-0.36, 0.35)	0.19 (-0.22, 0.6)	0.81 (-0.19, 1.8)
South Asia	4.21 (2.85, 5.56)	1.93 (0.6, 3.25)	1.91 (-1.12, 4.94)
Sub-Saharan Africa	3.26 (2.22, 4.3)	3.61 (2.57, 4.64)	1.58 (-0.47, 3.63)
PHYSICAL ACTIVITY			
Daily physical activity	reference	reference	reference
3-5 times/week	0.07 (0.01, 0.14)	0.11 (0.01, 0.22)	0.19 (-0.06, 0.45)
1-2 times/week	0.26 (0.19, 0.34)	0.51 (0.4, 0.62)	0.74 (0.46, 1.01)
Less than once / week	0.48 (0.39, 0.57)	1.03 (0.9, 1.17)	1.38 (1.06, 1.7)
No physical activity	0.76 (0.66, 0.86)	1.20 (1.06, 1.35)	1.32 (1.00, 1.65)

Figures are β coefficients (95% CI) that predict the change in HbA1c (mmol/mol). The effect of physical activity is presented for comparison. Example of interpretation: after accounting for included covariates, East Asian ethnicity predicts 3.79 mmol/mol higher HbA1c among persons on diet and lifestyle modifications. Model adjustments: age, sex, age at onset of diabetes, duration of diabetes, quadratic effect of duration of diabetes, BMI, smoking status, history of cardiovascular disease, physical activity, income, education, lipid lowering medication and eGFR.

PROBABILITY OF FAILURE TO ACHIEVE THE TARGET LEVEL DURING THE SECOND YEAR

Low-income Europe, Middle East and North Africa, East Asia, Sub-Saharan Africa and South Asia displayed substantially higher odds of not achieving the target-level for HbA1c (Figure 18, below). Odds ratios (95% CI) for East Asia, Sub-Saharan Africa and South Asia were 1.76 (1.22, 2.54), 1.78 (1.29, 2.45) and 2.11 (1.35, 3.29), respectively. The effects of income and education were significant, although less pronounced. Not being physically active was associated with 57% higher odds of failure, as compared to daily physical activity.

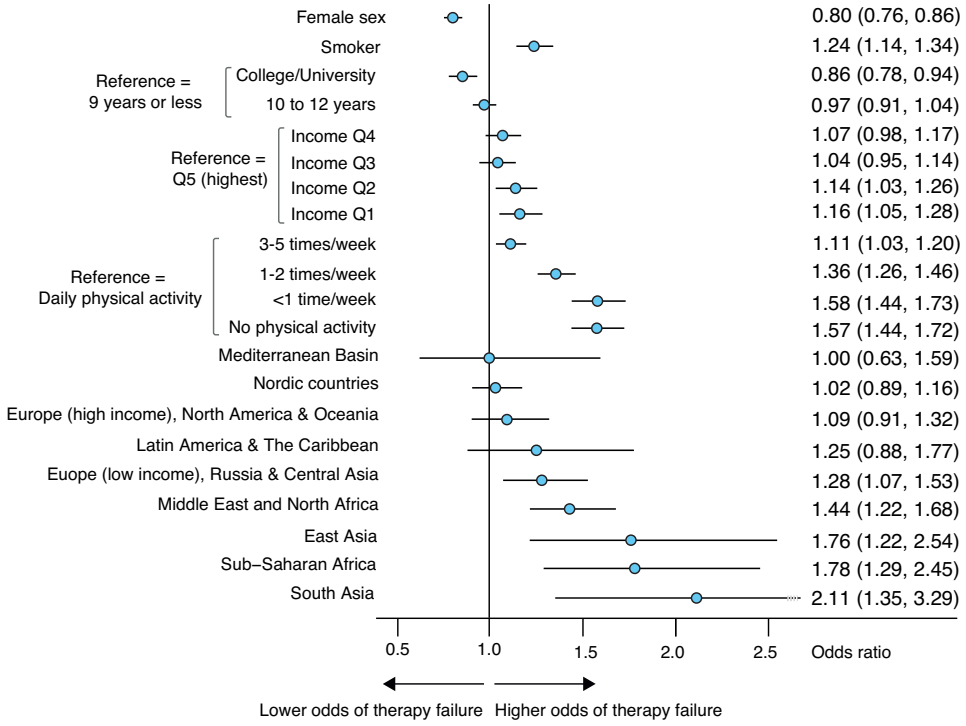


Figure 18 | Probability (odds ratio) of achieving glycaemic control (<52 mmol/mol) during the second year after diagnosis. Adjusted for ethnicity, sex, age, BMI, income, education, smoking status, physical activity and type of glucose lowering treatment.

PROBABILITY OF HAVING ALBUMINURIA DURING THE SECOND YEAR

Immigrants had 6% to 92% higher odds of having albuminuria (Figure III). The risk of albuminuria was particularly high (51% to 92% higher risk) in Non-Western and low-income groups.

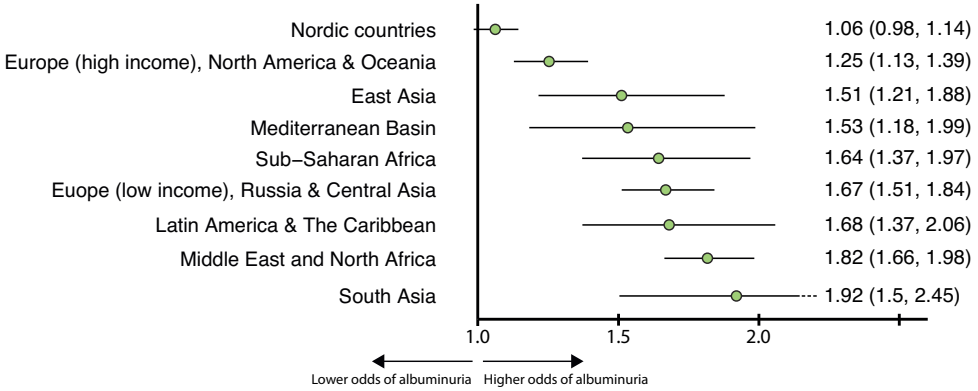


Figure 19 | Probability (odds ratio) of having albuminuria during the second year after diagnosis. Adjusted for age, sex, systolic blood pressure and eGFR.

TIME TO START OF PHARMACOLOGICAL TREATMENT

Median time to start of pharmacological treatment was shorter for non-Western populations compared with Western populations (Figure 20, below).

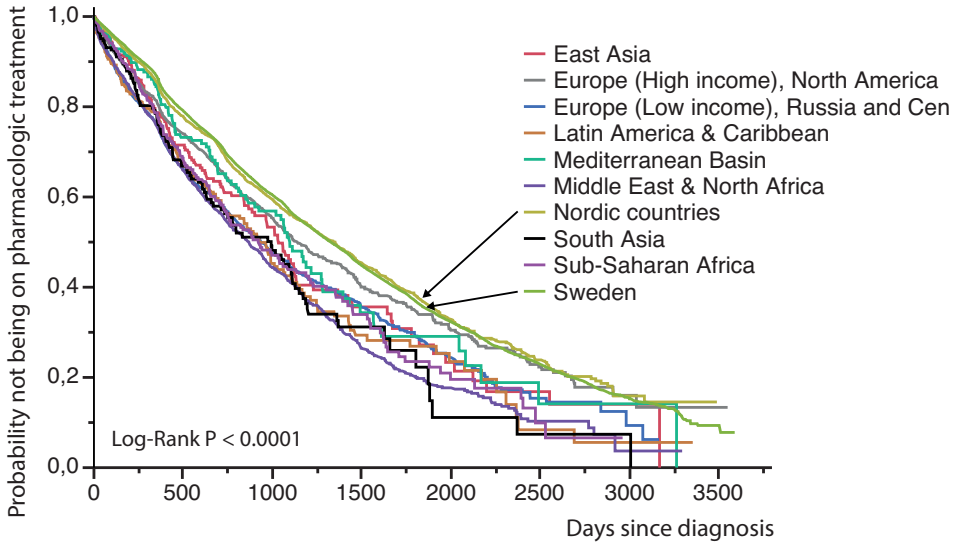


Figure 20 | Kaplan-Meier curves displaying the time until initiation of pharmacologic treatment according to ethnicity.

DISCUSSION

Our study provides firm evidence that ethnicity is a strong predictor of glycaemic control, on a par with physical activity. We also show ethnic differences in glycaemia for all major ethnic groups and how these disparities are mirrored in

another important risk marker, i.e. albuminuria. We believe that our results call for a more individualized management and increased efforts to eliminate ethnic inequalities.

Glucose control is a cornerstone of diabetes care. Previous studies on ethnic differences in glycaemic control might be compromised in several ways; unequal access to—or use of—health care, inappropriately broad categories of ethnicity, cross-sectional design, small samples and short follow-up are frequent flaws, which might explain contradictory results.[126,284,285]

We noted marked ethnic differences in HbA1c both at the time of diagnosis and during follow-up. Immigrants consistently exhibited poorer glycaemic control. High-income Western groups remained below the target-level of HbA1c for 4–5 years after diagnosis, whereas low-income Europe, Russia and Central Asian patients maintained the target level for an average of only 3 years. Non-Western populations had substantially higher HbA1c throughout the study and never reached the guideline target level. Adjusted figures showed 2–5 mmol/mol higher HbA1c among non-Western groups. These disparities translated into a 28–111% higher risk of not achieving target level of HbA1c and a 51–92% higher risk of developing albuminuria among non-Western groups compared with native Swedes. After the end of follow-up, 40–45% of individuals from high-income Western countries were in glycaemic control, compared to 5%, 25% and 30% for Sub-Saharan Africa, South Asia and the Middle East and North Africa, respectively. These differences could not be explained by disparities in instituting glucose-lowering medications, use or access to health care.

The risk of albuminuria was assessed in order to determine whether ethnic differences in glycaemic control were reflected in the development of diabetes-related complications. Poor glycaemic control is a main cause of albuminuria and renal lesions in diabetes, making albuminuria a suitable marker for complications.[286,287] Studies have shown that African Americans and Hispanics have a higher prevalence of albuminuria compared with Caucasians.[288] Jolly *et al* reported that this was also true for Asians.[289] Our study describes the adjusted risk of albuminuria in all major ethnic groups; immigrants, particularly those of non-Western origin, have a substantially higher risk of developing albuminuria. This predicts a high future risk of developing cardiovascular disease. It also suggests that ethnic differences in HbA1c reflect actual differences in glucose-levels. Above all it underlines the need for ethnic-specific screening and management.

The groups with the poorest glycaemic control and greatest risk of albuminuria in our study were Asia, Sub-Saharan Africa, the Middle East & North Africa, low-income Europe, Russia and Central Asia. They represent a large and growing proportion of the population in high-income areas such as North American and the EU. We believe our results can be generalized to economically developed Western countries. Clinicians and health care planners should be aware of the challenges posed by immigrants and adjust the management accordingly. Effective strategies to reduce these health disparities remain elusive and need to be addressed. The problem might be further complicated by a potential interaction between ethnicity and the effectiveness of glucose-lowering medications. Although our study was not designed to explore these associations, we show that there was an effect-modification of ethnicity on glucose-lowering therapy. A previous studies revealed ethnic differences in the efficacy of insulin,[290] but there are considerable gaps in the knowledge that is currently available on this topic.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Despite earlier start of glucose-lowering therapies, full access to health care at a minimal cost and more appointments, immigrants – particularly those of non-Western origin – with type 2 diabetes have substantially higher HbA1c, greater risk of therapy failure and higher probability of developing albuminuria than native Swedes. The impact of ethnicity on glycaemic control is greater than the effect of income and educational level, and on a par with the effect of physical activity. Thus, ethnicity is integral glycaemic control and needs to be carefully considered if diabetes care is to improve.

STUDY V

In this study we examined the impact of ethnicity on the risk of heart failure (HF) in diabetes. We hypothesized that there would be an excess risk of HF among non-Western immigrants, after accounting for known and presumed risk factors. We included 215,138 patients with type 2 diabetes in the Swedish National Diabetes Register during 2007–2012. Patients were followed until hospital admission for HF, death, or end of follow-up on Dec 31, 2012. Poisson regression was used to calculate incidence rates of HF. Cox regression, with adjustments for known and presumed risk factors of HF, was used to assess the association between patients' characteristics and HF.

RESULTS

In all 8,250 patients were hospitalized for heart failure. The proportion of patients experiencing an event ranged from 3% to 5% for Western groups and 0.8% to 2% for non-Western groups. The range of events in absolute numbers was 13 (East Asia) to 6885 events (Sweden).

Age at time of event was 75–77 years for high-income Western groups; 72–74 years for low income Western groups and 61–70 years for non-Western groups. The largest difference was noted between Sweden (mean age 77.4) and Sub-Saharan Africa (mean age 61.4).

South Asia, Nordic countries, and low-income Europe, Russia & Central Asia displayed the highest incidence rates. Sub-Saharan Africa, Latin America & the Caribbean and East Asia displayed the lowest incidence rates (Figure 21, below).

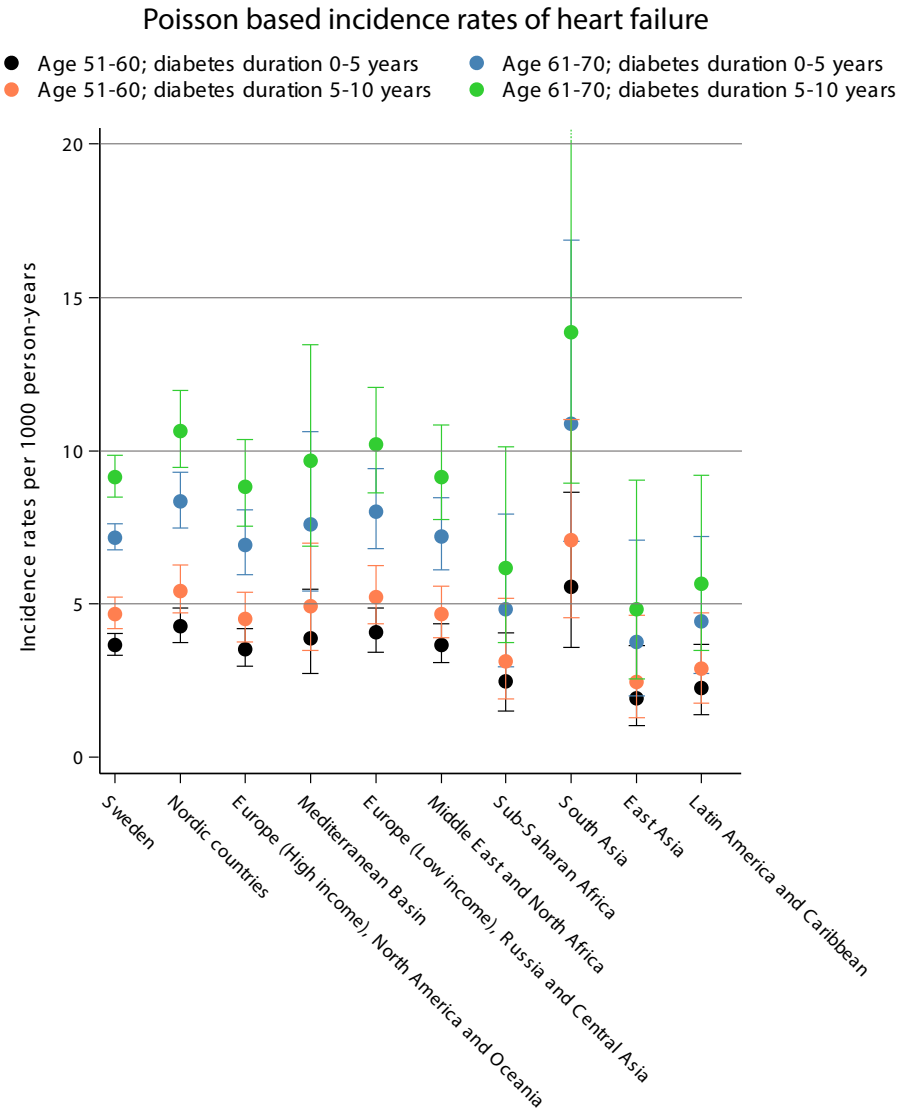


Figure 21 | Poisson based incidence rates of heart failure per 1,000 person-years.

ADJUSTED HAZARD RATIOS

When controlling for age at inclusion, age at onset of diabetes and sex, low-income Europe, Russia & Central Asia, Middle East & North Africa, Nordic countries and South Asia had 18–51 % higher risk of event (model 1, Table 3, below). Latin America and the Caribbean had 37% lower risk of event. The full Cox regression, adjusted for 15 covariates, showed that the hazard ratio (95% CI) for HF was 1.20 (1.08, 1.33) for Nordic countries, 1.69 (1.06, 2.69) for South Asia

and 0.36 (0.18, 0.71) for Latin America and the Caribbean. Remaining ethnic groups did not differ significantly from Swedes. Excluding income from the models made little difference. The hazard ratio (95% CI) was 1.97 (1.24, 3.14) for South Asia, 1.24 (1.11, 1.37) for Nordic countries and 0.40 (0.20, 0.79) for Latin America & The Caribbean.

TABLE 4: HAZARD RATIOS FOR DEVELOPING HEART FAILURE ACCORDING TO ETHNICITY

	Model 1	Model 2	Model 3	Model 4
ETHNICITY (ref = Sweden)				
East Asia	0.50 (0.29, 0.85)	0.38 (0.21, 0.71)	0.48 (0.23, 1.01)	0.49 (0.22, 1.09)
Europe (HI), North America and Oceania	1.00 (0.89, 1.14)	1.02 (0.90, 1.16)	0.97 (0.83, 1.13)	1.05 (0.90, 1.23)
Europe (LI), Russia and Central Asia	1.30 (1.13, 1.49)	1.05 (0.89, 1.23)	0.94 (0.77, 1.14)	1.03 (0.85, 1.25)
Latin America and Caribbean	0.63 (0.41, 0.96)	0.54 (0.34, 0.84)	0.31 (0.15, 0.61)	0.36 (0.18, 0.71)
Mediterranean Basin	1.14 (0.85, 1.52)	1.14 (0.85, 1.52)	1.17 (0.85, 1.61)	1.24 (0.90, 1.72)
Middle East and North Africa	1.18 (1.03, 1.35)	0.76 (0.63, 0.90)	0.74 (0.60, 0.91)	0.85 (0.69, 1.05)
Nordic countries	1.31 (1.20, 1.42)	1.23 (1.12, 1.34)	1.17 (1.06, 1.30)	1.20 (1.08, 1.33)
South Asia	1.51 (1.03, 2.21)	1.28 (0.86, 1.92)	1.50 (0.94, 2.39)	1.69 (1.06, 2.69)
Sub-Saharan Africa	0.79 (0.52, 1.21)	0.69 (0.43, 1.11)	0.82 (0.47, 1.41)	0.90 (0.51, 1.59)

Model 1 is adjusted for age, age at onset of diabetes, sex and ethnicity.
Model 2: additionally income and education.
Model 3: additionally cholesterol/HDL-ratio, smoking status, systolic BP, HbA1c, BMI.
Model 4: additionally eGFR, glucose lowering treatment, blood pressure lowering treatment and comorbidities.
HI = high-income. LI = low-income.

DISCUSSION

After controlling for age at inclusion, age at onset of diabetes and sex, immigrants from Nordic countries, low-income Europe, Russia & Central Asia, Middle East

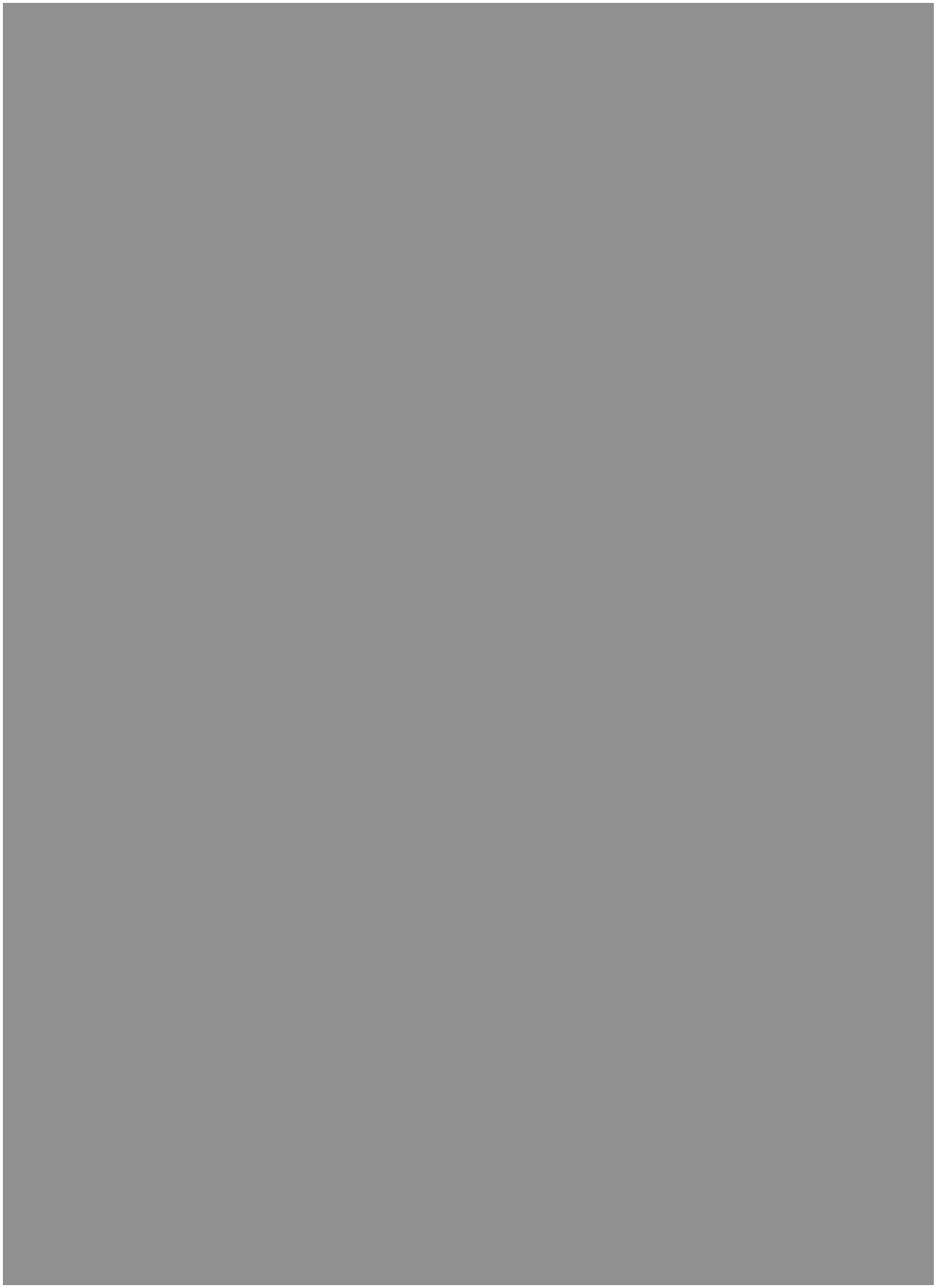
and North Africa and South Asia had 31%, 30%, 18% and 51% higher risk of heart failure, respectively. These differences were reduced or eliminated with further risk factor adjustment. After adequate adjustment we note that Nordic countries and South Asia still had 20% and 70% higher risk of developing heart failure, respectively. These findings surprised us, particularly since non-Western immigrants developed heart failure 6–16 years earlier in life. Nordic countries share borders, language, culture and life-style with Sweden. These immigrants should theoretically manage better than non-Western immigrants but this was not the case. There might be several explanations for this. Non-Western groups differed markedly from Swedes at baseline and they experienced few events. This might render the groups non-comparable, despite advanced regression methods. We used competing risk regression, matching and splines but the results remained unchanged.

Persons from Nordic countries represent the largest immigrant group in Sweden. They had plenty of events and were indeed comparable to Swedes at baseline. South Asians, a fairly small group in Sweden, displayed an unexpectedly high risk of heart failure. South Asians appear to be more susceptible in diabetes; they develop the disease early in life, at lower BMI and so on.[73,101,157] To our knowledge this is the first study to report the excess risk of heart failure among South Asians with diabetes.[291]

Another explanation for the relatively low risk among immigrants could be the healthy migrant effect, which has been discussed previously. The finding that Latin Americans have 64% lower risk of heart failure could be such a phenomenon. One can, however, not rule out lifestyle and dietary habits could be an important contributor.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

There are ethnic differences in risk of heart failure in diabetes. Persons from South Asian appear to be at high risk of developing heart failure while persons from Latin America and the Caribbean display substantially lower risk than Europeans.



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CONCLUSIONS

Although the primary purpose of the Swedish National Diabetes Register is quality assurance, it provides a unique source for diabetes research. Important health questions can be elucidated with real-world data and extraordinary power.

The incidence of type 1 diabetes in 15–34 year olds is two to three times higher than previously reported. The Prescribed Drug Register is the gold standard for monitoring the incidence of type 1 diabetes. The method is feasible, reliable and cost-effective. Furthermore, important evidence supporting the spring harvest theory is discarded.

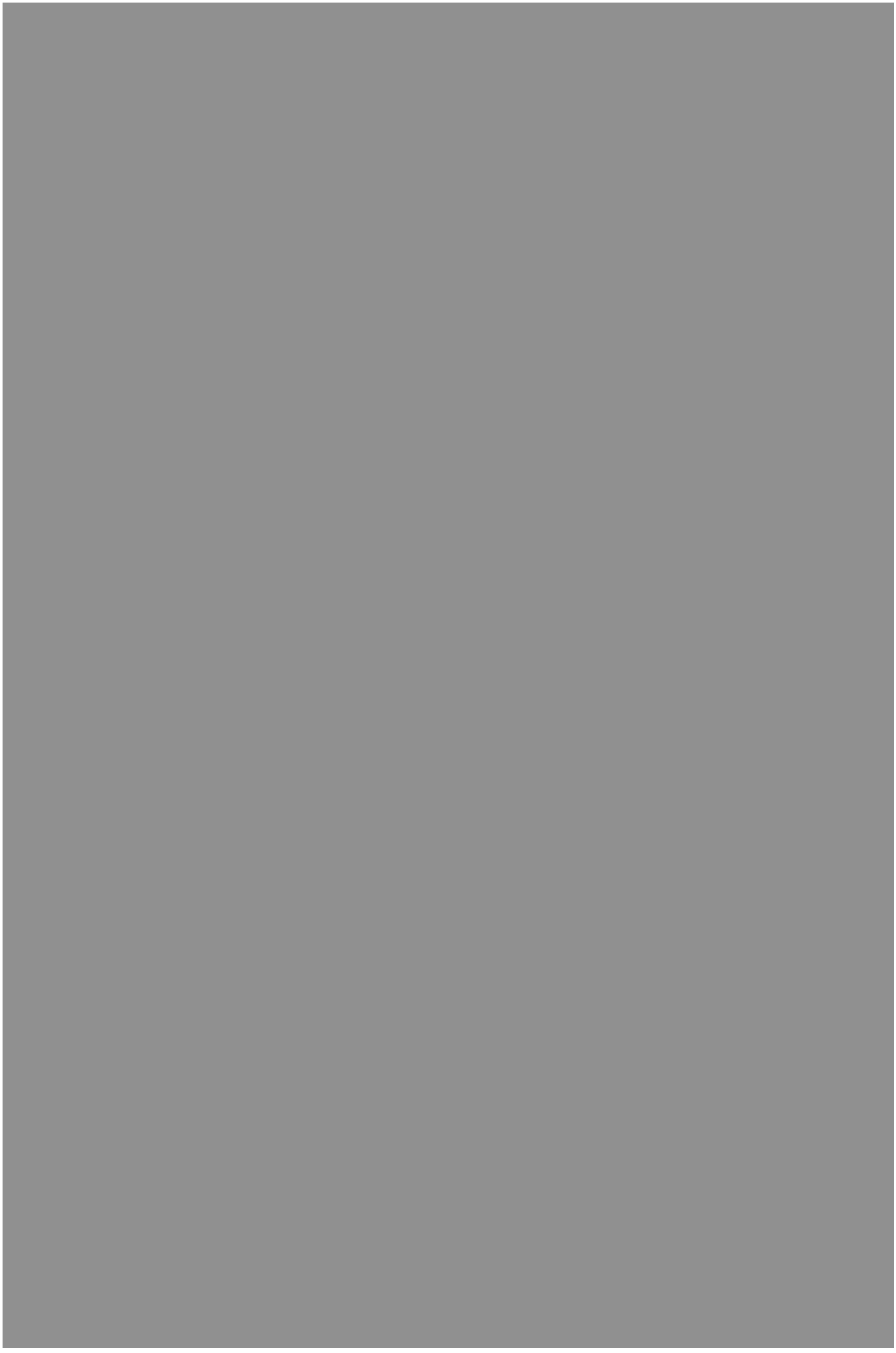
There are staggering socioeconomic disparities despite the resources of the Swedish healthcare system.

Low income and education is associated with two to three times as great a risk of serious cardiovascular events and death in type 1 diabetes. Being male, divorced, single or widowed was also associated with a substantially higher risk of adverse outcomes. Targeted and stringent risk factor control is warranted to reduce these disparities.

Cardiovascular risk factors have improved in the past two decades among patients with type 1 diabetes. However, the improvement has neither been uniform nor universal. Smoking cessation has been successful, but socioeconomic inequalities remain marked. The same disparities are observed for physical activity. Improvement in HbA1c has not been stable over time, whereas blood pressure has been lowered efficiently. The marked increase in BMI is worrisome. Individuals with type 1 diabetes are now overweight on average.

Despite earlier start of glucose-lowering therapies, equitable access to health care and more appointments, immigrants—particularly those of non-Western origin—with type 2 diabetes have substantially higher HbA1c, greater risk of therapy failure and higher probability of developing albuminuria than native Swedes. The impact of ethnicity on glycaemic control is greater than the effect of income and educational level and on a par with the effect of physical activity. Thus, ethnicity needs to be carefully considered if diabetes care is to improve.

There are ethnic differences in risk of heart failure in type 2 diabetes. Persons from South Asia appear to be at high risk of developing heart failure while persons from Latin America and the Caribbean display substantially lower risk than Caucasian Europeans.



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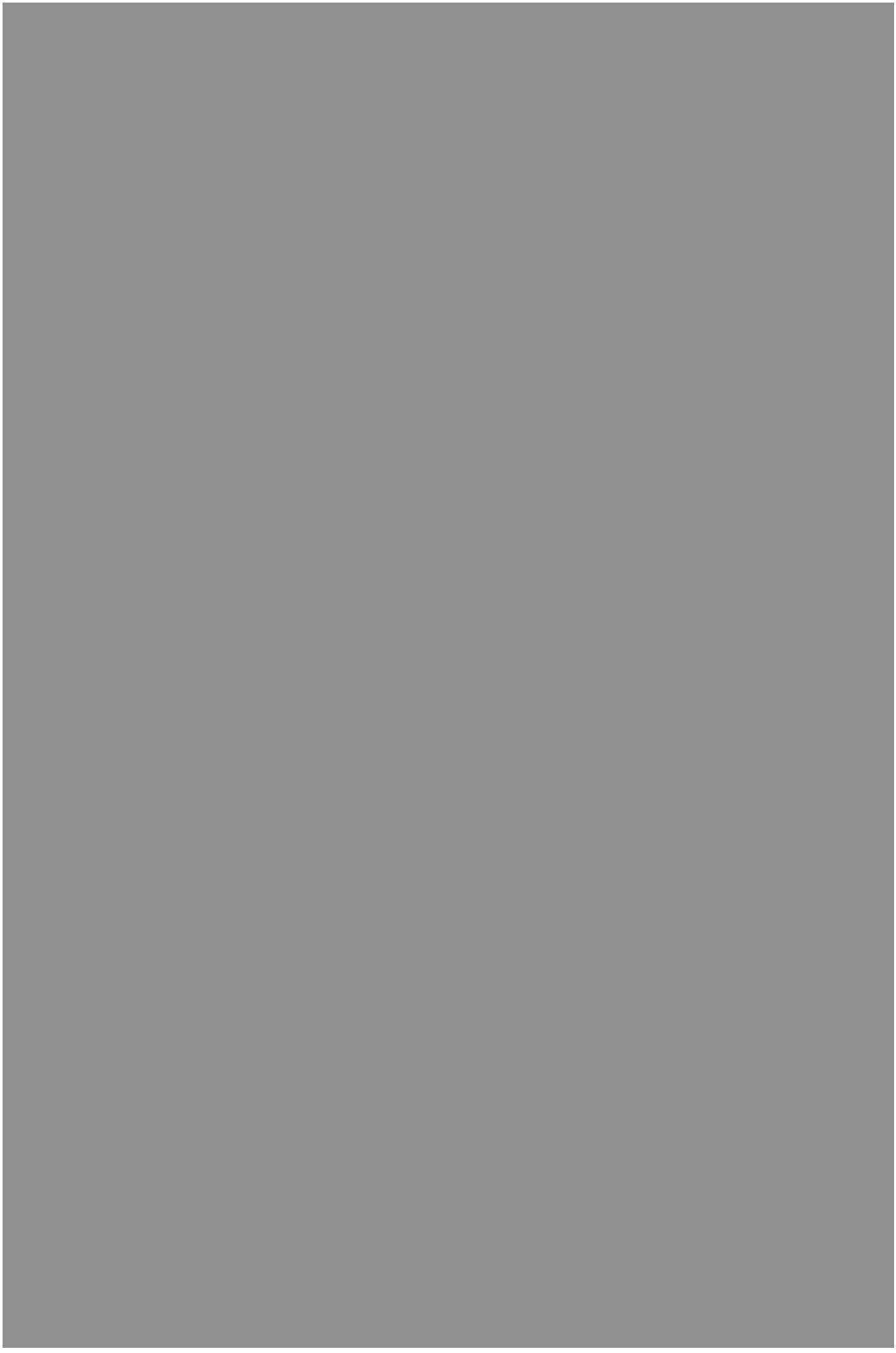

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STUDY I

STUDY II

STUDY III

STUDY IV

STUDY V