Risk factors of type 2 diabetes and excess risk of stroke in patients with diabetes

Christina Hedén Ståhl

UNIVERSITY OF GOTHENBURG

2016

Risk factors of type 2 diabetes and excess risk of stroke in patients with diabetes

christina.heden-stahl@vgregion.se

ISBN 978-91-628-9921-9 (hard copy)
ISBN 978-91-628-9922-6 (e-pub)
http://hdl.handle.net/2077/44858

Printed by Kompendiet, Gothenburg, Sweden 2016

To my family

ABSTRACT

The incidence of type 2 diabetes is increasing worldwide, mainly because of increasing life expectancy and changes in lifestyle. However, several other factors may also increase the risk of type 2 diabetes and their importance at a longer follow-up are not well explored. People living with diabetes have an increased risk of stroke but there are still gaps in knowledge about the excess risk at different risk factor levels. The first purpose of this thesis was to explore two risk factors for type 2 diabetes, high-normal blood pressure and low socioeconomic position defined by occupation, based on data from the Multifactor Primary Prevention study in Gothenburg. The second aim was to estimate the excess risk of stroke in people with type 2 diabetes in respect to their blood pressure level and in people with type 1 diabetes in respect to their metabolic control measured by HbA1c. For these studies, data on people with diabetes were collected from the National Diabetes Register and the excess risk of stroke was compared to controls from the general population.

Out of 7494 middle aged men in Gothenburg examined in 1970-1973 and followed until the end of 2011, 13% had a registered diagnosis of diabetes mellitus at any time. Men with systolic blood pressure 130-139 mmHg (high-normal blood pressure) at the screening examination had a 43% increased risk of developing diabetes compared to men with systolic blood pressure below 130 mmHg. Men in the lowest occupational class had a significantly increased risk of diabetes compared to men in the highest occupational class even after adjusting for stress and several other risk factors for diabetes. The conditional probability of developing diabetes after 35 years taking death attributable to other causes into account was 43% in the lowest occupational class compared to 23% in the highest occupational class.

As a group, people with type 2 diabetes had an increased risk of stroke compared to the risk of the general population. When the risk was estimated at different blood pressure levels, the increased risk of ischemic stroke at all blood pressure levels was offset by a significant reduced risk of hemorrhagic stroke at lower blood pressure levels. Therefore people with type 2 diabetes and a blood pressure below 130/80 mmHg had a risk of stroke comparable to the general population.

The risk of stroke was increased for people with type 1 diabetes in all HbA1c categories compared to the general population. However, the risk rose from 75% excess in risk for people with type 1 diabetes and good metabolic control to an eightfold excess in risk for the least well controlled group. HbA1c was more important as a risk factor for ischemic compared to hemorrhagic stroke in people with type 1 diabetes.

In conclusion, this thesis showed that high-normal blood pressure and low occupational class remain as risk factors for type 2 diabetes even after an extended follow-up into older ages. People with type 2 diabetes and low blood pressure have a risk of stroke comparable to the general population. The thesis also underlines the importance of assisting people with type 1 diabetes in every possible way to maintain a good metabolic control in order reduce the risk of stroke.

Keywords: type 2 diabetes, type 1 diabetes, stroke, high-normal blood pressure, occupational class, blood pressure, glycemic control

ISBN: ISBN 978-91-628-9921-9 (hard copy) http://hdl.handle.net/2077/44858
978-91-628-9922-6 (e-pub)

LIST OF PAPERS

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

I Hedén Stahl C, Novak M, Lappas G, Wilhelmsen L, Björck L, Hansson P-O, Rosengren A. High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men.
BMC Cardiovasc Disord. 2012;12:89. http://www.biomedcentral.com/1471-2261/12/89

II Hedén Stahl C, Novak M, Hansson P-O, Lappas G, Wilhelmsen L, Rosengren A. Incidence of Type 2 diabetes among occupational classes in Sweden: a 35-year follow-up cohort study in middle-aged men.
Diabet Med. 2014;31(6):674-80.

III C. Hedén Stahl, M. Lind, A-M. Svensson, M. Kosiborod, S. Gudbjörnsdottir, A. Pivodic, M. Clements, A. Rosengren. Long-term excess risk of stroke in people with type 2 diabetes in Sweden according to blood pressure level: A population-based case-control study
Accepted for publication in Diabetic Medicine 2016

IV C Hedén Ståhl, M Lind, A-M Svensson, S Gudbjörnsdottir, A Mårtensson, A Rosengren. Glycaemic control and excess risk of ischaemic and haemorrhagic stroke in patients with type 1 diabetes: a cohort study of 33,453 patients
Accepted for publication in Journal of Internal Medicine 2016

SAMMANFATTNING PÅ SVENSKA

Antalet människor som lever med diabetes ökar i världen. Framför allt ökar förekomsten av typ 2 diabetes som till stor del orsakas av övervikt, för lite fysisk aktivitet och andra livsstilsfaktorer. Att ha diabetes innebär en ökad risk för flera hjärt-kärlsjukdomar däribland stroke.

Denna avhandling hade två övergripande mål. Det första var att undersöka om blodtrycksläge i det högre normalområdet samt låg socioekonomisk position (definierad av yrke) hos män i 50-års åldern innebar en ökad risk för senare utveckling av typ 2 diabetes. Dessa två studier gjordes på data från Primärpreventiva studien i Göteborg. Det andra huvudmålet för avhandlingen var att beräkna den ökade risken för stroke vid olika blodtrycksnivåer för personer med typ 2 diabetes och för personer med typ 1 diabetes vid olika nivåer av medelblodsockret (metabol kontroll) jämfört med risken i normalbefolkningen. Data och deltagare med diabetes erhölls från Nationella Diabetesregistret och köns- och åldersmatchade kontrollpersoner från normalbefolkningen erhölls från befolkningsregistret.

Männen i Primärpreventiva studien följdes från början på 70-talet och fram till och med 2011. Under den tiden registrerades en diabetesdiagnos hos 13% av de 7494 männen. Studien visade att män med blodtryck inom det högre normalområdet när de var ca 50 år hade en ökad risk att senare insjukna i typ 2 diabetes, jämfört med män med lägre blodtryck. Dessutom hade män med manuella yrken en signifikant ökad risk för diabetes jämfört med högre tjänstemän och motsvarande. En stor del av den ökade risken förklarades av de klassiska riskfaktorerna för diabetes som tex övervikt och låg fysisk aktivitet vilka var mer vanligt förekommande i de lägre socioekonomiska klasserna men en oberoende riskökning kvarstod.

Patienter med typ 2 diabetes hade en ökad risk för ischemisk stroke (blodpropp i hjärnans kärl) vid alla blodtrycksnivåer jämfört med kontroller ur befolkningen. Dock var risken för hemorrhagisk stroke (blödning i hjärnan) hos personer med typ 2 diabetes och blodtryck 120-139/70-89 mmHg lägre än för kontroller. Detta gjorde att personer med typ 2 diabetes och blodtryck under 130/80 mmHg hade en total risk för stroke som var jämförbar med den hos personer utan diabetes.

För patienter med typ 1 diabetes var risken för stroke ökad vid alla nivåer av metabol kontroll jämfört med risken i normalbefolkningen. Dock ökade risken kraftigt vid sämre metabol kontroll. Risken steg från 75% ökning av strokerisken bland de med bäst metabol kontroll till en åtta gånger ökad risk för stroke i gruppen med sämst metabol kontroll jämfört med normalbefolkningen.

CONTENTS

ABBREVIATIONS

WHO	World Health Organization
ADA	American Diabetes Association
OGTT	oral glucose tolerance test
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
BMI	body mass index
SEP	socioeconomic position
SBP	systolic blood pressure
DBP	diastolic blood pressure
NDR	National Diabetes Register
NPR	National Patient Register
CDR	Cause of Death Register
ICD	International Classification of Diseases
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies register
ESRD	end-stage renal disease
IFCC	International Federation of Clinical Chemistry and laboratory medicine
NGSP	National Glycohemoglobin Standardization Program
AF	atrial fibrillation
HF	heart failure
CHD	coronary heart disease
AMI	acute myocardial infarction
HR	hazard ratio
CI	confidence interval

INTRODUCTION

Diabetes is an important cause of morbidity and mortality worldwide by causing both micro- and macrovascular complications (1-3). The most common results of microvascular angiopathy are loss of renal function, blindness, and neuropathy while the macrovascular complications result in cardiovascular diseases such as ischemic heart disease and stroke (2).

There are two main forms of diabetes - type 1 and type 2. Elevated blood glucose level is a common feature but the pathogenesis in the two forms is very different. Type 1 diabetes is caused by an autoimmune destruction of the insulin-producing beta cells in the pancreas leading to insulin deficiency, while the main feature of type 2 diabetes is insulin resistance. The vast majority of all diabetes worldwide is type 2 diabetes (>90%) and the prevalence has increased in the world in the last decades (4), mainly due to rapidly increasing overweight and obesity. Therefore, it is important to determine risk factors for diabetes in order to improve knowledge about what action should be taken to prevent diabetes type 2.

Stroke is a vascular disorder affecting the vessels in the brain, frequently resulting in long-lasting neurological deficits or death. According to the Global Burden of Disease study stroke was the second most common cause of death in the world and the third most common cause of disability-adjusted life-years in 2010 (3, 5). Patients with diabetes are more affected by stroke than persons without diabetes (6). Therefore it is important to determine what factors increase the risk of stroke in diabetes patients in order to protect them from this condition with potentially huge impact on everyday life.

Diagnosis of diabetes

Diabetes is diagnosed by clinical symptoms in the patients and by measuring the glucose levels in plasma. Current diagnostic criteria for diabetes defined by the World Health Organization (WHO) have been in use since 1998 when the cut-off limit for fasting plasma glucose was lowered (7, 8). Since 2010 both WHO and the American Diabetes Association (ADA) also recommend the use of HbA1c as a method of diagnosing diabetes (9, 10). For diagnosis criteria, see Table 1.

The oral glucose tolerance test (OGTT) is used for diagnosis when blood glucose levels are non-conclusive, during pregnancy or sometimes in epidemiology cohort studies. After overnight fasting, 75 g of glucose is ingested and plasma glucose values are measured after 2 hours (8).

Individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered to be normal, have been identified as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). These individuals have been shown to be at an increased risk for cardiovascular disease and future diabetes (11, 12).

Table 1. Diagnostic criteria for diabetes, IFG and IGT according to WHO (7)

	IFG (Impaired Fasting Glucose)	IGT (Impaired Glucose Tolerance)	Diabetes
Fasting	≥6.1- <7.0	<7.0	≥7.0*
2 hour post-load OGTT	<7.8	≥7.8 - <11.1	≥11.1*
HbA1C (mmol/mol)	*Not applicable*	*Not applicable*	≥48*
Random glucose	*Not applicable*	*Not applicable*	≥11.1 and classical symptoms

Glucose values in venous plasma glucose mmol/l. *For the diagnosis of diabetes a pathological plasma glucose value must be confirmed in a repeat sample with the same analysis method if not HbA1c value tested simultaneously indicates diabetes and vice versa.

Type 1 diabetes

Type 1 diabetes is an autoimmune disease leading to destruction of the insulin producing β-cells in the pancreas. Patients with type 1 diabetes have an absolute insulin deficit and require insulin treatment from the start.

Type 1 diabetes constitutes 5-10% of the diabetes worldwide and approximately 10-15% of the diabetes cases in Sweden (13, 14). The incidence and prevalence of type 1 diabetes vary substantially in the world with high rates in for example the Nordic countries, Canada and Sardinia (Italy) while China and India have much lower incidence and prevalence (15, 16). An increased incidence of type 1 diabetes has been seen in the last decades in particular in countries with historically high incidence. This increase has been most conspicuous among younger children (15). The mechanism underlying the difference in prevalence between countries and the increase in incidence rates during the last decades are unknown but are largely attributed to environmental influences.

Type 1 diabetes develops due to a combination of genetic predisposition and unknown environmental factors (16). Several loci on different chromosomes have been connected to type 1 diabetes and if this genetic susceptibility is combined with environmental factors the disease may appear. Environmental factors that have been discussed are dietary factors like substances in cows' milk and N-nitroso compounds in meat, vitamin D and different viruses (15, 17). Another factor discussed is the "the hygiene hypothesis". This hypothesis postulates that type 1 diabetes develops due to less microbial stimuli for the immune system in many developed societies (17).

The clinical characteristics of the patient with newly diagnosed diabetes together with symptoms at onset, measurement of autoantibodies and level of C-peptide are often enough to distinguish type 1 diabetes from other forms of diabetes (18). The autoantibodies are directed to different substances connected to the insulin producing β-cells. The C-peptide is formed when endogenous insulin is synthesized.

The development over the last decades of insulin analogues, better devices for self-monitoring of blood glucose, new mechanical technologies for insulin administration have improved treatment of type 1 diabetes. The goal for treatment of type 1 diabetes

patients is to maintain a blood glucose level which gives a minimum of symptoms of both high and low plasma glucose and to minimize secondary complications.

Type 2 diabetes

Over 90% of the diabetes cases in the world are diabetes type 2 (19). The prevalence in the world has been rising the last decades due to population ageing and changes in lifestyle (4). Global age-standardized prevalence of type 2 diabetes increased from 4.3% in 1980 to 9.0% in 2 014 for men and from 5.0% to 7.9% in women. The fastest increase in prevalence occurred in low- and middle-income countries (4). In Sweden, slightly surprisingly, no increase in incidence has been observed but there has been an increase in prevalence (20, 21), mostly due to increasing life expectancy overall and improved survival in patients with diabetes. The projection for the future is a further increase in prevalence of type 2 diabetes both in Sweden and in the rest of the world (19, 20).

Pathogenesis of type 2 diabetes

In a healthy individual without diabetes blood glucose level is maintained within a tight range through a feedback loop between insulin sensitive tissue (muscles, adipose tissue and liver) and the insulin producing β-cells in the pancreas. Insulin released from the β-cells stimulates the uptake of glucose, amino acids and fatty acids in insulin-sensitive tissues. The insulin-sensitive tissues feed back information to the β-cells about their need for insulin by a so far unidentified mediator (22).

Type 2 diabetes develops as a consequence of chronic fuel excess resulting in insulin resistance and β-cell dysfunction (10). When insulin resistance occurs in the insulin-sensitive tissue, as most often seen with obesity, the β-cells increase their insulin output in order to override the insulin resistance and maintain normal glucose levels. When the β-cells no longer are capable of producing enough insulin to overcome the resistance in the tissue, the glucose levels start to rise. It is the magnitude of β-cell dysfunction that determines the degree of elevation in plasma glucose. Insulin resistance is already well established when IGT is present and with declining β-cell function IGT progresses to type 2 diabetes. In recent years β-cell dysfunction has emerged as potentially the most important part in the pathophysiology of type 2 diabetes. Individuals with susceptible β-cell function fail to adapt to overnutrition and go on to develop type 2 diabetes (10).

Genes and environmental factors are both important in emerging insulin resistance and β-cell dysfunction. Since our gene pool will not have changed within a short time frame, environmental factors – lifestyle factors – are crucial in the emerging global type 2 diabetes epidemic (10, 22).

Risk factors of type 2 diabetes

A wide range of conditions have been associated with an increased risk of developing type 2 diabetes. The risk factors of type 2 diabetes can be divided into modifiable and non-modifiable risk factors. Below is a selection of some predictors of type 2 diabetes.

Non-modifiable risk factors

Several susceptible genetic loci have been associated with type 2 diabetes and the frequency of these loci alter between different ethnic groups (23). The prevalence of type 2 diabetes increases with age (20). Men develop type 2 diabetes at a lower BMI than women at the same age (24). In the last years interest has been directed towards the fetal intrauterine milieu. Adverse circumstances in the intrauterine milieu might lead to alterations in gene expression that are not associated with changes in DNA sequences (23). Low birth weight as well as high birth weight has been associated with a higher risk of developing type 2 diabetes later in life (25, 26). Gestational diabetes, a carbohydrate intolerance first presenting in pregnancy, is a risk factor for development of type 2 diabetes later in life for the afflicted woman and exposure to intrauterine hyperglycemia increases the risk of type 2 diabetes later in life for the offspring (27).

Modifiable risk factors

Obesity is the strongest risk factor for type 2 diabetes (28) and visceral adiposity is of special importance (29). Physical activity can affect the risk of developing type 2 diabetes by reducing weight and by decreasing insulin resistance (30). Dietary factors such as increasing the amount of vegetables, lower intake of meat, sweets, high-fat dairy and refined grains reduce the risk of type 2 diabetes (31). Lifestyle intervention programs with increased physical activity and diet changes reduce the risk of type 2 diabetes (32, 33). Other modifiable risk factors shown to affect the risk of developing diabetes are psychological stress (34) and smoking (35).

Hypertension and type 2 diabetes are two conditions well known to coexist and type 2 diabetes patients have higher blood pressure than persons without diabetes (36). The reasons for this association are not fully established but disturbances in the microcirculation causing insulin resistance, subsequent hyperinsulinemia and impaired endothelial function could be pathophysiological mechanisms linking the two conditions (37, 38). Studies have also shown that hypertension per se is a predictor of type 2 diabetes (39, 40). Studies with a follow-up of up to 10 years have shown that blood pressure within the upper normal range is associated with increased risk of diabetes (41, 42). However, if high-normal blood pressure persists as a risk factor for subsequent development of diabetes after a prolonged follow-up is unknown.

Socioeconomic position (SEP) refers to the social and economic factors that affect what position an individual or group of individuals hold in the society (43). It can be defined as a combined concept that includes both resource-based measures and prestige-based measures. Different indicators of SEP can be used, for example education, occupation and income (43). SEP affects overall and cause-specific mortality (44) and risk factors for cardiovascular diseases have been shown to be unevenly distributed across SEP categories (45). SEP has also been identified as a predictor for diabetes (46) at least in studies with a maximum of 15 years of follow-up. The difference in incidence of type 2 diabetes between different SEP groups is partly explained by differences in prevalence of classical risk factors for type 2 diabetes like obesity, mental stress and low physical activity (47). If SEP defined by occupation among Swedish men is an independent predictor for type 2 diabetes at a longer follow-up, into older age, has not been extensively examined.

Management of type 2 diabetes

While type 1 diabetes typically has a rapid onset with symptoms during some weeks before diagnosis, type 2 diabetes can be present for several years without much symptoms causing the patient to seek medical care. Type 1 diabetes patients have an absolute insulin deficiency and need insulin replacement therapy from start which type 2 diabetes patients seldom do. Lifestyle modification is nearly always needed for both types, but particularly in type 2 diabetes. Pharmacological therapies for managing hyperglycemia in type 2 diabetes can roughly be divided into one of three groups – insulin providers (insulin, sulphonylureas, meglitinides, glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidylpeptidase-4 [DPP-4] inhibitors), insulin sensitizers (metformin, pioglitazone) and glucose adsorption inhibitors (alpha-glucosidase inhibitors, sodium-glucose co-transporter-2 [SGLT2] inhibitors) (48). As for type 1 diabetes patients, the goal with the treatment is to have a glucose level without symptoms in everyday life and to minimize secondary complications.

Stroke

WHO defines stroke as an acute neurological deficit caused by a focal injury of the central nervous system with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (49). Stroke is classified as ischemic or hemorrhagic based on the underlying pathology. For correct classification neuroimaging with either computer tomography (CT) or magnetic resonance imaging (MRI) is required.

Ischemic strokes appear when a blood vessel in the brain becomes partly or totally obstructed. This leads to lack of blood supply "down-stream" from the obstruction causing focal ischemia in the tissue and later cell necrosis in the affected area. Hemorrhagic stroke arises when a blood vessel ruptures and causes a bleeding. The blood distorts and compresses the cerebral tissue causing necrosis. Ischemic stroke represents the greater part of stroke subtypes, approximately 85% in high-income countries like Sweden, and thus the hemorrhagic strokes a lesser part, approximately 15%. However, in middle-and low-income countries hemorrhagic stroke represents a larger share of the stroke cases, up to approximately 25% (50).

Ischemic stroke can be classified into different subtypes based on the underlying pathophysiological mechanism causing the obstruction in the vessel. According to the TOAST (Trial of Org. 10172 in Acute Stroke Treatment) classification system these subtypes are: large vessel disease, small vessel disease, cardioembolic stroke, stroke of other determined etiology, undetermined stroke and cryptogenic stroke (51). Hemorrhagic stroke is subclassified as either intracerebral hemorrhage or subarachnoid hemorrhage depending on the site and origin of the bleeding.

Risk factors of stroke

There are several well-known risk factors for stroke. Age is one important risk factor although a non-modifiable one. However, from the INTERSTROKE and other studies we also know that hypertension, smoking, waist-to-hip ratio, diet, regular physical

activity, diabetes, heavy alcohol intake, psychological stress and depression, cardiac causes (for example atrial fibrillation) and lipid profile are risk factors for stroke. The INTERSTROKE study estimated that these ten modifiable risk factors accounted for approximately 90% of all strokes (52).

Diabetes per se confers an increased risk of stroke compared to people without diabetes. The figures differ between studies but having diabetes approximately doubles the risk of stroke (53, 54). While most studies have found an association between diabetes and ischemic stroke, there have been conflicting findings concerning if diabetes is a risk factor for hemorrhagic stroke or not. Some studies have found an association between diabetes and hemorrhagic stroke (55, 56) while others have not (57, 58).

Above all, diabetes seems to be an important risk factor for stroke in younger ages and for women (54). Risk factors for stroke like hypertension and atrial fibrillation are more prevalent in people with compared to people without diabetes (54, 59).

Stroke in patients with diabetes

Risk factors of stroke in patients with type 1 diabetes

Several of the risk factors of stroke in people without diabetes are also risk factors in people with type 1 diabetes. Studies have shown that higher age, longer diabetes duration, hypertension, diabetic nephropathy, history of smoking, level of glycemic control and cholesterol levels affect the risk of stroke in type 1 diabetes patients (60, 61)

Glycemic control and risk of stroke

In the last decade, an increasing number of studies have shown that HbA1c level affects the risk of cardiovascular disease in type 1 diabetes patients (60, 62). However, the number of stroke in these studies has often been limited (61-63). The often cited Diabetes Control and Complication Trial (DCCT) where they found that lower HbA1c gave less cardiovascular events only had 6 cases of stroke (62). There is no large study on patients with type 1 diabetes with sufficient number of strokes that has estimated the excess risk of stroke in patients with type 1 diabetes compared to the general population.

Risk factors of stroke in patients with type 2 diabetes

The risk factors of stroke are virtually the same for people without diabetes as for people with type 2 diabetes. The hyperglycemic state is specific for people with diabetes and high HbA1c has been shown to be a risk factor of ischemic stroke (64). However, studies comparing intensive versus standard glucose control in type 2 diabetes patients have so far failed to show a reduced risk of stroke (65).

Blood pressure and risk of stroke

Blood pressure is a well-known risk factor for cardiovascular disease in type 2 diabetes patients (36). There has been an intensive debate how to interpret studies and what blood pressure target should be aimed for among patients with type 2 diabetes. In the beginning of the third millennium guidelines advocated a blood pressure treatment target of <130/80 mmHg for patients with type 2 diabetes based on findings in stud-

ies such as HOT (66), HOPE (67) and UKPDS (68). However, the evidence for benefits concerning cardiovascular outcomes when treating the blood pressure below 130 mmHg has been found to be weak. Additional, studies have indicated a J-shaped curve between achieved blood pressure and cardiovascular out-come (69). Therefore, recent European guidelines have advocated a more conservative view, aiming for a blood pressure goal of <140/85 mmHg and individualized goals for blood pressure targets taking in account age, duration of diabetes and co-morbidities (48). The subject is still highly controversial and several studies comparing patients with type 2 diabetes with different blood pressure levels have tried to determine what blood pressure should be aimed at when treating patients with type 2 diabetes (70, 71). However, studies estimating the excess risk of stroke for type 2 diabetes patients at several different blood pressure levels compared to the risk of the general population do not exist.

Management of stroke and stroke out comes in diabetes patients

Hyperglycemia often occurs in the acute phase of a stroke due to activation of the hypothalamic-pituitary-adrenal axis leading to raised amounts of glucocorticoids (65). This hyperglycemia can be seen both in patients with and without previous known diabetes. The hyperglycemia can be caused by pre-existing glucosintolerance or undetected diabetes but can also be the result of a stress respons. Hyperglycemia at admission for ischemic stroke has been shown to be associated with increased 30-day mortality and poor functional outcome in patients without previous diabetes (72). However, studies have failed to prove that glucose-lowering treatment improves clinical outcome in patients with acute ischemic stroke. In experimental studies hyperglycemia has been linked to several mechanisms which could increase brain damage in ischemic stroke, for example, reperfusion injury and impaired recanalization (65). Taken together, guidelines advocate treatment of glucose levels >10 mmol/L in the acute phase of an ischemic stroke (73) and monitoring of the risk of hypoglycemia.

Studies have shown that the distribution of subtypes of stroke differ between people with and without diabetes. People with diabetes have a larger proportion of lacunar infarcts (59), more subcortical infarcts and lower relative incidence of intracerebral haemorrhage (74) compared to people without diabetes. Stroke severity does not seem to differ between patients with or without diabetes (75).

The mortality rates during the first 3 months after an ischemic stroke do not differ between patients with diabetes compared to patients without diabetes, while mortality rates in one-year survivors after a stroke is increased among patients with compared to patients without diabetes (65). The risk of recurrent stroke is increased in patients with type 1 and type 2 diabetes compared to patients without diabetes (75).

In the present series of studies we used data from several sources, including population cohort studies with long-term follow up as well as the very large NDR with detailed data on patients with diabetes in combination with data from other registers. Type 2 diabetes often develops later in life and with the world's aging population it is becoming increasingly important to know to which extent the effect of risk factors persists into older ages. We wanted to ascertain if high-normal blood pressure and occupational class among middle aged men in Gothenburg persisted as predictors of

type 2 diabetes even after an extended follow-up, something that to our knowledge has not been examined. We also estimated the excess risk of stroke compared to the general population at several different blood pressure levels for patients with type 2 diabetes and at different HbA1c levels for patients with type 1 diabetes in uniquely large cohorts. Similar estimates of excess risk at different risk factor levels have not been assessed before. Excess risk of stroke for patients with diabetes is important information, for example to decision makers when deciding how to allocate resources from the common health care budget to risk factor control in patients with diabetes.

AIMS

There were two overall aims of this thesis. The first was to evaluate potential predictors of type 2 diabetes in middle aged men. The second aim was to estimate the excess risk of stroke in patients with type 1 and 2 diabetes compared to the general population by specific characteristics as detailed below.

Specific aims

Paper I To evaluate if high-normal blood pressure in middle-aged men predicts development of type 2 diabetes during an extended follow-up over 35 years.

Paper II To assess if low occupational class is an independent predictor of type 2 diabetes in Swedish men, after adjustment for conventional risk factors and psychological stress.

Paper III To estimate the excess risk of stroke for type 2 diabetes patients at different blood pressure levels compared to the general population.

Paper IV To estimate the excess risk of stroke in type 1 diabetes patients with different glycemic control compared to the general population

PATIENTS AND METHODS

Paper I and II of this thesis are based on the Multifactor Primary Prevention study. Paper III and IV, are based on cohorts of patients with diabetes derived from the National Diabetes Register (NDR) and sex, age and county matched control cohorts from the general population. All studies were approved by the regional ethical board of Gothenburg.

Study populations

The Multifactor Primary Prevention study (Paper I and II)

The Multifactor Primary Prevention study was launched in 1970 in order to explore if directed intervention against high levels of three predefined cardiovascular risk factors, hypertension, smoking and hypercholesterolemia, had any effect on cardiovascular outcomes (76, 77). The study included all men in the city born between 1915 and 1925 (except those born 1923 because these were eligible for participation in another cohort study). The men were 47 to 55 years of age (mean age about 51 years) at study start. The men were divided into three groups of approximately 10 000 men in each group, where one group was chosen as the intervention group and the two others as control groups. All men in the intervention group were sent a postal questionnaire. Those who responded to the questionnaire were invited to a physical examination where risk factors were identified and intervention started if required. The intervention criteria were antihypertensive treatment if systolic blood pressure was >175 mmHg or if diastolic blood pressure was >115 mmHg, dietary advice if serum cholesterol levels were >260 mg per 100 ml (>6.8 mmol/1), and referral to anti-smoking clinics for participants who smoked ≥15 cigarettes per day. Of the 10 000 men in the intervention group 7494 (75%) attended the basal physical examination. A small subsample (2%) of men in one of the control groups were sent the questionnaire and invited to physical examination in order to check comparability between the intervention and control groups (76). No action on risk factors was taken in the control group.

A first follow-up was done after 4 years where the whole intervention group was invited for a re-examination and effects of the intervention on risk factors were measured. A random subsample of 11% in one of the control groups were also invited to re-examination. Ten years after entry, a random sample of 20% of the intervention group and a random sample of 20% in one of the control groups were invited for a final examination.

Cardiovascular end-points and cause-specific mortality were registered for participants in all three groups (both the intervention group and the two controls groups). The end-points were collected from assembling all death certificates in the city and by matching against the computerized Cause-of-death register, the Gothenburg Myocardial Infarction register and Stroke register (76).

At the final follow-up in 1983 it was found that the risk factors levels had markedly decreased in the intervention group – but also in the control group. No difference was

found between intervention group and control group concerning total mortality, stroke and cardiovascular disease incidence. Except for having taken part in an intervention study, the thoroughly examined intervention group of 7494 men can therefore be regarded as representative of the middle aged male general population in Gothenburg in the beginning of the seventies.

Paper I

For the purpose of this paper we used data from the 7494 men in the intervention group of the Multifactor Primary Prevention study. We excluded 149 patients who reported known diabetes at the baseline examination. We also excluded 14 participants with missing information on blood pressure data.

Paper II

From the 7494 men in the intervention group of the Multifactor Primary Prevention study we excluded 238 men that reported preexisting diabetes, stroke or myocardial infarction. We also excluded 382 men that could not be classified according to Swedish socio-economic classification system.

Patients from the National Diabetes Register and matched controls (Paper III and IV)

The Swedish National Diabetes Register (NDR) was started in 1996 as a quality assurance tool in diabetes care. The purpose was to monitor the results from health care centers from year to year, compare the results with regional and national means and feed-back the information to the reporting health care center for quality improvement work (78). The health care centers report to the NDR, annually, basal clinical characteristics of the patients as well as measurements of risk factors and presence of complications of diabetes. The number of patients with diabetes reported to NDR have increased through the years. Type 1 diabetes patients are mainly taken care of at hospital based out-patients clinics and these started to report to NDR at an earlier stage compared to most primary care clinics where type 2 diabetes patients often are managed. Therefore, the coverage among type 1 diabetes patients was estimated to be 50% already in 2003, while the coverage increased more slowly for type 2 diabetes patients. In the annual report from NDR 2013 it was estimated that 88% of all patients with known diabetes in Sweden were reported to the NDR.

Paper III

In the NDR, type 2 diabetes is defined as diabetes treated with diet only, oral hypoglycemic agents only or insulin only or in combination with oral hypoglycemic agents if onset of diabetes ≥40 years (79).

For the purpose of Paper III, we included all type 2 diabetes patients with at least one registration in the NDR between 1998 and 2011. For every type 2 diabetes patient, 5 age-, sex-, and county-matched controls were included from the Swedish Total Population Registry held by Statistics Sweden (Statistiska centralbyrån). This procedure rendered us 435,660 people with type 2 diabetes and 2,144,567 controls from the general population. We excluded controls that had a registration in the NDR (394), type 2 diabetes patients and controls who died before the start of the study (26,981), and type

2 diabetes patients and controls with a diagnosis of stroke registered before the start of the study (231,269). After these exclusions, 408,076 people with and 1,913,507 without type 2 diabetes remained for analysis.

Paper IV

Type 1 diabetes is defined in the NDR as treatment with insulin and a diagnosis at ≤30 years of age. This definition has been validated in the register and was found to be accurate in 97% of the cases listed (80).

In this study, 33,965 type 1 diabetes patients with at least one registration in the NDR from January 1 1998 until December 31 2011 were included. We randomly selected five controls matched for age, sex, and county of residence for each type 1 diabetes patient from the Swedish Total Population Registry. Excluded from the study were controls who had a registration in the NDR (6967) and type 1 diabetes patients and controls with a diagnosis of stroke which were registered before starting the study (506 and 2715, respectively). Excluded were also type 1 diabetes patients and controls that died before starting the study (3 and 205, respectively), usually controls who died between the date when the random selection of controls was made and the date when the index case was registered in the NDR. We also excluded type 1 diabetes patients and their controls with missing vital status data in the NDR (3 and 14, respectively). After these exclusions, 33,453 type 1 diabetes patients and 159,924 controls remained for analysis.

Methods

Registers

Administrative health care registers detailed below are used in all four papers either for gathering data to the studies and/or collecting end-points.

The Swedish National Patient Register (Paper I-IV)

The Swedish National Patient Register (NPR), previously named the Swedish hospital discharge register, is an administrative health care register where all discharges from hospital in Sweden are registered with primary and contributing diagnoses. The diagnoses are coded according to the International Classification of Disease (ICD). The NPR has operated on a nationwide basis since 1987, but all discharges from Gothenburg hospitals have been entered in the national register since 1970 (except in 1976 owing to a legislative change for that year). The accuracy of the discharge diagnoses, and the positive predictive value, differ between different diagnoses, but is generally 85-95% for major cardiovascular categories (81). For stroke diagnoses, a study in 2004 showed a sensitivity for stroke diagnosis of 92% when combined with the Cause of death register (82).

The Cause of Death Register (Paper I-IV)

The Cause of Death Register (CRD) is another administrative health care register also held by the National Board of Health and Welfare in Sweden. All deaths in Sweden are mandatory to register in CDR with an ICD code for cause of death. The CRD holds information about cause of deaths since 1961.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies register (Paper III and IV)

The Longitudinal Integration Database for Health Insurance and Labour Market Studies register *(LISA)* is an administrative register held by Statistics Sweden. This register contains information about all citizens resident in Sweden and above 16 years of age. For the purpose of our studies, information about place of birth and educational level were retrieved from the LISA register.

The Multifactor Primary Prevention study (Paper I and II)

Data collection

Information collected from the questionnaire included self-reported previous health problems, including hypertension, smoking habits, physical activity, anti-hypertensive treatment, self-perceived psychological stress and occupation. Previous health problems were assessed by questions like "Has a physician ever told you that you have diabetes?" or "Have you ever had myocardial infarction/bleeding of the brain/thrombosis of the brain?" and considered existing if the participant answered "yes". Smoking status was defined as non-smoker, former smoker of >1 month's duration and current smoker. Physical activity during leisure time was divided into sedentary, moderate and regular exercise. Anti-hypertensive treatment was considered to be present if the participant answered "yes" to this question. Self-perceived psychological stress was assessed by a single question in the questionnaire defining stress as feeling tense, irritable, filled with anxiety or having sleeping difficulties as a result of conditions at work or at home. The alternative responses were on a six-point scale as follows: 1: never experienced stress; 2: some period of stress ever; 3: some period of stress in the past 5 years; 4: several periods of stress in the past 5 years; 5: permanent stress in the past year; and 6: permanent stress over the past 5 years. Occupational classes were coded according to the Swedish socio-economic classification system (83) (see next page).

The baseline examination took place 1970 and 1973 in the afternoon. Weight was measured to the nearest 0.1 kg and height to the nearest 0.01 m. Body mass index (BMI) (weight in kg divided by measured height in m^2) was categorized as <25 (normal), 25–30 (overweight) and >30 kg/m^2 (obese). Serum cholesterol concentration was determined according to standard laboratory procedures.

Blood pressure was taken in the right arm with the participant seated, after a 4–5 minute rest. A mercury manometer was used and measured to the nearest 2 mmHg. At the time for the study, the investigators noticed that a large proportion of the participants had high blood pressure. Therefore, a random subsample of the participants examined in the beginning of the study (84 out of the 2180 first examined) were re-examined concerning the blood pressure two weeks after the first examination. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were then lower in comparison to the values recorded during the screening examination, mean SBP was 7.6 mmHg lower and mean DBP 8.9 mmHg lower. For participants with the highest blood pressure levels during the screening, the mean SBP and DBP was even lower two weeks later; 16.1 mmHg and 18.0 mmHg lower respectively.

Blood pressure categories

According to their blood pressure, all participants were divided into one predefined systolic and diastolic blood pressure category based on World Health Organization-International Society of Hypertension (WHO-ISH) definitions (84). The SBP categories were: <130 (normal), 130–139 (high-normal), 140–159 (mild hypertension) and ≥160 (moderate and severe hypertension) mmHg. The DBP categories were: <85 (normal), 85–89 (high-normal), and ≥90 (hypertension) mmHg.

Occupational classes

Based on information from the questionnaire the participants were classified into the following five occupational classes and coded according to the Swedish socio-economic classification system (83): (1) unskilled and semi-skilled workers; (2) skilled workers; (3) foremen in industrial production and assistant non-manual employees; (4) intermediate non-manual employees; and (5) employed and self-employed professionals, higher civil servants and executives.

Ascertainment of diabetes in Paper I and II

Using the personal identification number (PIN), unique for every citizen in Sweden, the participants were followed from the date of their baseline examination until 31 December 2008. Cases of diabetes were identified by NPR and the CRD either as principal or secondary diagnosis of diabetes. The following ICD codes were used to identify cases of diabetes; 250 (ICD-8), 250 (ICD-9), or E10–E14 (ICD-10).

Patients from the National Diabetes Register and matched controls (Paper III and IV)

Data collection

By using the PIN, information concerning co-morbidities, place of birth and educational level was linked from the NPR and LISA registers, respectively, for participants with and without diabetes.

Place of birth was categorized as in Sweden or elsewhere, education was categorized as low (compulsory only), intermediate, and high (university or similar).

In order to exclude participants (with and without diabetes) with a prior stroke before the start of the study, the following codes were used: hemorrhagic stroke 431, 432X (ICD-9), I61, I62.9 (ICD-10); ischemic stroke 433, 434, 436, 437X (ICD-9), I63, I64, I67.9 (ICD-10).

In order to identify co-morbidities following ICD codes were used; acute myocardial infarction (AMI) 410 (ICD-9), I21 (ICD-10); coronary heart disease (CHD) 410–414 (ICD-9), I20–I25 (ICD-10); atrial fibrillation (AF) 427D (ICD-9), I48 (ICD-10); valve disease 394–397, 424 (ICD-9), I05-I09, I34-I36 (ICD-10); heart failure (HF) 428 (ICD-9), I50 (ICD-10); and cancer 140–208 (ICD-9), C00–C97 (ICD-10).

For the patients with diabetes, data on lifestyle, risk factors such as blood pressure and cholesterol levels, and complications of diabetes were retrieved from the NDR. No similar data was available for the controls. All data in the NDR is collected by

physicians and nurses at hospitals and health care centers in Sweden reporting to the register.

The standard for blood pressure measurement used in the NDR is the mean value (mmHg) of two readings in the supine position using a cuff of appropriate size and after at least 5 minutes of rest. Smoking was coded as present in active smokers and antihypertensive treatment as present or not. Analyses of microalbuminuria and HbA1c were performed at the local laboratory. All health care laboratory units in Sweden are regularly validated by a quality assessment organization. Renal impairment was categorized as normoalbuminuria, microalbuminuria, macroalbuminuria, or stage 5 chronic kidney disease (CKD). Microalbuminuria was defined as two out of three urine samples obtained within 1 year with either an albumin:creatinine ratio of 3–30 mg/mmol (approximately 30–300 mg/g) or a urinary albumin clearance of 20–200 µg/min (20–300 mg/L). Urinary albumin excretion was defined as macroalbuminuria if the albumin:creatinine ratio was >30 mg/mmol (close to ≥300 mg/g) or a urinary albumin clearance >200 µg/min (>300 mg/L). Stage 5 CKD (also called End-Stage Renal Disease, ESRD) was defined as an estimated glomerular filtration rate of <15 ml/min or the need for renal dialysis or renal transplantation. Health care units in Sweden previously used the HbA1c method calibrated to the high performance liquid chromatography mono-S method. In September 2010, there was a national change to the calibration recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the National Glycohemoglobin Standardization Program (NGSP). HbA1C values were converted according to the NGSP and are reported in percentages and in mmol/mol

Blood pressure categories

To estimate the risk of stroke for patients with type 2 diabetes at different blood pressure levels compared to the controls from the general population, the patients with diabetes were assigned to one of the following predefined blood pressure categories; <110/<65, 110-119/65-69, 120-129/70-79, 130-139/80-89, 140-159/90-99, and ≥160/≥100 mmHg. Participants with discordant systolic and diastolic blood pressure were classified into the higher category.

HbA1c categories

For the purpose of Paper IV, patients with type 1 diabetes were divided according to their HbA1c into one of the following categories in order to estimate the risk of stroke at different HbA1c levels compared to the general population (NGSP% / IFCC mmol/mol) ; ≤6.9% (≤52 mmol/mol) 7.0–7.8% (53–62 mmol/mol) 7.9–8.7% (63–72 mmol/mol) 8.8–9.6% (73–82 mmol/mol) ≥9.7% (≥83 mmol/mol).

Ascertainment of stroke in Paper III and IV

In both Paper III and IV patients with diabetes and controls from the general population were followed from inclusion in the study to admission to hospital with a principal diagnosis of stroke, to death, or to 31st of December 2011, whichever event occurred first. Following ICD-10 codes as primary diagnosis in NPR or CDR were used to identify stroke end-points; any stroke (I61, I62.9, I63, I64, I67.9), ischemic stroke (I63, I64, I67.9), and hemorrhagic stroke (I61, I62.9).

Statistical analyses

All papers in this thesis are observational prospective cohort studies.

Descriptive statistics (Paper I-IV)
Descriptive statistics are presented as frequencies and percentages for categorical variables and in terms of means with standard deviations for continuous variables.

In Paper I and II differences in the distribution of baseline characterises across the blood pressure and occupational classes were analysed by Chi-square trend test (Cochran-Armitage trend test) for categorical variables and by Spearman correlation test (Paper I) and the ANOVA linear trend test (Paper II) for continuous variables. In Paper III and IV no such significance testing were done in the baseline tables since this practice has been more and more abandoned and is now considered unnecessary and superfluous (85).

All p-values are 2-sided and values <0.05 are considered statistically significant.

Paper I
Follow-up time in the study was from the baseline examination (January 1970 to March 1973) to a first hospitalization with a diagnosis of diabetes (principal or secondary diagnosis), to death or to end of follow-up (31 December 2008). We calculated age-adjusted diabetes incidence rate per 100,000 person years for each blood pressure category.

The hazard for developing diabetes in the different blood pressure categories were analyzed through proportional hazard regression (Cox regression) models where the lowest blood pressure category was used as reference. Three regression models were constructed with different sets of covariates. The multiple adjusted model was adjusted for age, BMI, cholesterol level, antihypertensive treatment, smoking, physical activity and occupational class. In an attempt to take the possibility of residual confounding into account we performed stratified analyses across different BMI and smoking categories. Estimates from the proportional hazard regression models are presented as hazard ratios (HR) and 95% confidence intervals (95% CI). The assumption of proportional hazard was tested and holds for all our models.

A large proportion of the men (75%) had died at the end of the study due to the long follow-up and age at study entry. Therefore a figure with cumulative risk for diabetes within each blood pressure category where risk of death from other causes than diabetes has been accounted for is presented (competing risk methodology).

All analyses were performed using SAS software version 9.2 (SAS institute, Cary, NC, USA) and Statistical package R2.15 version.

Paper II
Follow-up time was as in Paper I. Age-adjusted diabetes incidence rates per 100,000 person years for each occupational class were calculated as in Paper I.

To even further take into account the long follow-up and the fact that a considerable proportion of the participants died during the study, competing risk regression was used to analyze and compare the hazards of developing diabetes in the different occupational classes. The highest occupational class (high officials) was used as a reference. To account for the non-proportionality in some variables, these were time-averaged according to Schemper et al (86). Three regression models with different sets of covariates were constructed. The multiple adjusted model were adjusted for age, BMI, hypertension, smoking, physical activity and psychological stress. For 395 participants there were missing data on psychological stress. For these men we created a dummy variable which was entered into the model. Subdistribution hazard ratios (SHRs) and associated 95% CIs for diabetes are presented.

One figure presents the cumulative incidence of diabetes and death across the occupational classes and another figure presents the conditional probability of diabetes by occupational class.

All statistical analyses were performed using SAS software version 9.3 (SAS institute, Cary, NC, USA) and Statistical package R version 3.00.

Paper III and IV

Unadjusted incidence rates for stroke end-points were estimated and presented as events per 1000 person-years of follow-up with 95% confidence intervals. Confidence intervals for event rates are based on Poisson distribution. In Paper III incidence rate ratios with associated confidence interval are also presented.

Cox regression models were constructed to study the relationship between diabetes patients with different updated mean blood pressure (Paper III) or HbA1c (Paper IV) and controls (reference). Updated mean blood pressure/HbA1c was defined as the mean value of all preceding measures and updated for each new measurement (e.g. when the third measurement from baseline was performed, the updated mean blood pressure/HbA1c was the mean of the three first measurements). In the first unadjusted model the matching was taken into account by stratifying the Cox analysis on matched set of individuals. In the adjusted models, age and sex were entered as covariates along with the other covariates adjusted for and the patients with diabetes in each blood pressure/HbA1c category were compared to all controls grouped together. Diabetes duration was added as a stratification variable in the Cox regression models, the controls were assigned to the same stratification category as the patients in the diabetes group with whom they were matched. Subgroup analysis by sex, age and presence of previous cardiovascular disease in Paper III and by sex, diabetes duration category and renal impairment in Paper IV were performed. The subgroup analyses are presented by hazard ratios as well as forest plots.

We also constructed Cox regression models to estimate the risk of stroke at different blood pressure/HbA1c categories within the groups of patients with diabetes. Type 2 diabetes patients with an updated blood pressure of 120-129/70-79 mmHg were used as a reference in Paper III and type 1 diabetes patients with an updated HbA1c level of ≤6.9% (≤52 mmol/mol) were used as reference in Paper IV. In these models we

could adjust the analyses for several variables available in NDR since these data also were available in the control group in these analyses. The variables were entered as time-updated or time-updated mean variables i.e. when new information is registered in the NDR, the variables is updated.

Hazard ratios (HRs) and associated 95% confidence intervals (CIs) for stroke were estimated in all Cox regression models. The assumption of the proportional hazard was tested for all Cox regression analyses and was found to hold. All analyses were performed using SAS software version 9.3 in Paper III and SAS software version 9.4 in Paper IV.

RESULTS

High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men (Paper I)

The aim of this study was to evaluate if high-normal blood pressure in men at mid-life predicted later development of diabetes after an extended follow-up of 35 years.

Baseline characteristics for participants in the different SBP groups are presented in Table 2. Participants in the higher SBP groups were slightly older, had higher BMI and cholesterol levels, were more likely to use antihypertensive medication, and at the same time less likely to be physically active, a current smoker or having a non-manual occupation.

Table 2. Baseline characteristics according to systolic blood pressure categories

		Systolic blood pressure categories				
Characteristics	**All N=7 333**	**<130 mm Hg (n=1278)**	**130-139 mm Hg (n=1315)**	**140-159 mm Hg (n=2623)**	**≥160 mm Hg (n=2117)**	**p-values***
Age, years, mean (SD)	51.6 (2.3)	51.2 (2.3)	51.3 (2.4)	51.6 (2.3)	51.9 (2.1)	<0.0001
Body Mass Index kg/m², mean (SD)	25.5 (3.2)	24.4 (2.9)	25.2 (2.9)	25.6 (3.2)	26.3 (3.5)	<0.0001
Obesity. BMI ≥30, % (n)	8.1 (597)	3.4 (43)	5.6 (73)	8.2 (214)	12.6 (267)	<0.0001
Diastolic blood pressure, mm Hg, mean (SD)	95 (13)	82 (8)	88 (8)	94 (8)	107 (12)	<0.0001
Hypertension treatment, % (n)	5.4 (396)	0.7 (9)	0.7 (9)	3.2 (85)	13.8 (293)	<0.0001
Serum cholesterol mmol/L, mean (SD)	6.46 (1.15)	6.22 (1.08)	6.47 (1.10)	6.47 (1.17)	6.61 (1.18)	<0.0001
Never smokers, % (n)	29.5 (2152)	27.2 (347)	27.1 (355)	29.7 (775)	32.0 (675	0.0004
Former smokers, % (n)	20.4 (1493)	19.0 (242)	20.9 (273)	21.3 (555)	20.0 (423)	0.68
Current smokers, % (n)	50.1 (3660)	53.8 (686)	52.0 (681)	49.0 (1279)	48.0 (1014)	0.0004
Physically active, % (n)	16.0 (1156)	18.3 (232)	17.6 (228)	16.1 (414)	13.5 (282)	<0.0001
Non-manual occupation, % (n)	27.9 (2044)	31.2 (399)	29.4 (386)	27.8 (728)	25.1 (531)	<0.0001

SD= standard deviation. BMI=Body Mass Index. *P-values calculated by chi-square trend test for categorical variables and by Spearman correlation test for continuous variables.

After 35 years of follow-up (mean follow-up 28 years), 956 out of 7333 (13%) participants had received a diagnosis of diabetes in the NPR or CDR. The crude incidence of diabetes was 509 per 100,000 person years.

The risk of developing diabetes increased by higher SBP and DBP level as can be seen in Table 3. BMI had a major attenuating effect on the risk of developing diabetes, but even after adjustment for BMI and other covariates, the risk to develop diabetes was significant higher for men with high-normal SBP (130-139 mmHg) at baseline compared to men with SBP <130 mmHg (HR 1.43 95% [1.12-1.84]).

The risk of developing diabetes during 35 years of follow-up, given death did not occur, was 19%, 30%, 31% and 49% if SBP at baseline was <130 mmHg, 130-139 mmHg, 140-159 mmHg and >160 mmHg, respectively (Figure 1).

Table 3. Hazard ratios for diabetes incidence by blood pressure categories

Blood pressure categories/treatment	Number at risk	Diabetes cases	Diabetes cases per 100 000 person years	Age adjusted hazard ratios (95% CI)	Age and BMI adjusted hazard ratios (95% CI)	Age and multivariable adjusted* hazard ratios (95% CI)
Systolic blood pressure						
<130 mm Hg (normal)	1 279	109	300	ref.	ref.	ref.
130–139 mm Hg (high-normal)	1 315	159	447	1.56 (1.22-1.99)	1.39 (1.09-1.78)	1.43 (1.12-1.84)
140–159 mm Hg (mild hypertension)	2622	330	472	1.66 (1.34-2.07)	1.40 (1.13-1.75)	1.43 (1.14-1.79)
≥160 mm Hg (moderate/severe)	2117	358	693	2.68 (2.16-3.32)	2.03 (1.63-2.52)	1.95 (1.55-2.46)
Increase per 10 mm Hg				1.16 (1.13-1.18)	1.12 (1.08-1.14)	1.10 (1.07-1.14)
Diastolic blood pressure						
<85 mm Hg (normal)	1628	157	345	ref.	ref.	ref.
85–89 mm Hg (high normal)	896	83	343	1.02 (0.78-1.33)	0.95 (0.72-1.23)	0.93 (0.70-1.22)
≥90 mm Hg (hypertension)	4809	716	579	1.82 (1.53-2.16)	1.41 (1.18-1.68)	1.34 (1.12-1.62)
Increase per 5 mm Hg				1.14 (1.12-1.17)	1.09 (1.06-1.11)	1.08 (1.06-1.11)

*Multivariable adjusted model included age, body mass index, cholesterol level, antihypertensive treatment, smoking, physical activity and occupational class.

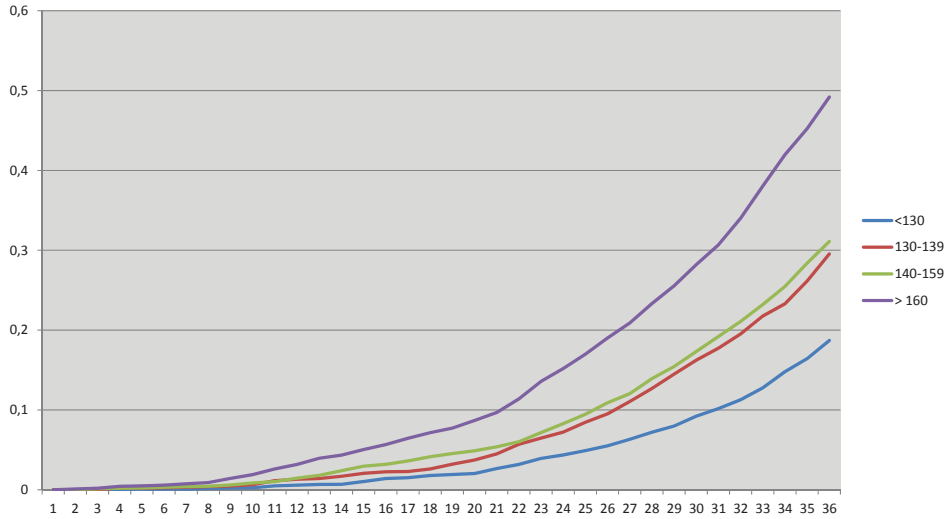

Figure 1. Conditional probability of diabetes according to different SBP classes, taking death attributable to other causes into account.

Incidence of type 2 diabetes among occupational classes in Sweden: a 35-year follow-up cohort study in middle-aged men (PaperII)

In this study we estimated the risk of developing diabetes in different occupational classes at mid-life. We evaluated to what extent any potential differences could be explained by conventional risk factors for diabetes and by psychological stress and if the differences persisted into older ages.

The classical risk factors for diabetes were more prevalent in the lower occupational classes i.e. slightly higher mean BMI, and obesity rates, higher mean blood pressure, rates of smoking and a more sedentary lifestyle. The men in the lower occupational classes also reported more permanent stress than men in higher occupational classes (Table 4).

Table 4. Baseline characteristics according to occupational class

Characteristics	All (n=6874)	High officials, professionals (n=793)	Intermediate, non-manual employees (n=1231)	Assistant non-manual employees (n=1348)	Skilled workers (n=1871)	Unskilled and semiskilled workers (n=1631)	P-value
Age, years, mean (SD)	51.6 (2.3)	51.6 (2.3)	51.5 (2.3)	51.5 (2.2)	51.7 (2.2)	51.5 (2.3)	0.40
BMI kg/m², mean (SD)	25.5 (3.2)	25.3 (3.0)	25.4 (3.1)	25.4 (3.1)	25.6 (3.1)	25.7 (3.4)	0.01
Obesity, BMI ≥30, % (n)	7.7 (532)	6.7 (53)	6.9 (85)	7.3 (99)	7.8 (146)	9.1 (149)	0.012
Height cm (SD)	175.7 (6.3)	178.0 (6.1)	176.7 (6.2)	175.9 (6.3)	174.5 (6.1)	174.8 (6.4)	<0.001
Systolic blood pressure, mmHg, mean (SD)	149 (22)	145 (21)	148 (21)	149 (22)	150 (22)	148 (22)	<0.001
Diastolic blood pressure, mmHg, mean (SD)	95 (13)	93 (13)	94 (13)	95 (13)	95 (13)	94 (13)	0.022
Hypertension, % (n)	70.0 (4802)	63.1 (500)	69.4 (854)	72.5 (976)	71.7 (1340)	69.7 (1132)	0.006
Current smokers, % (n)	50.1 (3444)	47.2 (374)	45.9 (565)	49.8 (671)	51.1 (957)	53.8 (877)	<0.001
Sedentary, % (n)	25.3 (1716)	20.1 (159)	18.4 (226)	22.8 (308)	28.4 (532)	30.1 (491)	<0.001
Permanent stress*, % (n)	14.9 (966)	13.9 (110)	11.5 (141)	13.9 (187)	15.0 (281)	15.1 (247)	0.020

BMI=body mass index. *P-value* for trends in distribution of baseline characteristics. *Self-perceived psychological stress category 3=permanent stress

During a 35-year follow-up (median follow-up 28 years) 907 (13%) of the 6874 men were diagnosed with diabetes.

Table 5 shows the estimates of SHR for diabetes in the different occupational classes. In the age adjusted competing risk model there was a significant higher SHR of diabetes in the two lowest occupational classes compared to the highest occupational class (SHR 1.28 95% CI [1.01-1.64] and SHR 1.48 95% CI [1.16-1.89] for skilled workers and unskilled/semiskilled workers respectively).

The SHR attenuated in the multiple adjusted model where we adjusted for conventional risk factors for diabetes and psychological stress but SHR remained significantly increased for unskilled and semiskilled workers also in this model (SHR 1.39 95% CI [1.08-1.78]).

Table 5. Age and multivariable-adjusted subdistributional hazard ratios (SHRs) and 95% confidence intervals (CIs) of the incidence of diabetes in different occupational classes over a 35-year follow-up period

Occupational class	Number at risk	Diabetes cases	Diabetes cases per 100,000 person-years	Age adjusted SHR (95% CI)	Multivariable adjusted* SHR (95% CI)
High officials, professionals	793	88	391	Ref	ref
Intermediate, non-manual employees	1231	139	409	1.05 (0.80-1.37)	0.98 (0.75-1.29)
Assistant non-manual employees	1348	171	496	1.21 (0.92-1.58)	1.18 (0.90-1.54)
Skilled workers	1871	255	530	1.28 (1.01-1.64)	1.18 (0.93-1.51)
Unskilled and semiskilled workers	1631	254	630	1.48 (1.16-1.89)	1.39 (1.08-1.78)

*Adjusted for age, BMI, hypertension, smoking, physical activity and self-perceived psychological stress.

Figure 2 presents the cumulative incidence of diabetes and death across the occupational classes. As can be seen, the cumulative incidence of diabetes, when taking into account death as a competing event, gradually increased by decreasing occupational class with the lowest cumulative incidence among higher officials and professionals (11%) and the highest cumulative incidence among unskilled and semiskilled workers (16%). Cumulative mortality was inversely related to occupational class with the highest death rate among unskilled and semiskilled workers (65%) and the lowest among higher officials and professionals (53%).

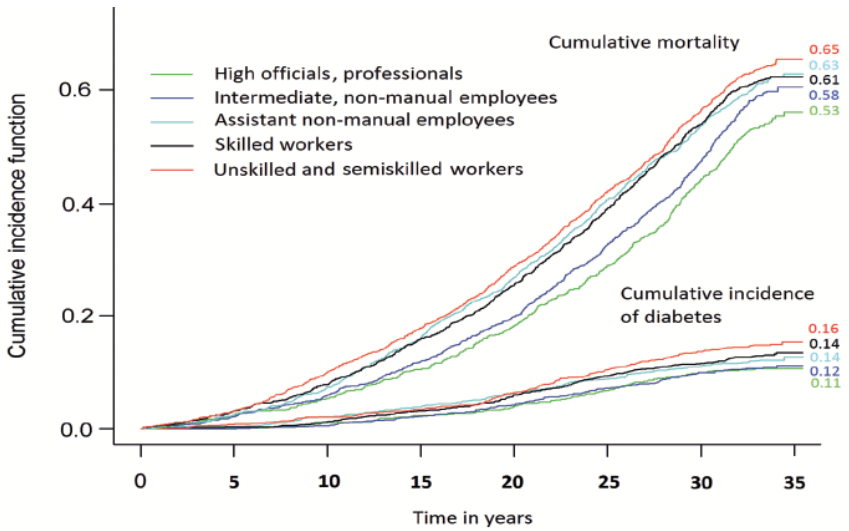

Figure 2. Cumulative incidence curves of diabetes and mortality across the occupational classes.

Figure 3 shows the conditional probability of diabetes by occupational class when taking death from other causes into account. Under the condition that a participant did not die, the probability of diabetes after 35 years of follow-up was 43% for unskilled and semiskilled workers, 35% for skilled workers, 31% for assistant non-manual employees, 26% for intermediate non-manual employees, and 23% for high officials.

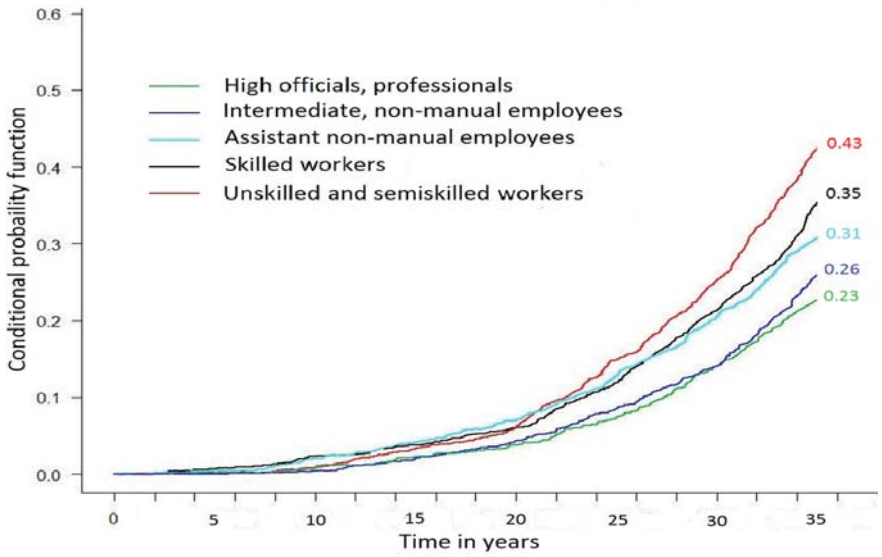

Figure 3. Conditional probability of diabetes according to different occupational classes, taking death attributable to other causes into account.

Long-term excess risk of stroke in people with type 2 diabetes in Sweden according to blood pressure level: a population-based case-control study

Here we wanted to estimate the excess risk of stroke for type 2 diabetes patients at different blood pressure levels compared to the risk in the general population.

Baseline characteristics for type 2 diabetes patients and controls are presented in Table 6. Type 2 diabetes patients as a group had less education and were less often born in Sweden compared to controls. Among type 2 diabetes patients 64% used antihypertensive treatment and baseline comorbidities (CHD, AF, HF) were more common among type 2 diabetes patients compared with controls.

During a median follow-up of 4.0 years 19,548 (4.8%) out of 408,076 type 2 diabetes patients received a diagnosis of stroke. Among the controls, 61,690 out of 1,913,507 (3.2%) received a diagnosis of stroke during a median follow-up of 4.1 years.

Table 6. Characteristics of people with type 2 diabetes at first inclusion in the NDR, 1998-2011, and of controls, all free of previous stroke

	Controls n=1,913,507	All type 2 diabetes n=408,076
Women	869,045 (45.4%)	182,486 (44.7%)
Age, years (SD)	64.6 (12.5)	65.3 (12.6)
Born in Sweden	1,673,823 (87.5%)	337,235 (82.6%)
Education category		
Low	682,929 (36.3%)	175,217 (43.9%)
Mid	744,627 (39.6%)	160,153(40.1%)
High	453,805 (24.1%)	63,730 (16.0%)
Registrations in the NPR† prior to baseline		
CHD§ (I20-I25)	137,957 (7.2%)	62,037 (15.2%)
AF‖ (I48)	89,814 (4.7%)	32,166 (7.9%)
HF¶ (I50)	53,104 (2.8%)	25,986 (6.4%)
Variables in the NDR only*		
Systolic BP‡, mmHg (SD)		140.3 (18.3) n=351,847
Diastolic BP‡, mmHg (SD)		78.6 (9.8) n=351,847
HbA1c, mmol/mol (SD), NGSP % (SD)		54.3 (14.6), 6.3 (1.4) n=364,237
Diabetes duration, y (SD)		5.53 (6.96) n=363,024
Antihypertensive treatment		245,495 (64.0%)

Categorical variables are shown as n (%) and continuous variables are shown as mean (SD). †NPR=National Patient Register, §CHD=coronary heart disease, ‖AF=atrial fibrillation, ¶HF=heart failure, *NDR=National Diabetes Register and ‡BP=blood pressure

The multiple adjusted HR (adjusted for updated age, sex, stratified by diabetes duration, being born in Sweden, maximum education level and baseline comorbidities) of any stroke for type 2 diabetes patients as a group was 1.43 (95% CI 1.41-1.46) compared with people without diabetes. Corresponding values for ischemic stroke and hemorrhagic stroke for type 2 diabetes patients as a group compared with the controls were 1.48 (95% CI 1.46-1.51) and 1.08 (95% CI 1.02-1.14) respectively.

When estimating the multiple adjusted HR for any stroke in each blood pressure category compared to the controls, we found a significantly increased risk in the three highest blood pressure categories with HRs of 1.20 (95% CI 1.16-1.24), 1.47 (95% CI 1.43-1.50), and 1.97 (95% CI 1.90-2.03) for blood pressure categories of 130-139/80-89, 140-159/90-99, and ≥160/≥100 mmHg, respectively (Figure 4).

For ischemic stroke, the risk compared to the controls was significantly increased also in blood pressure categories below 130/80, however only very slightly. For hemorrhagic stroke, type 2 diabetes patients in blood pressure categories 120-129/70-79 mmHg and 130-139/80-89 mmHg had a significantly decreased risk of hemorrhagic stroke compared with controls (multiple adjusted HRs of 0.66 (95% CI 0.55-0.79) and 0.87 (95% CI 0.78-0.97), respectively).

Glycaemic control and excess risk of ischaemic and haemorrhagic stroke in patients with type 1 diabetes: a cohort study of 33,453 patients

In this study we wanted to estimate the excess risk of stroke in type 1 diabetes patients at different updated HbA1c categories compared to the general population.

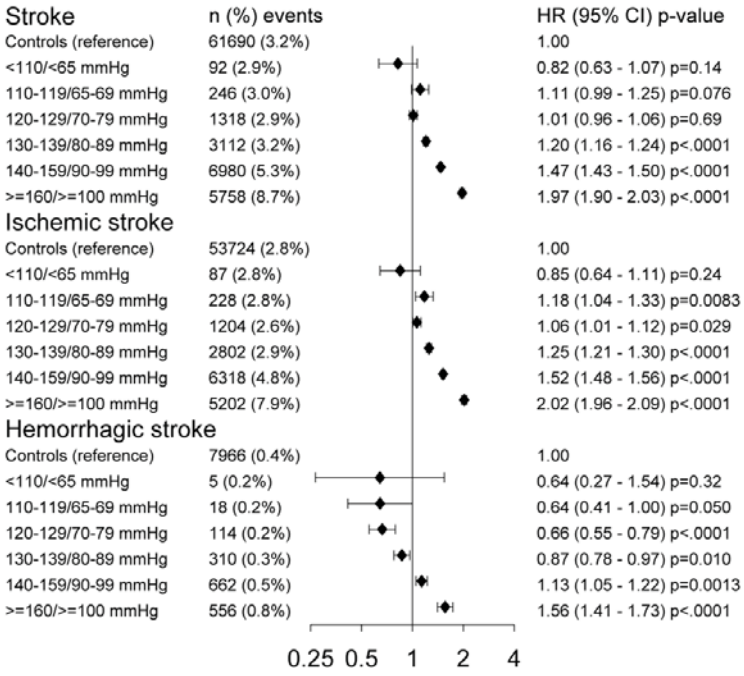

Figure 4. Adjusted hazard ratios of stroke and stroke subtypes by time updated blood pressure category. Hazard ratios (HR) and 95% confidence intervals (CIs) were estimated by means of Cox regression adjusted for time-updated age, sex, stratified by diabetes duration, being born in Sweden, maximum education level and baseline comorbidities (atrial fibrillation, coronary heart disease, and heart failure).

Patients with type 1 diabetes were more often born in Sweden, had more of the comorbidities AMI, CHD, HF and cancer at baseline compared to controls (Table 7). Within the group of patients with diabetes, diabetes duration, BMI and average systolic blood pressure initially increased by each higher HbA1c category and then decreased slightly in the highest HbA1c categories. However, the difference in average blood pressure between the highest and lowest HbA1c category was only 2.6 mmHg for systolic and 3.0 mmHg for diastolic blood pressure. The proportion of smokers and the presence of baseline comorbidities increased by higher HbA1c categories.

During a mean follow-up of 7.9 years, 762 (2.3%) out of 33,453 type 1 diabetes patients received a diagnosis of stroke as compared with 1122 (0.7%) out of 159,924 controls during a mean follow-up of 8.2 years.

The Cox regression model adjusted for time-updated age, sex, stratified by diabetes duration, maximum education category and baseline comorbidities (CHD and AF) showed that compared with controls, type 1 diabetes patients as a group had a HR of 3.14 (95% CI 2.85–3.46) for any stroke, 3.29 (95% CI 2.96–3.66) for ischemic stroke and 2.49 (95% CI 1.96–3.16) for hemorrhagic stroke.

Table 7. Characteristics of type 1 diabetes patients, by baseline HbA1c category, and population-based controls at first registration in the NDR 1998–2011, all free of previous stroke

			HbA1c categories at baseline[a]					
	Controls *n* = 159,924	**All type I diabetes *n* = 33,453**	**≤6.9% (≤52 mmol/mol) *n* = 6071**	**7.0–7.8% (53–62 mmol/mol) *n* = 7643**	**7.9–8.7% (63–72 mmol/mol) *n* = 8824**	**8.8–9.6% (73–82 mmol/mol) *n* = 5377**	**≥9.7% (≥83 mmol/mol) *n* = 3940**	**Missing value *n* = 1598**
Female	72,846 (46%)	15,120 (45%)	2689 (44%)	3426 (45%)	3940 (45%)	2420 (45%)	1913 (49%)	732 (46%)
Baseline age, years	35 (14)	36 (14)	34 (14)	37 (15)	37 (15)	36 (14)	33 (13)	32 (14)
	n = 15,9924	*n* = 33,453	*n* = 6071	*n* = 7643	*n* = 8824	*n* = 5377	*n* = 3940	*n* = 1598
Born in Sweden	138,571 (87%)	31415 (94%)	5669 (93%)	7224 (95%)	8342 (95%)	5053 (94%)	3673 (93%)	1454 (91%)
Education category[b]								
High	53,716 (34%)	10,156 (31%)	2496 (41%)	2601 (34%)	2603 (30%)	1279 (24%)	725 (19%)	452 (29%)
Registration in the NPR prior to baseline								
Coronary heart disease	1107 (<1%)	1351 (4%)	162 (3%)	315 (4%)	408 (5%)	244 (5%)	166 (4%)	56 (4%)
Heart failure	281 (<1%)	464 (1%)	57 (1%)	90 (1%)	143 (2%)	73 (1%)	69 (2%)	32 (2%)
Variables in the NDR only								
HbA1c, NGSP% (SD)		7.4 (2.4)	5.4 (1.4)	6.6 (1.1)	7.5 (1.2)	8.5 (1.2)	10.3 (2.0)	
HbA1c, IFCC mmol/mol (SD)		65.8 (15.8) *n* = 31,855	45.6 (5.5) *n* = 6071	57.3 (2.6) *n* = 7643	67.2 (2.8) *n* = 8824	76.9 (2.8) *n* = 5377	95.0 (11.3) *n* = 3940	
Duration of diabetes, years		20.2 (14.6) *n* = 33,453	16.1 (15.7) *n* = 6071	21.7 (14.9) *n* = 7643	22.6 (14.2) *n* = 8824	21.2 (13.4) *n* = 5377	18.1 (12.7) *n* = 3940	16.5 (14.7) *n* = 1598
BMI, kg/m²		25.0 (4.0) *n* = 29,206	24.6 (4.0) *n* = 5385	25.0 (3.8) *n* = 6945	25.3 (3.8) *n* = 7965	25.4 (4.1) *n* = 4836	25.0 (4.6) *n* = 3436	24.6 (5.0) *n* = 639
LDL, mmol/L		2.66 (0.83) *n* = 11,260	2.53 (0.76) *n* = 2341	2.60 (0.79) *n* = 2715	2.69 (0.82) *n* = 2989	2.74 (0.86) *n* = 1760	2.87 (0.94) *n* = 1314	2.58 (0.82) *n* = 141
Systolic blood pressure, mmHg		126.7 (16.9) *n* = 31102	124.2 (15.7) *n* = 5749	126.6 (16.5) *n* = 7318	128.3 (17.0) *n* = 8448	127.6 (17.1) *n* = 5150	126.8 (18.0) *n* = 3692	123.5 (16.6) *n* = 745
Diastolic blood pressure, mmHg		73.5 (9.1) *n* = 31,102	72.1 (8.9) *n* = 5749	73.0 (8.9) *n* = 7318	73.8 (9.1) *n* = 8448	74.3 (9.3) *n* = 5150	75.1 (9.5) *n* = 3692	72.9 (9.4) *n* = 745
Antihypertensive treatment[b]*, n (%)*		6895 (22%)	869 (15%)	1566 (21%)	2097 (25%)	1250 (24%)	902 (24%)	211 (17%)
Smoker[b]*, n (%)*		4206 (14%)	505 (9%)	764 (11%)	1099 (13%)	849 (17%)	837 (23%)	152 (13%)

All cases and controls were free of previous stroke. Data for categorical variables are shown as *n* (%); data for continuous variables are shown as mean (SD). [a]HbA1c expressed as % (mmol/mol), in accordance with the NGSP and IFCC, respectively. [b]Percentages of these variables represent proportion of participants with non-missing data on each variable. Type 1 diabetes patients with non-missing data were: Education category 33190, Antihypertensive treatment 33732 and smoking 31019. NPR, National Patient Register; NDR, National Diabetes Register; NGSP, National Glycohemoglobin Standardization Program; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

Table 8 shows the multiple adjusted HRs for stroke and subtypes of stroke over the HbA1c categories compared to the risk among the controls. For ischemic stroke, the risk was significantly increased in all HbA1c categories and for hemorrhagic stroke it was increased in all but the lowest HbA1c category. The excess risk for any stroke ranged from a 75% increased risk in the lowest HbA1c category to an eight-fold increased risk in the highest.

Table 8. Adjusted hazard ratios for stroke (and 95% confidence intervals) for time-updated mean HbA1c categories versus population-based controls as examined by Cox regression

	HR (95% CI)[a] *P*-value HbA1c categories at baseline[b]					
	Controls (reference)	**≤6.9% (≤52 mmol/mol)**	**7.0–7.8% (53–62 mmol/mol)**	**7.9–8.7% (63–72 mmol/mol)**	**8.8–9.6% (73–82 mmol/mol)**	**≥9.7% (≥83 mmol/mol)**
Stroke (events/individuals) 1855/191,004	1.00	1.74 (1.35–2.25) <0.0001	2.16 (1.83–2.55) <0.0001	3.52 (3.08–4.03) <0.0001	4.38 (3.67–5.21) <.0001	7.98 (6.46–9.85) <0.0001
Ischaemic stroke (events/individuals) 1544/191,004	1.00	1.89 (1.44–2.47) <0.0001	2.20 (1.84–2.64) <0.0001	3.82 (3.31–4.41) <0.0001	4.57 (3.78–5.53) <0.0001	7.94 (6.29–10.03) <0.0001
Haemorrhagic stroke (events/individuals) 311/191,004	1.00	1.10 (0.52–2.33) 0.81	2.00 (1.34–3.00) 0.0007	2.19 (1.49–3.22) <0.0001	3.52 (2.23–5.54) <0.0001	8.17 (5.00–13.35) <0.0001

[a]HRs adjusted for time-updated age, sex, stratified by diabetes duration category, maximum educational level and baseline comorbidities (coronary heart disease and atrial fibrillation). [b]HbA1c categories expressed as % (mmol/mol), in accordance with the National Glycohemoglobin Standardization Program and International Federation of Clinical Chemistry and Laboratory Medicine, respectively.

Figure 5 shows the result from the Cox regression for any stroke subgroup by sex. There were no signs of interaction concerning sex.

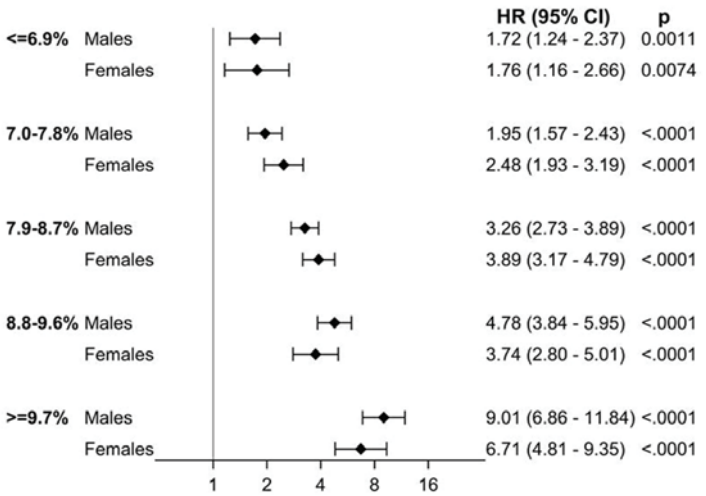

Figure 5. Adjusted hazard ratios (HRs) for stroke (and 95% confidence intervals) for time-updated mean HbA1c categories stratified by sex versus population-based controls as examined by Cox regression; adjusted for time-updated age, stratified by diabetes duration, maximum educational level and baseline comorbidities (coronary heart disease and atrial fibrillation). HbA1c categories expressed as % in accordance with the National Glycohemoglobin Standardization Program.

DISCUSSION

Is high-normal blood pressure at mid-life a predictor of later development of diabetes? (Paper I)

It is well known that type 2 diabetes and hypertension are two conditions that often co-exist (87) and persons with hypertension are more prone to develop diabetes (40). It has also been shown that persons with high-normal blood pressure have a higher risk of developing diabetes (41, 42). From the Framingham study (87) and a multitude of subsequent studies we know that risk factors in mid-life are important for long-term outcomes. However, not all risk factors persist as important risk factors at a prolonged follow-up. For example, data based on the Multifactor Primary Prevention study has shown that smoking, a strong risk factor for coronary heart disease after 10 years became less important and was no longer a significant risk factor after 21 years (88).

In our study, the median follow-up was 28 years, and we found that high-normal systolic blood pressure in men at midlife indicated increased risk of later development of diabetes even at this prolonged follow-up. Blood pressure is a continuous variable and the definitions of what we call hypertension and high-normal blood pressure are not limits created by nature but arbitrary and made up by the medical profession. Since hypertension has been associated with an increased risk of diabetes it is easy to imagine that high-normal blood pressure might also imply an increased risk of diabetes. Since an elevated blood pressure level remains a risk factor even after a prolonged follow-up it can be assumed that this is a process that starts many years before the development of diabetes. One study of men who had developed diabetes at middle-age was found to have had significantly higher blood pressure already in young adulthood compared to men who did not develop diabetes (39). Whether this applies to blood pressure measured in middle age and subsequent development of diabetes over an extended period has not been investigated. Changes in the microcirculation could be the common denominator for hypertension and type 2 diabetes since alteration in the microcirculation is known to precede both hypertension and type 2 diabetes (37, 38).

Some antihypertensive medications, chiefly β-blockers and thiazide diuretics, have been recognized as potentially associated with an increased risk of diabetes (89). In our study, we adjusted for use of antihypertensive treatment at baseline but we had no information on medication during follow-up. However, even though certain antihypertensive medications might marginally increase the risk of developing diabetes it has also been shown that the greatest risk of develop diabetes is associated with the existence of hypertension (40).

Our study has shown that high-normal blood pressure indicates an increased risk of diabetes. In addition, other studies have shown that high-normal blood pressure indicate increased risk of cardiovascular disease (90). Still, this cannot be taken to mean that we should consider to start antihypertensive treatment for persons with high-normal blood pressure. The European Society of Hypertension (ESH) and European Society of Cardiology guidelines from 2007 (91) suggested that antihypertensive drug therapy should be introduced for patients with blood pressure in the high-normal

range if concomitant diabetes, cardiovascular disease or renal disease. However, the evidence in favor of this early intervention has been found to be weak (92). According to "2013 EHS/ESC Guidelines for the management of arterial hypertension" lifestyle changes such as salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits and other types of diet, weight reduction and regular physical activity (92) should be introduced in patients with high-normal blood pressure but antihypertensive medications are not recommended. Lifestyle changes have been shown to reduce blood pressure (93) and are also factors that affect the risk of developing diabetes. In addition, smoking cessation should be advocated in order to reduce cardiovascular risk (92).

To sum up, for people with high-normal blood pressure and their physicians, it is important to continue to monitor the blood pressure level as well as consider what lifestyles factors that could be modified in order to prevent not only cardiovascular diseases but also diabetes.

Were there differences in development of diabetes over the occupational classes in Gothenburg and to what extent could they be explained by conventional risk factors and psychological stress? (Paper II)

Studies in high income countries with up to 15 years of follow-up have shown that people with low SEP are more affected by type 2 diabetes compared with people in higher SEP groups (46). A significant proportion of this excess risk of diabetes is due to a greater prevalence of conventional risk factors for diabetes in lower SEP groups (94). Stress and other psychological factors have been suggested to account for some of the remaining excess risk of diabetes in lower SEP groups. Stress is a risk factor for type 2 diabetes (34) and lower SEP groups report a higher psychological burden (95).

We found an inequality in the incidence of diabetes between different occupational classes among Swedish men and that this difference persists into older ages. Adjustment for conventional risk factors for diabetes as well as stress attenuated the difference but a significantly increased risk of diabetes persisted in the lowest occupational class compared to the highest.

In our study we used occupation as an indicator of SEP. The indicator of SEP that has shown the strongest association with incidence of diabetes is education (46). It can be argued that education often tend to lead to higher occupational positions and in many cases higher income but it has been shown that the different indicators of SEP cannot be used interchangeably (96). The indicators represent different underlying pathways and causal mechanisms and are also said to represent different time-periods of the life. The only indicator of SEP available to us in our study was occupation. Since most studies have found a higher correlation between educational level and incidence of diabetes (46), we might potentially have found a stronger association to SEP if education had been our indicator.

Even though permanent stress was somewhat more prevalent in lower SEP in our study, we could not find that our indicator of stress could explain the difference in incidence of diabetes over the SEP categories to any great extent. Psychological factors

are difficult to define and to measure. Many different methods are in use to measure stress. We used a single question to estimate the amount of stress experienced by the participants. The same question has been used as a measurement of stress in large international studies such as INTERHEART (97) and INTERSTROKE (57). Even though this question showed strong correlation with other measurements of stress in the INTERHEART study (97), all aspects of stress and psychological burden experienced will not have been captured. Previous studies have come to divergent findings as to whether psychological aspects explain parts of the difference in incidence of diabetes across the SEP categories (95, 98).

In our study, as well as in many other studies, there remains an increased risk of diabetes among persons in the lower SEP levels even after having accounted for conventional risk factors. This remaining increase in risk for diabetes could have several causes. Psychological factors not captured as discussed above could contribute but also early life factors like prenatal and perinatal circumstances. Low birth weight and preterm birth have been found to be associated with later in life insulin resistance and increased risk of type 2 diabetes (99). At the period that the men in our study were born (1915-1925) the risk for the mothers of the men to be exposed to factors that might have an adverse influence on the fetus might very well have varied over the SEP categories. Also poor nutritional status during childhood has been associated with increased risk of later development of type 2 diabetes (100). Since it is common to adopt the same SEP as your parents (101) a greater proportion of men in lower SEP probably had parents in lower SEP. Therefore, more men in lower SEP might have encountered these adverse early life experiences making them more susceptible to later in life development of type 2 diabetes.

A large proportion of the increased risk of diabetes in the lower occupational classes is explained by the conventional risk factors. This is important information in order to know where to direct preventive action most effectively. Even though these risk factors of course are important in all SEP, they are more prevalent in the lower SEP. In addition, different approaches might be needed to reach people with health behavior messages. Reducing inequality in health is an important issue not only to reduce cost for society but as a matter of letting more people achieve higher potential when it comes to health.

What is the excess risk of stroke in type 2 diabetes patients at different blood pressure levels compared to the general population? (Paper III)

During the last decade there has been a discussion of what blood pressure level should be aimed at when treating the blood pressure in patients with diabetes in order to protect them from cardiovascular disease. In this article we did not aim at estimating the most optimal blood pressure target in type 2 diabetes patients but to estimate the excess risk of stroke at different blood pressure in relation to an age and sex matched general population.

We found, not unexpectedly, that type 2 diabetes patients as a group have an increased risk of any stroke compared to an age and sex matched general population. However, when we estimated the risk according to their updated blood pressure, the risk of

any stroke was not increased for type 2 diabetes patients with blood pressure below 130/80 mmHg. The excess risk of ischemic and hemorrhagic stroke at different blood pressure levels in comparison with the risk of the general population was markedly dissimilar. For ischemic stroke, the risk was increased in relation to the general population at all updated blood pressure levels, even though the risk was not increased to a great extent for blood pressure levels below 130/80. In contrast, for patients with type 2 diabetes and blood pressure between 120-139/70-89 mmHg the risk of hemorrhagic stroke was significantly reduced compared to the general population.

Some previous studies have found type 2 diabetes to be a risk factor for hemorrhagic stroke (55, 56) even though not a very strong one. Other studies have not found hemorrhagic stroke or primary intracerebral hemorrhage to be more common among patients with than without diabetes (58). The large case-control study INTERSTROKE with more than 3000 intracerebral hemorrhages found a history of diabetes or HbA1c >6.5% to significantly reduce the risk of intracerebral hemorrhage (52). Potentially, our finding of lower risk of hemorrhagic stroke among patients with type 2 diabetes except in those with high blood pressure could improve the understanding of the association between diabetes and risk of hemorrhagic stroke.

A protective role of diabetes has been suggested concerning the development of abdominal aortic aneurysm (56, 102) and subarachnoid hemorrhage (56) since patients with diabetes seem to be spared with respect to those conditions. Diabetes has been associated with thicker extracellular matrix of the vessels and deposition of advanced glycation end products (AGEs) that induce cross linkage between components in the matrix, all enhancing the stiffness of the wall (102). One can only speculate if these mechanisms could be of importance concerning our finding of reduced risk of hemorrhagic stroke for patients with type 2 diabetes in the lower blood pressure categories. Another possible protective feature for patients with diabetes when it comes to hemorrhagic stroke is the lipid pattern. High LDL levels is common in patients with type 2 diabetes (103) and high cholesterol and LDL levels have been associated with reduced risk of hemorrhagic stroke (104).

Our finding of increased risk of ischemic stroke in all blood pressure categories compared to the general population was perhaps more expected. This finding is in concordance with the one other study we have found that has estimated the excess risk of stroke for diabetes patients at different blood pressure levels (55). In our study, a slight J-shaped association was found over the blood pressure categories concerning the risk of ischemic stroke compared to the general population with the lowest risk in category 120-129/70-79 mmHg. The same J-shaped association between blood pressure and risk of ischemic stroke was also seen in our analysis within the group of type 2 diabetes patients. The increased risk of ischemic stroke in category 110-119/65-69 mmHg compared to category 120-129/70-79 mmHg can be caused by a greater number of people with a higher baseline risk of stroke in this category. Low blood pressure is often reflective of poor health (105). The lower blood pressure categories comprised a larger proportion of patients with CHD, AF, and HF compared to the higher categories. Even though we adjusted for baseline comorbidities in our models, we cannot exclude the possibility of low blood pressure as an indicator of comorbidities, implying a higher stroke risk. A recent publication, also based on NDR data, points

out higher frequencies of comorbidities in the lowest blood pressure categories as responsible for the J-shaped association over the blood pressure categories and different cardiovascular out-comes (71).

We believe that the estimates in our study on excess risk of stroke at different blood pressure levels can be of interest for both patients with type 2 diabetes and their physicians. Today, patients are often well informed and aware of the greater risk of cardiovascular disease they face as a result of having type 2 diabetes. This study can encourage patients with type 2 diabetes in showing that they can have a risk of stroke comparable to the general population if their blood pressure is below 130/80. For physicians, information from this study can be a used as a motivator for patients with type 2 diabetes who might not be willing to start antihypertensive medication. Hypertension is often asymptomatic but is still very important to treat in order to reduce morbidity and mortality in type 2 diabetes patients.

What is the excess risk of stroke for type 1 diabetes patients at different updated HbA1c levels compared to the general population? (Paper IV)

For long, HbA1c level in type 1 diabetes patients has been associated with risk of development of microvascular complications like nephropathy, retinopathy and neuropathy (106). Lately, an increasing amount of studies has also linked HbA1c level in type 1 diabetes patients to macrovascular complications (62). Many studies attempting to estimate the association between HbA1c and cardiovascular outcomes in type 1 diabetes patients have been relatively small, participants have been young and in combination with comparatively limited follow-up also had few events (61-63). Above all, this has been a problem regarding stroke events, in particular hemorrhagic stroke, which constitutes a minor part of the subtypes of stroke.

In our study we followed a cohort of 33,453 type 1 diabetes patients with a baseline mean age of 36 years during a mean follow-up of approximately 8 years. During the follow-up 762 events of stroke were diagnosed. This is far more than most previous studies. We found an increased risk of ischemic stroke in all HbA1c categories compared to persons without diabetes. For hemorrhagic stroke the risk was increased in all but the lowest HbA1c category. In addition, we found a correlation between HbA1c level and both subtypes of stroke with an increased risk of ischemic and hemorrhagic stroke by higher updated HbA1c levels compared to the controls.

Previous studies have found HbA1c level to be a predictor of all and ischemic stroke (60, 62, 63). For hemorrhagic stroke, some studies have found elevated HbA1c to be a predictor (61) while others have not (60). Even if the number of hemorrhagic stroke cases in our lowest HbA1c category only was 5, the number increased in the higher HbA1c categories and the total number of hemorrhagic stroke in our study was 107. Higher HbA1c level indicated an increased risk of hemorrhagic stroke in the analysis comparing with the general population as well as in the analysis within the group of diabetes patients. In the analysis within the group of patients with type 1 diabetes we could adjust our models for several risk factors for stroke. An increased risk remained at least in the highest HbA1c category in all models. This suggests HbA1c as a predic-

tor for hemorrhagic stroke even though maybe not as strong predictor as for ischemic stroke.

Hypertension is an important risk factor for stroke (52). In the estimates of excess risk of stroke for type 1 diabetes patients compared to the general population we did not have blood pressure measurements of the controls and were thus unable to adjust for blood pressure. Hypertension is more common in people with type 1 diabetes than in people without diabetes (107). However, in our study the average blood pressure in the group of type 1 diabetes patients was 127/74 mmHg which is not very high. The difference in blood pressure between the lowest HbA1c category and the highest was only 2.4 mmHg for systolic and 3.0 mmHg for diastolic blood pressure. Still we found a difference in risk of stroke over the HbA1c categories. Additionally, in the analysis within the group of type 1 diabetes patients we could adjust for systolic blood pressure and we still saw an effect of HbA1c level on the risk of stroke. Therefore, it seems unlikely that blood pressure level could explain more than a minor part of the excess risk of stroke in patients with type 1 diabetes compared to the general population or the increase in risk of stroke by higher HbA1c category.

Our finding of an increased risk of stroke among type 1 diabetes patients even with HbA1c levels within treatment target compared to an age matched general population can be discouraging. However, one must bear in mind that the absolute risk of stroke in this young population is low. Moreover, HbA1c level is important – the risk increased from a 75% excess risk among the best controlled patients to an eightfold excess risk in the highest HbA1c category. Technological developments in recent years have resulted in new glucose monitoring utensils that can estimate glucose levels in the subcutaneous tissue like Continuous Glucose Monitoring (CGM) and Flash Glucose Monitoring (FGM). These new utensils have shown being able to assist patients to achieve better HbA1c levels (108, 109). One drawback with these new utensils is the cost. However, the costs of complications of type 1 diabetes are large as well. A stroke in a young person living with possible lifelong sequelae are enormous, let alone loss of quality of life. Therefore, we believe that information from this study is important to further emphasize the importance of providing the best possible support for type 1 diabetes patients in order to keep as good glycemic control as possible.

Strengths and limitations

Strengths in Paper I and II include a large number of unselected participants from the general population, the prospective longitudinal design of the study, the extended follow-up and a large number of diabetes cases.

The limitations in Paper I and II include several issues. First, the lack of blood glucose samples or glucose tolerance test at the baseline examination is a limitation in that patients with undiagnosed diabetes might have been included among the participants. However, the majority of diabetes cases (approximately 90%) were detected more than a decade after the baseline screening. Therefore it seems unlikely that the number of undiagnosed diabetes cases at baseline would have affected our results in a significant manner. Second, we captured a diagnosis of diabetes from hospital

discharge registers – not primary healthcare registers. Type 2 diabetes is often managed at primary healthcare level, at least during the first years, and participants with diabetes not hospitalized will be missed by our studies. However, due to the long follow-up, the majority of men did visit hospital at some point during the studies (approximately 95%). Diabetes is a condition affecting many other disorders and accordingly diabetes is likely to have been registered at least as a contributing diagnosis even though not being the primary reason why the participant was hospitalized. Men with diabetes managed in primary care only or who died without being hospitalized would, however, still have been missed. Finally, we only have access to baseline data of all the covariates. A study estimating secular trends in men aged 50 years between 1963 and 1993 in Gothenburg showed that smoking rates, mean systolic blood pressure and cholesterol level decreased while BMI and triglycerides increased during these 30 years (110). We do not know if these secular trends will have applied to the participants in our study but fluctuations can occur in the covariates and we might not have captured the total effect of the covariates on the development of diabetes.

The strengths in Paper III and IV are that they include a large number of patients with type 1 and type 2 diabetes respectively and the presence of a control group from the general population. The number of included patients with diabetes provided a large number of strokes, both ischemic and hemorrhagic, especially in the case of type 1 diabetes patients, where there were more stroke cases than in any previous study. The data also represent diabetes patients on routine treatment in hospital or primary care centers nationwide and we had access to repeated measurements on several important risk factors in the group of diabetes patients. In addition we have information on comorbidities and education for both individuals with and without diabetes.

However, there are also limitations to Paper III and IV. First, we did not have data on risk factors for the controls corresponding to the risk factor data we had in the group of diabetes patients. In Paper III, we did not have the blood pressure of the controls and therefore were unable to estimate the risk between patients with and without diabetes at every blood pressure level. The estimates of excess risk for type 2 diabetes patients at different blood pressure levels are estimates of excess risk compared to all controls pooled together as one reference group. Nor were we able to adjust the models for all the covariates that we had in the diabetes group since corresponding data were unavailable for the controls. However, we believe that the information of excess risk of stroke for type 2 diabetes patients estimated towards a sex and age matched general population may still be of interest. In Paper IV, concerning HbA1c level and stroke risk in type 1 diabetes patients, average blood pressure level was 127/74 mmHg in the group of diabetes patients, which is not very high. Moreover, we did have information on comorbidities of importance for the risk of stroke such as AF for both diabetes patients and controls. Smoking rates may be slightly lower among diabetes patients than in the general population. Taken together, we do not believe that information on these variables would have altered our results more than in a minor way.

Second, during the first years of the study the coverage of the NDR was incomplete, particularly for type 2 diabetes. Type 1 diabetes patients are, however, mainly managed at hospital out-patient clinics and were reported to the NDR to a higher extent

from the outset. Primary care units where many of the type 2 diabetes patients are managed in the beginning started to report to the NDR at a later stage. However, a unit reporting their patients to NDR generally reports all their patients irrespective of how well controlled they are. Therefore we do not believe that the incomplete coverage of the NDR during the first half of the study ought to have affected our results to a great extent. Third, the diagnosis of hemorrhagic and ischemic stroke are captured from registers, they were not formally validated. However, computed tomography scans are routinely used in all suspected stroke cases in Sweden which ought to minimize misdiagnosis. In our papers based on the NDR the proportion with hemorrhagic strokes was 9% in Paper III and 14% in Paper IV. RIKSTROKE, a quality register in Sweden where currently 90% of all stroke cases are registered, estimates that approximately 10% of the strokes are intracerebral bleedings, 5% are subarachnoidal bleedings and 85% are ischemic strokes (www.riksstroke.org/general-information). Therefore we believe that the classification of subtypes of stroke reflect the true situation among diabetes patients in Sweden. Finally, all our studies are observational and as for all observational studies we cannot totally exclude the possibility of residual confounders.

CONCLUSIONS

High-normal blood pressure as well as hypertension at midlife in men is a significant risk factor of later development of type 2 diabetes even at a longer follow-up of 35 years. The association between blood pressure level and risk of diabetes remained after adjustment for BMI and other conventional risk factors for diabetes. Also, low occupational class at midlife implies a significantly increased risk of development of type 2 diabetes compared to higher occupational classes. The increased risk of diabetes in the lower occupational classes is partly explained by an increased prevalence of conventional risk factors of type 2 diabetes. However, stress could not explain the difference over the occupational classes.

On a group level, patients with type 2 diabetes have an excess risk of stroke compared to a sex and age matched general population. The risk was noticeably higher for ischemic than for hemorrhagic stroke. However, when estimating the excess risk at different blood pressure levels we could not find that type 2 diabetes patients with blood pressure below 130/80 mmHg had any increased risk of stroke compared to the general population. The slightly increased risk of ischemic stroke in lower blood pressure categories for diabetes patients was off-set by a significantly reduced risk of hemorrhagic stroke.

Likewise, type 1 diabetes patients have an excess risk of stroke compared to the general population, higher for ischemic than hemorrhagic stroke. The risk of any stroke was increased even in the group of type 1 diabetes patients with HbA1c within target. However, the risk rose considerably with worse metabolic control and elevated HbA1c therefore appears to be a risk factor for both ischemic and hemorrhagic stroke.

ACKNOWLEDGEMENTS

I wish to express my gratitude to everyone who has supported me and contributed in different ways to this thesis. In particular I want to thank;

Annika Rosengren, my principal supervisor. You saw my interest in epidemiology research, encouraged me and offered to be my supervisor. I am thankful for your interest, support, valuable ideas and for sharing your vast knowledge about research and cardiovascular epidemiology.

Per-Olof Hansson, my co-supervisor but also colleague for many years in clinical work. You are always helping out, sharing your knowledge about research and clinical work, and always being so kind and supportive in all those areas.

Masuma Novak, my co-supervisor. For your valuable support and co-operation with my first two papers. You introduced me to scientific writing and taught me a lot about the "handicraft" of being a researcher. Thanks for all nice talks about research and life in general.

Henry Eriksson – head of section 352 when I was employed at the department of Medicin SU/Östra and co-supervisor in the beginning of my PhD studies. You introduced me to epidemiology research and gave valuable support and encouragement.

Maria Taranger – head of department of Med/Ger/Akut, SU/Östra and *Mikael Dellborg*- head RND Med/Ger/Akut SU/Östra for resources and time off clinical work. *Anna-Clara Collén* – head of the stroke section and former PhD colleague – for all advices and assist during the completion of my PhD studies.

Georgios Lappas and *Aldina Pivodic* for your patience and willingness to discuss and explain statistical matters.

Annika Dotevall- my clinical supervisor during Internship in Internal Medicine. You have been a role model in being a doctor. Thank you for all advices concerning clinical work, research, children and many other aspects of life.

My fellow doctoral colleagues at SU/Östra for sharing both the fun and hardship during PhD studies; *Susanne Nielsen* – for your friendship and all nice supportive chats about research and everything else under the sun, *Kok Wai Giang* – for our fine cooperation and all discussions in our common endeavor to learn more about cardiovascular epidemiology, *Paolina Weidinger* – for your friendship and helping each other out during several courses in statistics.

Research colleagues at the Department of Molecular and Clinical Medicine at SU/Östra; *Lena Björck*, *Martin Adiels*, *Tatiana Zverkova Sandström, Christina Persson, Pär Parén, Martin Lindgren, Samuel Adamsson Eryd* and *Jon Edqvist* for support and fruitful discussions.

Eva Thydén – for helping out with every detail surrounding the PhD studies, practicalities concerning the dissertation and the layout of this book.

Christel Jansson – for your excellent help with administrative issues.

Friends and colleagues at the Stroke section of Med/Ger/Akut SU/Östra; *Shirin Pazireh, Martin Lindén, Claes Gustafsson, Björn Lundin, Bodil Lernfelt, Denislava Samoilova Mintcheva*, and many more at the Department of Med/Ger/Akut SU/Östra.

My mother and father – *Karin* och *Karl-Göran* for your endless love and support throughout my life. *Ulrika* **–** for being my sister and the special relation that comes with sisterhood.

Olof, my love and best friend, always supporting me and making me laugh. Our sons *Carl Johan, Gustav* and *Filip,* constantly reminding me of what is essential, you are my everything.

This work was supported by grants from: the Swedish state under an agreement between the Swedish government and the county councils concerning economic support of research and education of doctors, ALF-agreement (grants and research position); the Göteborg Medical Society; the Swedish Heart and Lung Foundation; the Swedish Research Council; and the Swedish Council for Health, Working Life and Welfare (FORTE); Diabetes Wellness (FORTE, Epilife); King Gustaf V:s and Queen Victorias Freemasons' Foundation, the Swedish Diabetes Foundation.

REFERENCES

1. Global Burden of Metabolic Risk Factors for Chronic Diseases C. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. Lancet Diabetes Endocrinol. 2014;2(8):634-47.

2. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. Eur J Cardiovasc Prev Rehabil. 2010;17 Suppl 1:S3-8.

3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.

4. Ezzati M. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet. 2016;387(10027):1513-30.

5. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.

6. Sander D, Sander K, Poppert H. Review: Stroke in type 2 diabetes. The British Journal of Diabetes & Vascular Disease. 2008;8(5):222-9.

7. WHO - Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006.

8. Definition W. diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva: World Health Organization. 1999.

9. Committee IE. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes care. 2009;32(7):1327-34.

10. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet. 2011;378(9786):169-81.

11. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78(3):305-12.

12. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol. 2010;55(13):1310-7.

13. Daneman D. Type 1 diabetes. Lancet. 2006;367(9513):847-58.

14. NDR annaul report 2013. 2013.

15. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014(1474-547X (Electronic)).

16. Haller MJ, Atkinson Ma Fau - Schatz D, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. 2005(0031-3955 (Print)).

17. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293-300.

18. Thunander M, Torn C, Petersson C, Ossiansson B, Fornander J, Landin-Olsson M. Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. European journal of endocrinology / European Federation of Endocrine Societies. 2012;166(6):1021-9.

19. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nat Rev Endocrinol. 2012;8(4):228-36.

20. Andersson T, Ahlbom A, Carlsson S. Diabetes Prevalence in Sweden at Present and Projections for Year 2050. PLoS One. 2015;10(11):e0143084.

21. Jansson SP, Fall K, Brus O, Magnuson A, Wandell P, Ostgren CJ, et al. Prevalence and incidence of diabetes mellitus: a nationwide population-based pharmaco-epidemiological study in Sweden. Diabet Med. 2015;32(10):1319-28.

22. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383(9922):1068-83.

23. Kwak SH, Park KS. Recent progress in genetic and epigenetic research on type 2 diabetes. Experimental & molecular medicine. 2016;48:e220.

24. Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, McKnight JA, et al. Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia. 2011;54(12):3003-6.

25. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. Jama. 2008;300(24):2886-97.

26. Wei JN, Sung FC, Li CY, Chang CH, Lin RS, Lin CC, et al. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among schoolchildren in taiwan. Diabetes Care. 2003;26(2):343-8.

27. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2010;23(3):199-203.

28. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790-7.

29. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care. 2005;28(9):2322-5.

30. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. Eur J Epidemiol. 2015;30(7):529-42.

31. Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2011;21 Suppl 2:B32-48.

32. Lindstrom J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinanen-Kiukaanniemi S, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia. 2013;56(2):284-93.

33. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.

34. Pouwer F, Kupper N, Adriaanse MC. Does emotional stress cause type 2 diabetes mellitus? A review from the European Depression in Diabetes (EDID) Research Consortium. Discov Med. 2010;9(45):112-8.

35. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007;298(22):2654-64.

36. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434-44.

37. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. Circulation. 2008;118(9):968-76.

38. Houben AJ, Eringa EC, Jonk AM, Serne EH, Smulders YM, Stehouwer CD. Perivascular Fat and the Microcirculation: Relevance to Insulin Resistance, Diabetes, and Cardiovascular Disease. Curr Cardiovasc Risk Rep. 2012;6(1):80-90.

39. Golden SH, Wang NY, Klag MJ, Meoni LA, Brancati FL. Blood pressure in young adulthood and the risk of type 2 diabetes in middle age. Diabetes Care. 2003;26(4):1110-5.

40. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med. 2000;342(13):905-12.

41. Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. Eur Heart J. 2007;28(23):2937-43.

42. Meisinger C, Doring A, Heier M. Blood pressure and risk of type 2 diabetes mellitus in men and women from the general population: the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg Cohort Study. J Hypertens. 2008;26(9):1809-15.

43. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). J Epidemiol Community Health. 2006;60(1):7-12.

44. Weires M, Bermejo JL, Sundquist K, Sundquist J, Hemminki K. Socio-economic status and overall and cause-specific mortality in Sweden. BMC Public Health. 2008;8:340.

45. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. Trends in cardiovascular risk factors across levels of education in a general population: is the educational gap increasing? The Tromso study 1994-2008. J Epidemiol Community Health. 2014;68(8):712-9.

46. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. Int J Epidemiol. 2011;40(3):804-18.

47. Sacerdote C, Ricceri F, Rolandsson O, Baldi I, Chirlaque MD, Feskens E, et al. Lower educational level is a predictor of incident type 2 diabetes in European countries: The EPIC-InterAct study. Int J Epidemiol. 2012;41(4):1162-73.

48. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035-87.

49. Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke. 1989;20(10):1407-31.

50. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355-69.

51. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41.

52. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-75.

53. Bousser MG. Stroke prevention: an update. Front Med. 2012;6(1):22-34.

54. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA, et al. Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. Diabetologia. 2006;49(12):2859-65.

55. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.

56. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105-13.

57. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23.

58. Sturgeon JD, Folsom AR, Longstreth WT, Jr., Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007;38(10):2718-25.

59. Tuttolomondo A, Pinto A, Salemi G, Di Raimondo D, Di Sciacca R, Fernandez P, et al. Diabetic and non-diabetic subjects with ischemic stroke: differences, subtype distribution and outcome. Nutr Metab Cardiovasc Dis. 2008;18(2):152-7.

60. Hagg S, Thorn LM, Forsblom CM, Gordin D, Saraheimo M, Tolonen N, et al. Different risk factor profiles for ischemic and hemorrhagic stroke in type 1 diabetes mellitus. Stroke. 2014;45(9):2558-62.

61. Secrest AM, Prince CT, Costacou T, Miller RG, Orchard TJ. Predictors of and survival after incident stroke in type 1 diabetes. Diab Vasc Dis Res. 2013;10(1):3-10.

62. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-53.

63. Davis TM, Bruce DG, Davis WA. Predictors of first stroke in Type 1 diabetes: The Fremantle Diabetes Study. Diabet Med. 2005;22(5):551-3.

64. Hankey GJ, Anderson NE, Ting RD, Veillard AS, Romo M, Wosik M, et al. Rates and predictors of risk of stroke and its subtypes in diabetes: a prospective observational study. J Neurol Neurosurg Psychiatry. 2013;84(3):281-7.

65. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11(3):261-71.

66. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351(9118):1755-62.

67. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000;355(9200):253-9.

68. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000;321(7258):412-9.

69. Nilsson PM. U-shaped Relationship of Blood Pressure to CVD Risk and Relevance to Treatment Goals in Diabetes. Current Cardiovascular Risk Reports. 2014;8(1):1-6.

70. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ. 2016;352:i717.

71. Adamsson Eryd S, Gudbjornsdottir S, Manhem K, Rosengren A, Svensson AM, Miftaraj M, et al. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. Bmj. 2016;354:i4070.

72. McCormick MT, Muir KW, Gray CS, Walters MR. Management of hyperglycemia in acute stroke: how, when, and for whom? Stroke. 2008;39(7):2177-85.

73. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.

74. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. Neurology. 2004;62(9):1558-62.

75. Putaala J, Liebkind R, Gordin D, Thorn LM, Haapaniemi E, Forsblom C, et al. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. Neurology. 2011;76(21):1831-7.

76. Wilhelmsen L, Berglund G, Elmfeldt D, Tibblin G, Wedel H, Pennert K, et al. The multifactor primary prevention trial in Goteborg, Sweden. Eur Heart J. 1986;7(4):279-88.

77. Wilhelmsen L, Tibblin G, Werko L. A primary preventive study of Gothenburg, Sweden. Prev Med. 1972;1(1):153-60.

78. Eliasson B, Gudbjornsdottir S. Diabetes care--improvement through measurement. Diabetes Res Clin Pract. 2014;106 Suppl 2:S291-4.

79. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjornsdottir S. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care. 2008;31(10):2038-43.

80. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S, et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33(7):1640-6.

81. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

82. Koster M, Asplund K, Johansson A, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. Neuroepidemiology. 2013;40(4):240-6.

83. Statistics S. [Socioekonomisk indelning (SEI). Meddelande i samordingsfrågor 1982:4 (Swedish socio-economic classification SEI) Reports on statistical coordination, in Sweden with an english summary]. 1983.

84. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens. 1999;17(2):151-83.

85. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007;4(10):e297.

86. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. Statistics in medicine. 2009;28(19):2473-89.

87. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.

88. Wilhelmsen L, Lappas G, Rosengren A. Risk of coronary events by baseline factors during 28 years follow-up and three periods in a random population sample of men. J Intern Med. 2004;256(4):298-307.

89. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007;369(9557):201-7.

90. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. Am J Med. 2006;119(2):133-41.

91. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25(6):1105-87.

92. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

93. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006;24(2):215-33.

94. Stringhini S, Tabak AG, Akbaraly TN, Sabia S, Shipley MJ, Marmot MG, et al. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. BMJ. 2012;345:e5452.

95. Agardh EE, Ahlbom A, Andersson T, Efendic S, Grill V, Hallqvist J, et al. Explanations of socioeconomic differences in excess risk of type 2 diabetes in Swedish men and women. Diabetes Care. 2004;27(3):716-21.

96. Geyer S, Hemstrom O, Peter R, Vagero D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J Epidemiol Community Health. 2006;60(9):804-10.

97. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953-62.

98. Kumari M, Head J, Marmot M. Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. Arch Intern Med. 2004;164(17):1873-80.

99. Kaijser M, Bonamy AK, Akre O, Cnattingius S, Granath F, Norman M, et al. Perinatal risk factors for diabetes in later life. Diabetes. 2009;58(3):523-6.

100. van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, et al. Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes. 2012;61(9):2255-60.

101. Kuh D B-SY, editor. A life course approach to chronic disease epidemiology Oxford University press; 2007.

102. Shantikumar S, Ajjan R, Porter KE, Scott DJ. Diabetes and the abdominal aortic aneurysm. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2010;39(2):200-7.

103. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab. 2009;5(3):150-9.

104. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke. 2013;44(7):1833-9.

105. Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence for a positive linear relation between blood pressure and mortality in elderly people. Lancet. 1995;345(8953):825-9.

106. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329(14):977-86.

107. Norgaard K, Feldt-Rasmussen B, Borch-Johnsen K, Saelan H, Deckert T. Prevalence of hypertension in type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1990;33(7):407-10.

108. Dover AR, Stimson RH, Zammitt NN, Gibb FW. Flash Glucose Monitoring Improves Outcomes in a Type 1 Diabetes Clinic. Journal of diabetes science and technology. 2016.

109. Langendam M, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2012;1:Cd008101.

110. Rosengren A, Eriksson H, Larsson B, Svardsudd K, Tibblin G, Welin L, et al. Secular changes in cardiovascular risk factors over 30 years in Swedish men aged 50: the study of men born in 1913, 1923, 1933 and 1943. J Intern Med. 2000;247(1):111-8.