Obesity in diabetes
Cardiovascular outcomes and risk factor trajectories

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To my family

Linnéa, Noa, Maja, Leif, Lisa, mum and dad

ABSTRACT

Introduction: The association between body mass index (BMI) and mortality in diabetes is complex and sparsely investigated for cardiovascular (CVD) outcomes. We aimed to investigate these relationships among patients with type 1 and type 2 diabetes using data from the Swedish national diabetes registry (NDR), with focus on potential reverse causality. Considering recent findings of marked excess risks among patients with early onset of type 1 diabetes we aimed to investigate risk factor trajectories based on age at onset.

Methods: The thesis is based on data from the Swedish national diabetes registry (*Study I-IV*) and matched controls taken from the general population (*Study I* and *III*), using statistical methods such as Cox regression, linear regression, mixed models and machine learning.

Results: *Study I*, the short-term risk of death (<5 years from baseline) in patients with type 2 diabetes was slightly lower among obese patients than in age- and sex matched controls, with a nadir among obese patients varying between 30-<40 kg/m^2, depending on age. Long-term mortality (≥5 years from baseline) exhibited a stepwise increase from BMI 25-<30 kg/m^2, where patients with BMI ≥40 kg/m^2 had a 2-fold risk of death compared to the general population, with similar findings for CVD death. In *Study II*, we found a slight increase in the risk of death, CVD death, major CVD (stroke or acute myocardial infarction [AMI]) and heart failure (HF) with rising BMI in patients with type 1 diabetes, but no increase in risk in patients with normal weight after exclusion of individuals with poor metabolic control, smokers and patients with follow-up shorter than 10 years. In *Study III*, the association between BMI and the risk of AMI was essentially flat but worsened with poor glycemic control, while, in contrast, there was a markedly increasing risk for HF with rising BMI with a nadir as low as ~18.5 kg/m^2. The risk of HF was further exaggerated by poor glycemic control with an 8-fold excess risk of HF among patients with BMI ≥40 kg/m^2 and hemoglobin A1c (HbA1c) ≥70 mmol/mole. In *Study IV*, patients with an onset of type 1 diabetes ≤15 years had a high mean HbA1c of ~70 mmol/mole in early adulthood, whereas patients with a later onset (16-30 years) displayed a gradual increase in HbA1c up to a mean at ~65 mmol/mole, common for all groups regardless of age at onset. Machine learning models showed that baseline HbA1c (duration of diabetes >1 year) was linked to age, educational level and CVD risk factors.

Conclusions: Among patients with type 1 and type 2 diabetes our analyses provided no support for an obesity paradox for the outcomes of death (type 1 diabetes) and CVD complications including HF after considering the influence of reverse causality. The strong relationship between obesity and HF which was worsened by poor glycemic control, was absent for AMI, indicating different pathophysiological mechanisms behind these two outcomes. The age at onset of type 1 diabetes seems to be an important predictor of glycemic control during the first years of adulthood, as well as for the prevalence of albuminuria leading to a more rapid decline in eGFR from an early age. Our study also stresses the importance of early optimization of CVD risk factors, in particular glycemic control, in patients with type 1 diabetes.

Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, body mass index, cardiovascular disease, epidemiology, reverse causality, mortality, heart failure, myocardial infarction, trajectories, machine learning

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LIST OF PAPERS

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

I Jon Edqvist, Araz Rawshani, Martin Adiels, Lena Björck, Marcus Lind, Ann-Marie Svensson, Sofia Gudbjörnsdottir, Naveed Sattar, Annika Rosengren. BMI and Mortality in Patients With New-Onset Type 2 Diabetes: A Comparison With Age- and Sex-Matched Control Subjects From the General Population.
Diabetes Care. 2018;41:485-493.

II Jon Edqvist, Araz Rawshani, Martin Adiels, Lena Björck, Marcus Lind, Ann-Marie Svensson, Sofia Gudbjörnsdottir, Naveed Sattar, Annika Rosengren. BMI, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes: Findings Against an Obesity Paradox.
Diabetes Care. 2019;42:1297-1304.

III Jon Edqvist, Araz Rawshani, Martin Adiels, Lena Björck, Marcus Lind, Ann-Marie Svensson, Sofia Gudbjörnsdottir, Naveed Sattar, Annika Rosengren. Contrasting Associations of Body Mass Index and Hemoglobin A1c on the Excess Risk of Acute Myocardial Infarction and Heart Failure in Type 2 Diabetes Mellitus.
J Am Heart Assoc. 2019;8:e013871.

IV Jon Edqvist, Araz Rawshani, Aidin Rawshani, Martin Adiels, Stefan Franzén, Lena Björck, Ann-Marie Svensson, Marcus Lind Naveed Sattar, Annika Rosengren. Trajectories in HbA1c and other risk factors among adults with type 1 diabetes by age at onset.
Manuscript submitted.

SAMMANFATTNING PÅ SVENSKA

Introduktion

Sambandet mellan body mass index (BMI) och mortalitet bland personer med diabetes är komplex och inte så väl studerat för kardiovaskulära (CVD) utfall. Syftet med avhandlingen var att undersöka BMI och kardiovaskulära utfall inklusive hjärtsvikt (HF) bland personer med diabetes typ 1 och diabetes typ 2 med hjälp av data från nationell diabetesregistret (NDR), genom att ta hänsyn till faktorer som är associerade med reverse causality. Med bakgrund av nyligen publicerad data som funnit en överrisk för död, CVD och HF bland personer med diabetes typ 1, ville vi även undersöka utveckling över tid i riskfaktorer baserat på ålder vid insjuknande.

Metodik

Avhandlingen bygger på data från NDR och kontroller från totalbefolkningsregistret med tillämpning av ett flertal statistiska metoder som Coxregression, linjär regression, mixade modeller och machine learning. I Studie I och III jämfördes varje patient med 5 kontroller från den generella befolkningen utan diabetes matchade för kön och ålder.

Resultat

Studie I. På kort sikt (<5år) var risken för död något lägre bland patienter med diabetes typ 2 jämfört med ålders- och könsmatchade kontroller, och risken var lägst vid måttlig fetma (nadir vid BMI 30-<35 för död). På lång sikt däremot var kurvan linjärt stigande från BMI 25-<30 där de med mycket svår fetma uppvisade fördubblad risk för död jämfört med normalbefolkningen.

Studie II. Vi fann en måttlig linjär riskökning mellan BMI och risk för död, major CVD och hjärtsvikt. Efter att vi uteslutit individer med låg grad av metabol kontroll, rökare och patienter med kort uppföljningstid, fann vi att patienter med diabetes typ 1 och lågt BMI inte hade någon överrisk för något av utfallen.

Studie III. Risken för att drabbas av HF jämfört med matchade kontroller steg linjärt med BMI och förvärrades med sämre metabol kontroll, och var upp till 8 ggr risken bland patienter med BMI ≥40 kg/m^2 och HbA1c >70 mmol/mol. Risken för hjärtinfarkt ökade med sämre metabol kontroll men påverkades inte nämnvärt av BMI.

Studie IV. Patienter med tidig debutålder 0-15 år hade påtagligt höga HbA1c-värden omkring 70 mmol/mol vid 18-20 års ålder. Först i 35-40 års ålder planade värdena ut till omkring 65 mmol/mol. Patienter med debutålder 16-30 år hade ett lågt HbA1c 1 år efter debut kring target level 52 mmol/mol men nivåerna steg efter några år till ca 65 mmol/mol. Machinelearningmodeller visade att ett högt baseline HbA1c (efter minst 1 års diabetesduration) var associerat med låg ålder, albuminuri, högt eGFR, rökning, låg utbildning, förhöjt diastoliskt blodtryck och förhöjt LDL-kolesterol oavsett debutålder och kön.

Slutsatser

Studie I-III. För patienter med diabetes typ 1 och diabetes typ 2 visade våra studier att det varken fanns någon obesitasparadox eller förhöjd risk bland normalviktiga patienter för varken död (diabetes typ 1), CVD-komplikationer (HF inkluderat), efter att ha tagit hänsyn till reverse causality. Bland patienter med diabetes typ 2 fann vi ett starkt samband mellan fetma och HF, vilket inte var fallet med hjärtinfarkt, sannolikt beroende på två olika patofysiologiska mekanismer bakom dessa två utfall vilket indikerar riktade medicinska insatser hos patienter med diabetes typ 2 för att undvika framtida HF.

Studie IV. Debutålder spelar en viktig roll för den glykemiska kontrollen de första åren i vuxen ålder samt för förekomsten av albuminuri med stora skillnader fram till tidig medelålder, där patienter med låg debutålder företer en högre glykemisk belastning och tecken på tidigare försämrad njurfunktion genom livet jämfört med patienter med senare debutålder. Vår studie pekade också på vikten av riskfaktorbehandling för alla patienter med diabetes typ 1 oavsett debutålder.

CONTENTS

ABBREVIATIONS

AMI	Acute myocardial infarction
BMI	Body mass index
CI	Confidence interval
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
eGFR	Estimates glomerular filtration rate
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HF	Heart failure
HR	Hazard ratio
LADA	Latent Autoimmune Diabetes in Adults
LDL	Low density lipoprotein
LISA	Longitudinal Database for Health Insurance and Labor Market
MODY	Maturity Onset Diabetes in Young
NDR	Swedish national diabetes registry
PIN	Personal identification number
RTB	Total population register
SBP	Systolic blood pressure
SGLT-2	Sodium-glucose transport protein 2
WHO	World health organization

INTRODUCTION

Milestones of diabetes mellitus

One of the earliest known descriptions of symptoms resembling those of diabetes mellitus (Ebers papyrus) may be dated back to 1500 BC, where symptoms such as thirst and large quantities of urine were observed[1]. A physician named Aretaios described a condition he called "diabetes" approximately 2,000 years ago, alluding to the extensive volume of urine which one could not compensate for by drinking, which in the end led to death, however, if this was diabetes mellitus is not known, and the etiology was thought by some to be snakebite from the snake Dipsas (the thirst snake)[2]. Centuries later (17th century) Thomas Willis described "diabetes mellitus", where "mellitus" referred to honey, while in the 19th century Richard Bright discovered that high volumes of urine were due to pancreas dysfunction[2]. Paul Langerhans discovered the presence of the Langerhans islets in the pancreas, later to be identified to produce insulin by other researchers[2, 3]. Even if there was progress in the understanding in the pathophysiology of diabetes, a major dilemma was the lack of effective treatment. For instance, cures are described based on different forms of diets in order to lower the intake of carbohydrates[4]. Two main sides emerged, with patients recommended either forms of simple starvation or a high fat diet where "moderate" alcohol intake and opium drops were prescribed in order for patients to be able to endure the monotonous diet, however, these rather unsuccessful diets would sooner or later lead to an inevitable death[5].

Charles Best and Grant Banting who worked in the laboratory of John Macleod in Toronto became the first to extract and inject insulin, using dogs as test subjects, and with the help from James B. Collip they managed to refine the process of insulin manufacturing, hence, in 1922 the first human patient was injected successfully with exogenous insulin, with an immediate improvement of clinical symptoms[2]. Macleod and Banting were jointly awarded the Nobel prize, although conflicts had risen between the two pioneers, while Best was completely overlooked by the Nobel committee. Thus, in the end, neither Macleod nor Banting attended the ceremony in Stockholm, however, Banting split the award with Best and Macleod split the prize sum with Collip[2]. Since the discovery of insulin in 1921, the treatment and care for patients with diabetes have been developed further in many ways[1-3].

Dietary modifications are still important, however, rather as a complementary treatment in type 1 diabetes and type 2 diabetes alike[4], where strict regimens have been shown to lessen, or even result in remission of type 2 diabetes[6, 7]. Modern treatment includes insulin pumps, continuous glucose monitoring (CGM) and closed loops[8], which have resulted in a substantial improvement in glycemic control in the past decade[8]. With very precise and refined types of insulin[9], clinicians of today also have access to better treatment in type 2 diabetes with new analogues such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose transport protein-2 (SGLT-2) inhibitors which are thought to lower the risk of late complications and to improve blood glucose control among patients with diabetes[10].

Current definitions of diabetes mellitus and it's etiology

Diabetes is characterized by hyperglycemia which is the basic criterion for all types of diabetes, and the World Health Organization (WHO) has defined diagnostic criteria to diagnose diabetes[3]. There are currently two main classifications of diabetes. Type 1 diabetes, with a prevalence of about ~10% of the population with diabetes[3,11], is to a large degree an autoimmune disease, characterized by the destruction of ß-cells, whereas the remainder may have an unclear pathogenesis which may include patients classified with Maturity Onset Diabetes of Young (MODY)[12]. Primary and secondary prevention of type 1 diabetes is currently not available since no intervention has been proven effective[13]. There are several hypotheses regarding triggers of type 1 diabetes relating to environmental factors such as psychological stress, diet related to diet deficiencies and high body weight which have been speculated to lead to ß-cell exhaustion and later ß-cell destruction due to autoimmunity[14]. While the exact causes of type 1 diabetes are yet to be discovered, increasing difficulties have risen due to the increasing numbers of overweight and obese children, sometimes making it a challenge for clinicians to distinguish and classify diabetes in the young[15] although antibodies are an important biomarker of type 1 diabetes and may sometimes be present in other forms of diabetes[16].

The second type of diabetes is type 2 diabetes with a prevalence estimated to ~80-90% of all people with diabetes[3], characterized by an initial hypersecretion of insulin due to a reduced sensitivity to insulin in the cells, which over time may lead to a decreased secretion of insulin and resulting hyperglycemia[17]. Obese individuals have ~30% lower insulin sensitivity than lean people, however, insulin resistance may also occur among lean people which suggests that the pathogenesis in some cases are independent of body fat[17]. However, obesity is still the main predictor for type 2 diabetes where individuals with obesity may suffer a 7-fold risk of incident type 2 diabetes compared to individuals with normal weight[18]. There are also less common subgroups of diabetes such as Latent Autoimmune Diabetes in Adults (LADA), with a prevalence ~10% of the population with diabetes and MODY with an estimated prevalence of ~1-5% of the population with diabetes, although the prevalence of all diabetes types may vary depending on population and classification methods[3].

The increasing numbers of overweight and obesity in the general population

In the industrialized western society, body weight has increased dramatically the last decades, particularly in English-speaking nations, however, mean body mass index (BMI) has increased among Swedish citizens in both adolescents and adults and in both sexes[19]. The increasing rates of obesity may lead to rising rates of cardiovascular disease (CVD), heart failure (HF)[20] and type 2 diabetes in the general population, which may be concerning from a public health perspective.

Large registry- and cohort-based studies has shown that BMI is a predictor for mortality in the general population, with increasing hazard ratios (HRs) starting below BMI 25 kg/m^2[21-23], confirming that overweight and obesity is associated with death and CVD complications.

Epidemiology of type 2 diabetes - prevalence and the excess risks of late complications

The increasing prevalence of type 2 diabetes worldwide is taking epidemic proportions. Fourhundred sixtytwo million individuals i.e 6.28% of the world's population is estimated to suffer from type 2 diabetes[24]. Similar to the distribution of obesity, the industrialized western society and the Pacific Ocean nations have the highest prevalence of type 2 diabetes[24]. With increasing rates of obesity, the prevalence of type 2 diabetes in the Swedish adult population could, in a worst-case scenario, be estimated to be >12% by the year 2050[25]. These numbers may be worrying due to the excess risks of mortality[26, 27] and several CVD outcomes including HF[27, 28]. Glycemic control and kidney function are two crucial predictors of mortality, where poor glycemic control is thought to initiate a 4-fold excess risk of mortality in patients aged <55 years, while an estimated glomerular filtration rate (eGFR)<15 mL/min/1.73 m^2 may lead to an excess risk of 14 times that of the general population[26]. Likewise, younger individuals with type 2 diabetes have been shown to have a 4-fold risk of HF compared to the general population[28]. Not only may glycemic control and kidney function play an important role as independent predictors of late complications, but overall inadequate risk factor control, such as the accumulated burden of hyperglycemia, dyslipidemia, elevated blood pressure, smoking and albuminuria not at target, has also been shown to influence the excess risks of mortality and CVD, with markedly elevated risks of these outcomes when target levels are not reached, however, among non-smokers and CVD risk factors at target, the absolute risk may be on a par with the risk of the general population, or just slightly higher[27]. Treatment of CVD risk factors such as lipid-lowering and antihypertensive treatment along with intensive glycemic regimens may reduce risks among patients with type 2 diabetes significantly[29].

Type 2 diabetes, BMI, mortality and CVD outcomes

The incidence of type 2 diabetes is strongly associated with overweight and obesity[30], thus increasing rates of type 2 diabetes might be a logical consequence of rising obesity rates globally. However, the effect of BMI on mortality and CVD in individuals already diagnosed with type 2 diabetes has been debated. Some studies have suggested an inverse association between body weight and mortality where increased body weight would be protective[31], and others where higher weight in patients with type 2 diabetes would be associated with higher mortality[32-34], while one study proposes a near linear positive association between BMI and mortality[35]. Such diverse results from the research community may lead to confusing messages to clinicians and patients alike. What may be more apparent is the increased risk of HF with increasing BMI, where reports are sparse compared to the outcome of mortality, with no increased risk among leaner men and just slightly elevated risk of HF among the leanest women (BMI 18.5-22.5 kg/m^2), and with an approximately 2-fold risk of HF in patients with BMI >40 kg/m^2[36]. How BMI relates to adverse outcomes in the cohort of patients diagnosed with type 2 diabetes compared to a general population has, however, been sparsely studied. The increased risk for HF among obese individuals with type 2 diabetes is thought to reflect obesity related complications[37] whereas incident HF has not declined to the same degree as acute myocardial infarction (AMI) and stroke in recent years[38], possibly indicating different pathophysiological mecha-

nisms. While the independent role of hemoglobin A1c (HbA1c) as predictor for atherosclerotic complications such as CVD death[26] as well as for HF[28] may also raise the question if obesity may be a stronger predictor of HF than for AMI and also about how the combined effect of type 2 diabetes, hyperglycemia and obesity relates to the risk of incident HF.

Epidemiology of type 1 diabetes - incidence of type 1 diabetes and the excess risks of late complications

The Nordic countries have among the highest annual incidence of type 1 diabetes in the world, with rates in Sweden only second to Finland with approximately 40 individuals diagnosed with type 1 diabetes per 100,000 inhabitants per year[12]. Even though the Swedish prevalence of type 1 diabetes is much lower than that of type 2 diabetes, type 1 diabetes usually starts early in life which may impair quality of life lifelong for many individuals worldwide[39]. An American study concluded that, over a lifetime, the excess societal costs for type 1 diabetes would be >$800 billion[40], However, incidence rates of type 1 diabetes may have levelled off in Finland, with a decrease among children but rates were continuing to increase in Sweden at least until 2015[41].

The excess risk of mortality and CVD complications including HF in type 1 diabetes, compared to the general population has been studied extensively. Hyperglycemia is probably the most important predictor of mortality and CVD, where patients with HbA1c levels ≥83 mmol/mole displayed an 8-fold risk of death and a 10-fold risk of death from CVD in comparison to the general population, and 29-fold respectively 41-fold risk of death and death from CVD causes in the case of stage 5 chronic kidney disease (CKD)[42]. Similar to type 2 diabetes, inadequate overall risk factor control of HbA1c, low-density lipoprotein (LDL) cholesterol and systolic blood pressure (SBP) to target levels, presence of albuminuria and being a smoker are associated with increasing excess risks of mortality and CVD, where risk increases with an increasing number of risk factors not reaching target levels[43].

Type 1 diabetes, BMI, mortality and CVD outcomes

The role of obesity as a predictor for mortality and CVD outcomes in type 1 diabetes are sparse and the associations found between BMI and mortality heterogeneous. Increased risks have been observed among patients with type 1 diabetes with BMI <18.5 kg/m^2, BMI <20 kg/m^2, while African Americans with type 1 diabetes displayed an obesity paradox (5% less probability to die per one unit increase in BMI)[44]. Weight loss among patients with type 1 diabetes has been suggested to be associated with increased mortality risk[45].

Concurrently, intensive insulin therapy has been shown to reduce blood glucose, with an initial reduced risk of CVD compared to the conventionally treated group, however, with the side effect of weight gain[46], the intensive therapy group after 13 years of follow-up went from lower risk of CVD to risk that was equivalent to that of the conventional therapy group[55]. With new recommendations on how to tackle phenomena such as reverse causality taking factors such as follow-up time, smoking and

frailty into consideration, previously findings of paradoxical effects of obesity with increased risks in normal weight individuals may be challenged and possibly lead to new discoveries or confirmations about why results might contradict the common recommendations of maintaining low weight and achieving weight loss among obese individuals in the general population.

Reverse causality in epidemiological studies

Residual confounding is a phenomenon thought to prevent researchers to discover causal relationships by unprecise or unreliable measurements[47], i.e the exact number of smoked cigarettes among smokers[21]. Residual confounding is acknowledged by many researchers, however, another phenomenon called reverse causality is less understood but may also lead to confusing results and unexpected associations to adverse outcomes[47]. Where obesity is found to be protective, sometime called an obesity paradox, this may be because there is confounding by other factors associated with lower weight, such as cigarette smoking, frailty, but also hidden diseases that may affect findings during a too short follow-up time and other coexisting conditions[47,48]. Some examples of studies considering such factors are Tobias DK et al.[35] who found a stepwise increase in mortality by BMI among patients with type 2 diabetes and Adamsson Eryd et al.[49], who identified lower risk of CVD events in patients with type 2 diabetes with SBP as low as <130 mmHg after the consideration of coexisting conditions. Hence, it is evident that factors that may contribute to reverse causality should be carefully considered when analyzing and interpreting epidemiological data.

Age at onset in type 1 diabetes

Recently published research from the Swedish national diabetes registry (NDR) displays a novel finding about the importance from age at onset, where death and the risk of late CVD complications were multiple times higher among patients with onset of type 1 diabetes at a young age (0-15 years) and where the estimated life span was roughly a decade lower than for age- and sex matched controls[50]. Reasons for the elevated risks of late complications may be explained by the glycemic load which may be greater among individuals with an onset of diabetes at the age of 15 years or less[50]. These findings along with the proposed importance of risk factor control[43], may lead to the question if risk factor trajectories over a life-span could provide some answers to the proposed high excess risks of mortality and late complications demonstrated for patients with an early onset of type 1 diabetes.

AIMS

Study I

Based on the heterogeneous results from previous research the aim of the study was to investigate the relationship between BMI, mortality and CVD mortality among patients with type 2 diabetes, taking factors into account known to influence findings by reverse causality.

Study II

Based on the proposed obesity paradox that has been observed in patients with type 1 diabetes, where previous research exhibited increased mortality among patients with type 1 diabetes and low weight and among patients who experienced weight loss, we wanted to investigate associations between BMI, mortality and other CVD outcomes including HF by taking factors potentially associated with reverse causality into consideration.

Study III

With the supposedly different pathophysiological mechanisms behind atherosclerotic disease and HF, we aimed to investigate the excess risk of HF and AMI by the combined exposures of BMI and HbA1c among patients with type 2 diabetes.

Study IV

Since onset of type 1 diabetes at an early age has been associated with a shortened life span and higher risk of complications, we aimed to study trajectories of glycemic control and CVD risk factors by stratifying groups of age at onset.

PATIENTS AND METHODS

Study population

The study population comprised patients with type 1 diabetes and type 2 diabetes registered in NDR between 1998 and 2012. In *Study I* and *Study III* we aimed to describe the excess risk for our main exposures by using controls taken from the general population ("Total population register" [RTB]), matched by age, sex and county. In order to identify coexisting conditions and define the outcomes we used the Swedish in-patient registry, which has been validated to a positive predicted value of ~85-95% of major CVD outcomes[51] and the cause of death registry, while identification of socioeconomic factors was taken from the Longitudinal Database for Health Insurance and Labor Market (LISA)-registry. All registries were linked via the personal identification number (PIN), unique for every Swedish citizen, thus allowing for studying the large majority of the population with diabetes living in Sweden.

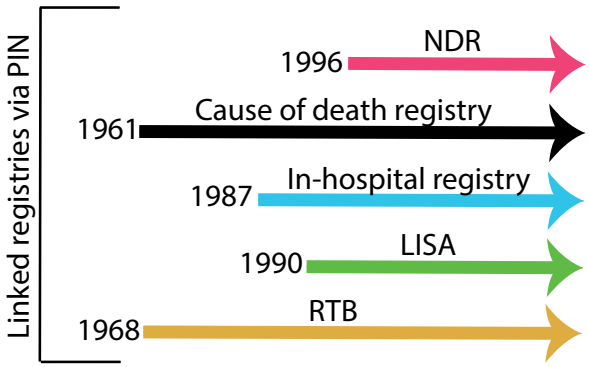

Figure 1. Linked registries via PIN.

The NDR has currently an approximate coverage of 95% of Swedish type 2 diabetes patients and roughly 90% of the type 1 diabetes population, where our studies include more than 100,000 patients with type 2 diabetes and more than 30,000 patients with type 1 diabetes. The ethics review board at the University of Gothenburg approved the study, with informed written or oral consent obtained from each patient in NDR. For *Study I-IV* all patients were intially registered between 1998-2012.

Study I initially comprised 457,473 patients with type 2 diabetes and 2,287,365 matched controls. We excluded 26,215 controls because of inconsistent follow-up data, probably caused by reused PIN. Other exclusions: 1) Patients with BMI <20 were excluded along with their matched controls (patients and controls after exclusion, n=452,999 and n=2,239,239, respectively), 2) Patients with >5 years of diabetes duration were excluded along with their matched controls, in order to avoid survival bias and to obtain a cohort relevant to modern treatment (patients and controls left

after exclusion, n=256,078 and n=1,268,540, respectively), 3) Patients and controls were excluded along with their matched set, if there was a history of cancer or dementia at baseline (patients and controls left after exclusion, n=172,090 and n=857,129, respectively), 4) For the sake of performing analyses based on short- and long term follow-up, patients with zero days of follow-up were excluded (patients and controls left after exclusion, n=172,087 and n=857,110, respectively), 5) Patient who had missing BMI were excluded along with their matched controls. After exclusions, the final cohort comprised 149,345 patients with type 2 diabetes and 743,907 controls.

Study II consisted of two separate cohorts, one for the start time at baseline and another cohort for the analyses of updated BMI with the new start time set to most recent measured BMI, measured 1-5 years from baseline. The initial cohort comprised 36,872 patients with type 1 diabetes, patients were then excluded if 1) not defined as type 1 diabetes (4,329 patients excluded), 2) due to previous cardiovascular conditions (AMI, stroke, CHD, AF or HF, renal dialysis/transplantation or amputation; 1,846 patients), 3) with BMI <18.5 kg/m^2 (483 patients excluded), 4) with missing BMI (4,089 patients excluded). After exclusions, the final baseline cohort comprised 26,125 patients for the final analyses. The follow-up cohort was based on the baseline cohort, where we additionally excluded patients if: 1) <2 visits or follow-up time <1 year (during the first five years of follow-up since baseline) (3,822 patients excluded), 2) patients who died within five years, or patients with a follow-up time of <5 years from baseline or events occurring, i.e AMI, stroke, AF, CHD or HF during this period (3,324 patients excluded). Thus, the final updated cohort for follow-up consisted of 18,979 patients.

The original cohort in *Study III* consisted of 457,473 patients and 2,287,365 controls. We excluded 1) Patients and controls if they had inconsistent survival data 2) Patients and controls with survival time zero 3) The complete matched set (1 patient along with 5 comparators) if a patient or control had a previous diagnosis of AMI, stroke, CHD or HF (patients and controls left after exclusions, n=216,183 and n=1,077,471, respectively), 4) if the patient had BMI <18.5 (patients and controls left after exclusions, n=215,590 and n=1,074,521, respectively) 5) Patients with missing BMI after imputation (patients and controls left after exclusions n=181,045, n=902,302 respectively)

The cohort in *Study IV* initially comprised 36,872 patients with type 1 diabetes. After exclusion of patients with: 1) Inconsistent follow-up data (3 patients excluded), 2) Other clinical definitions of diabetes than type 1 diabetes (4,286 patients excluded), 3) Age ≥76 years (163 patients excluded), 4) Previous registered amputation or CKD, defind as renal dialysis/transplantation or eGFR <15 mL/min/1.73 m^2 (415 patients excluded), the final cohort comprised 32,005 individuals with type 1 diabetes.

Definitions of type 1 diabetes and type 2 diabetes

For type 2 diabetes we used the epidemiological definition which comprised patients treated with diet only; oral antihyperglycemic treatment or ≥40 years of age in the case of insulin treatment with or without oral antihyperglycemic agents (*Study I* and *III*). For type 1 diabetes we used the epidemiological definition where patients had an

age at onset ≤30 years of age, treated with insulin only and further combined with a clinical definition where the caregiving physician had set the current diagnosis as type 1 diabetes (*Study II* and *IV*).

Variables from NDR

See Figure 2.

Data on risk factors were obtained and reported to the NDR by physicians and nurses.

Variable	Description
HbA1c	*Mono-s HPLC system, converted into International Federation of Clinical Chemistry units (mmol/mole)*
LDL cholesterol	*mmol/L*
Blood pressure	*mmHg*
BMI	*kg/m²*
eGFR	*Based on the Modification of Diet in Renal Disease study equation, where serum creatinine is measured in µmol/L*
Microalbuminuria	*2 out of 3 positive urine samples with an albumin/creatinine ratio of 3–30 mg/mmol/ ~U-albumin of 20–200 µg/min (~20–300 mg/L)*
Macroalbuminuria	*2 out of 3urine samples with an albumin/creatinine ratio of >30 mg/mmol/ ~U-albumin >200 µg/min (~>300 mg/L)*

Figure 2. Description of variables from NDR.

Outcomes

For *Study I-III* we used ICD-9 and ICD-10 where outcomes and preexisting conditions were defined as: CVD mortality (I00-I99 as underlying cause of death [*Study I*]); CVD mortality (I20-I25, I61, I63, I64, I67.9 [*Study II*]); major CVD (I21, I61, I62.9, I63, I64, I67.9 [*Study III*]); AMI (410, I21); stroke (431, 432X, 433, 434, 436, 437X, I61, I62.9, I63, I64, I67.9); HF (428, I50); atrial fibrillation (AMI), [427D, I48]); renal dialysis or transplantation (V42A, V45B, V56A, V56W, Z94.0, Z49, Z99.2); cancer (140-208, C00-C97); dementia (G30, F00-D03, F05); amputation (NHQ09, NHQ11, NHQ12, NHQ13, NHQ14, NHQ16, NHQ17, NHQ99, NGQ09, NGQ19, NGQ99, NFQ19, NFQ99).

Statistical analyses

All statistical analyses were performed with R (R Foundation for Statistical Programming).

Study I

Analyses of the outcomes

Crude incidence rates by BMI were calculated with confidence intervals (CI) 95% per 1,000 person years. Cox regression was used to analyze the risk of mortality and CVD mortality. Patients were stratified into five BMI categories: 20-<25, 25-<30,

30-<35, 35-<40, and ≥40 kg/m^2. We studied all-cause mortality and CVD mortality, short-term (outcomes that occurred within ≤5 years from baseline) as well as long-term (outcomes that occurred ≥5 years from baseline) overall and stratified by age: <65 and ≥65 years of age. In the short-term perspective data from patients and five age- and sex matched control subjects from the general population was used, while for the long-term perspective, data from patients and controls who survived the initial time-period was used. In the case of censoring or death, no reassigning of controls were done, thus censoring each patient and control subject individually. Each analysis was done separately per BMI group in order to fit the Cox regression model.

We adjusted the analysis for age by stratifying age into the overall HR, i.e quintiles of (18-50], (50-57], (57-63], (63-69] and (69- 101) years and by stratifying years of inclusion into the overall HR, i.e five equal-sized quintiles of (1998-2004], (2004-2007], (2007-2009], (2009-2010] and (2010-2012).

Additionally, the models were adjusted for sex, income, education, immigrant status, marital status, CHD, AMI, AF, renal dialysis/transplantation, HF and for the interaction between diabetes duration by age. If variables did not fulfill the assumption of proportional hazard varibles, likewise to age and years of inclusion, were stratified into the overall HR.

In order to stratify the continuous variable of income, income was divided into equally sized quartiles. Analyses which did not fulfill the long-term assumption of proportional hazards were tested with censoring at 12 years, if no substantial difference was observed we considered the model acceptable.

All tests were two-tailed and a value of 0.05 was considered statistically significant. The assumption of proportional hazards was fulfilled after stratifications.

Study II

BMI trajectories by year

Mixed linear regression was used to calculate the trajectories in BMI by calendar year from 1998-2012. We used 275,111 visits with registered BMI among 32,543 patients. Calendar year was set as fixed effect and adjusted for age, sex and diabetes duration with random effects set as random participant effect and as trend among subjects. To calculate mean BMI per calendar year, least square means were used with 95% CI.

Analyses of the outcomes

Crude incidence rates were calculated with CI 95% per 1,000 person years by BMI. Analyses regarding the outcomes of mortality, CVD mortality, major CVD event and HF were calculated using Cox regression adjusted for age, sex, duration of diabetes, marital status, immigrant status, income, education, smoking status and HbA1c, where BMI 25 kg/m^2 was set as reference. BMI was modelled using restricted cubic splines with three equally tied knots. We further analyzed the outcome of mortality reducing factors known to cause reverse causation, i.e we stepwise excluded 1) smokers,

2) smokers and patients with HbA1c ≥60 mmol/mole and lastly 3) smokers, patients with HbA1c ≥60 mmol/mole and patients with 2002 as the latest year of registration.

In a second cohort (see definition of the follow-up cohort in study population [*Study II*]) we used Cox regression to analyze how a change in BMI could influence the selected outcomes. BMI change was calculated by the absolute change in BMI between 1-5 years (last measured BMI minus baseline BMI), divided by days between measurements, then multiplied with 365.25 to receive the estimated yearly change in BMI. The new baseline was set to last registered BMI within the first five years from the day of inclusion in NDR. To analyze mortality, CVD mortality, major CVD event and HF, groups of <0; 0-<0.25 (reference); 0.25-<0.75; ≥0.75 kg/m^2 per year was used in Cox regression with cubic splines tied to three equally sized knots.

We assessed the Cox proportional hazard using Schoenfeld's residuals. The proportional hazard assumption was considered to be fulfilled.

Study III

Analyses of the outcomes

Age adjusted incidence rates for HF and AMI were calculated with 95% CI per 1,000 person years. Outcomes were analyzed by Cox regression models using five BMI groups of; 18.5-<25, 25-<30, 30-<35, 35-<40, and ≥40 kg/m^2. For each BMI category three HbA1c groups were used; <53, 53-70 and ≥71 mmol/mole. Age- and sex matched control subjects were used as reference for each HbA1c group, which were examined separately, thus generating three models by HbA1c with the main exposure of five BMI groups. The Cox regression models were adjusted for age, sex, diabetes duration, education, income, immigrant status, marital status, atrial fibrillation and renal dialysis/transplantation. The adjustment for diabetes was centered around the grand mean, thus representing the excess risk of AMI and HF with a 4.3 years duration of diabetes. We checked the analyses by using HF as the principal diagnosis only with similar results as the main findings.

AMI and HF were further analyzed with Cox regression, without using control subjects with the purpose of determining the association between the outcomes and BMI and HbA1c respectively. Models were adjusted for age, sex, socioeconomic factors, LDL-cholesterol, SBP and smoking status. BMI and continuous risk factors were modelled using cubic splines tied into equally tied knots. Since 8,622 patients with type 2 diabetes were diagnosed with AMI prior or the same day to the diagnosis of HF, we checked the association between BMI and HF by a time-updated Cox regression including adjustment for BMI, AMI during follow-up and the interaction term BMI by AMI during follow-up. Where AMI and HF occurred at the same day, one day was added to the follow-up time of HF.

The proportional hazards assumption was checked with Schoenfeldt´s residuals and there were no significant deviations from the assumption. The analyses were two-tailed where a value of 0.05 was considered statistically significant.

Study IV

Analyses of risk factors

In *Study IV* risk factor trajectories were analyzed by mixed linear regression and generalized linear models. Age at onset was stratified into groups consisting of: ≤10, 11-15, 16-20, 21-25 and 26-30 years at onset where the main exposure was age (18-75 years). Continuous outcomes (HbA1c, eGFR, LDL cholesterol, BMI, SBP and diastolic blood pressure [DBP]) were analyzed by mixed linear regression adjusted for sex with fixed effects of age, age at onset, the interaction term age by age at onset and a random participant effect. Analyses with the outcomes of BMI, LDL cholesterol, SBP and DBP were additionally adjusted for smoking status, statins and antihypertensives respectively. The outcomes of albuminuria (micro- or macro albuminuria) was modelled as a dichotomous variable analyzed by generalized linear models adjusted for sex with fixed effects of age groups defined as 18–25 years, and then by 4-year intervals up to 75 years of age, age at onset, the interaction term age group by age at onset and a random participant effect. All analyses were analyzed by least square means in order to generate mean values for each specific age, while albuminuria was back transformed into probability from the logit scale. Sex specific analyses were performed separately on HbA1c, eGFR (albuminuria present), LDL cholesterol, BMI and SBP.

Baseline imputation

Machine learning algorithms were used to examine the relationship between baseline HbA1c (≥1 year duration of diabetes) and various risk factors for CVD, socioeconomic status and previous CVD and HF. In order to obtain complete data, baseline variables were imputed with Multiple Imputation by Chained Equations (MICE), where missing data are imputed via mean values followed by linear and logistic regression. Imputed baseline data was solely used for machine learning models.

Machine learning

With a complete data set analyses were performed stratified on age at onset: 0-15 and 16-30 years of age and by sex. Two different algorithms were used, conditional random forest and gradient boosting machines. The output displayed the models feature importance (ranking of predictors) and were also compared to ordinal Linear regression models. In most cases both of the machine learning algorithms were superior to linear regression, which may reflect the potential of these algorithms with respect to the handling of interactions and non-parametrical approaches.

RESULTS

Study I

The study population comprised 149,345 patients with type 2 diabetes and 743,907 control subjects, where the median follow-up time was 5.5 years (mean age 59.5 years). Incidence rates are shown by the five stratified BMI categories: 20 to <25, 25 to <30, 30 to <35, 35 to <40 and ³40 kg/m^2. U-shaped curves were found short-term, with fairly low excess risk estimates compared to the general population (Figures 3 and 4). However, long-term analyses exhibited an increase in excess risks with J-shaped associations among patients with type 2 diabetes in the overall cohort as well as in the age stratified analyses (17,546 deaths and 7,218 cases of CVD mortality). HR ranged from HR 1.09 (CI 95% 1.14-1.36) among patients with BMI 25-<30 kg/m^2 (nadir of the analysis; or the lowest risk) up to HR 2.00 (CI 95% 1.58-2.54) among patients with BMI ≥40 kg/m^2, while patients with BMI 20-<25 displayed slightly higher risk of mortality than those of the nadir, with HR 1.55 (CI 95% 1.23-1.95) (Figure 3).

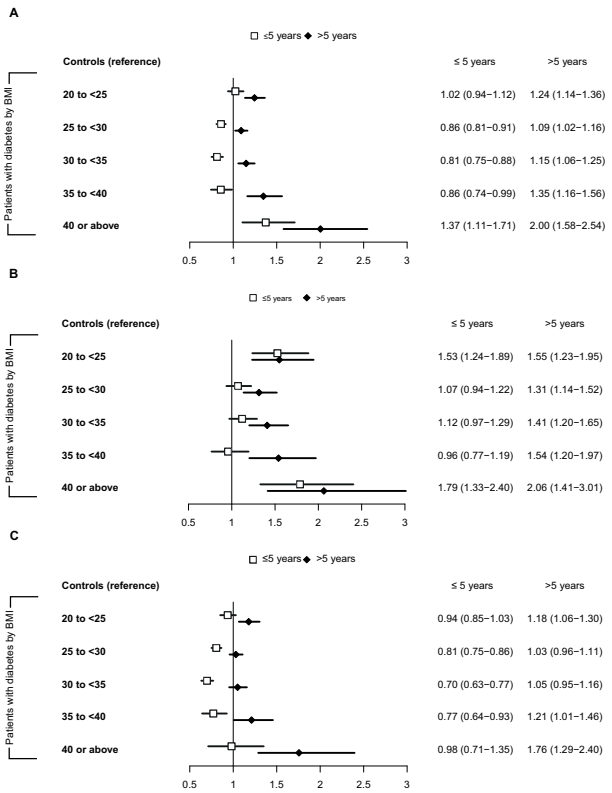

Figure 3. Adjusted HR for all-cause mortality according to BMI among patients with type 2 diabetes using age- and sex matched controls as reference*.

Panel A, CVD mortality (overall), panel B, CVD mortality (<65 years), panel C, CVD mortality (≥65 years). *American Diabetes Association [BMI and Mortality in Patients With New-Onset Type 2 Diabetes: A Comparison With Age- and Sex-Matched Control Subjects From the General Population, American Diabetes Association, [2018]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

Corresponding figures for the outcome of CVD mortality showed long-term HR of 0.99 (CI 95% 0.90-1.09) among patients with BMI 25-<30 (nadir) and 2.00 (CI 95% 1.37-2.91) in the most obese patients, while the group with normal weight (BMI 20-<25) had an HR of 1.09 (CI 95% 0.95-1.26). We noted that the leanest participants did not differ significantly from matched controls (Figure 4). Age-stratified analyses displayed similar associations, however with slight lower HR among patients <65 years of age and slightly lower HR among the elderly compared to the overall cohort (Figures 3 and 4).

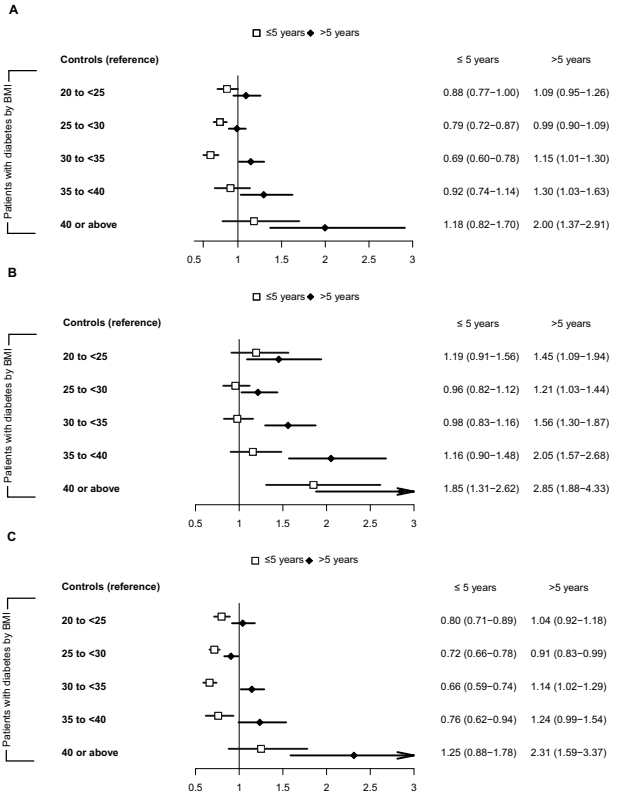

Figure 4. Adjusted HR for CVD mortality according to BMI among patients with type 2 diabetes using age- and sex matched controls as reference*

Panel A, CVD mortality (overall); panel B, CVD mortality (<65 years); panel C, CVD mortality (≥65 years). *American Diabetes Association [BMI and Mortality in Patients With New-Onset Type 2 Diabetes: A Comparison With Age- and Sex-Matched Control Subjects From the General Population, American Diabetes Association, [2018]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

Study II

Figure 5 shows an increasing trend in mean BMI ranging from 24.7 kg/m^2 in 1998 to BMI 25.7 kg/m^2 in 2012 among patients with type 1 diabetes. A fully adjusted Cox regression (Figure 6) showed a small but significant positive association with BMI for the outcomes of mortality, major CVD and HF, while the curve by BMI for CVD mortality was likewise positive but with no significant difference compared with the reference of 25 kg/m^2. BMI <25 kg/m^2 displayed no increased risk for neither CVD mortality, major CVD or HF. After excluding patients who were smokers at baseline, those with HbA1c >60 mmol/mole and those with a follow-up time <10 years, we did not identify any increased risk among patients with BMI less than the reference of 25 kg/m^2 for the outcome of mortality either. Among the 18,979 patients that were analyzed by updated BMI change (1-5 year from baseline) (Figure 6), we identified increased risks for the outcome of mortality and HF among patients with a BMI change of ≥0.75 kg/m^2/year. We noted no statistically significant increased risk for any of the outcomes among patients who experienced weight change <0 kg/m^2/year compared to the reference level of 0-<0.25 kg/m^2.

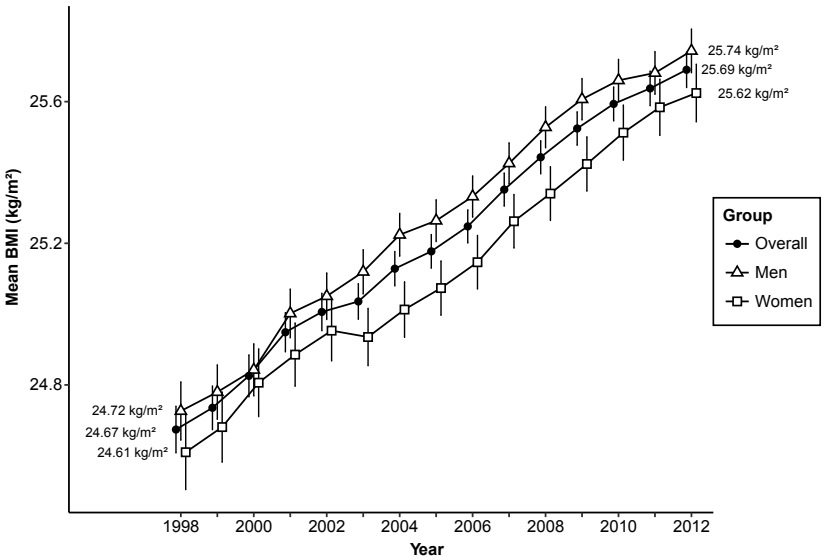

Figure 5. Trends in BMI between the years 1998-2012 among patients with type 1 diabetes overall and stratified by sex*

*American Diabetes Association [BMI, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes: Findings Against an Obesity Paradox, [2019]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

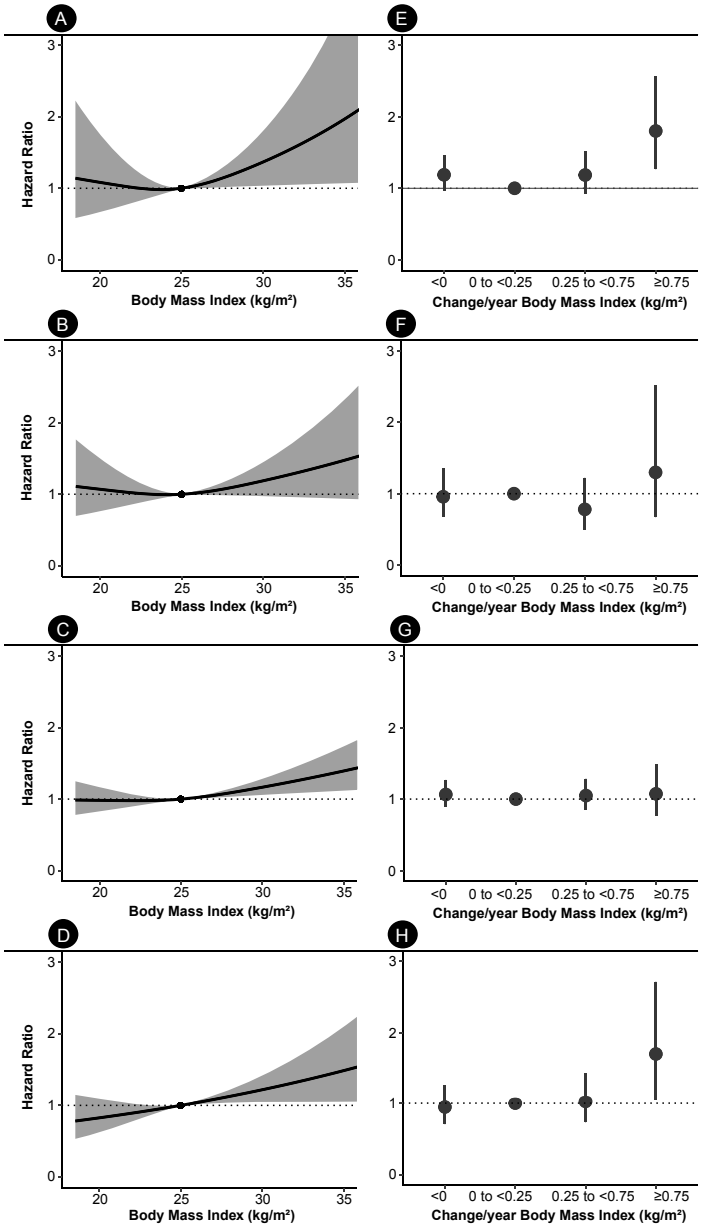

Figure 6. Adjusted HR for mortality, CVD mortality, major CVD and HF according to BMI at baseline and the estimated yearly BMI change among patients with type 1 diabetes*

Panels A (HR by baseline BMI) & E (HR by estimated yearly change in BMI), All-cause mortality; panels B (HR by baseline BMI) & F (HR by estimated yearly change in BMI), CVD mortality; panels C & G (HR by estimated yearly change in BMI), major CVD; panels D (HR by baseline BMI) & H (HR by estimated yearly change in BMI), HF. *American Diabetes Association [BMI, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes: Findings Against an Obesity Paradox, [2019]. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

Study III

Among 185,045 patients with type 2 diabetes and 902,302 age- and sex matched control subjects, there were 33,060 cases of AMI and 28,855 cases of HF (out of which 12,821 patients had HF as the principal discharge diagnosis) within a median follow-up time of 5.7 years. The most essential findings were, firstly, the flat relationship (incidence rates and HRs in Figures 7 and 8) observed between BMI and AMI where increased risks were mediated by poor glycemic control rather than BMI, whereas, secondly, we observed a strong, near linear increase in both incidence rates and adjusted HRs for HF by increasing BMI which worsened along with poor glycemic control. For patients with type 2 diabetes and BMI ≥40 kg/m^2 and HbA1c ≥71 mmol/mole, the risk of heart failure was near 8-fold compared to that of age- and sex matched control subjects (Figure 8). There were similar trajectories regarding the risk of HF among the very obese patients in the analyses containing patients only and with additional adjustments for smoking status compared with reference level of 25 kg/m^2 and a flat curve by BMI and the risk of AMI (Figure 9).

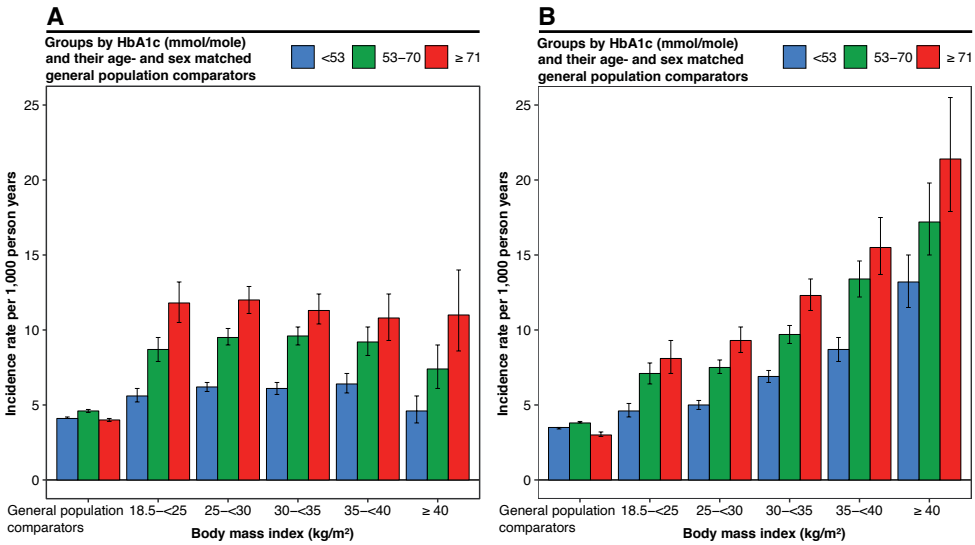

Figure 7. Age adjusted incidence rates per 1,000 person years for the outcomes of AMI and HF according to BMI and HbA1c among patients with type 2 diabetes and their age- and sex matched controls*

Panel A, AMI; panel B, HF. *Edqvist J, Rawshani A, Adiels M, Björck L, Lind M, Svensson AM, et al. Contrasting Associations of Body Mass Index and Hemoglobin A1c on the Excess Risk of Acute Myocardial Infarction and Heart Failure in Type 2 Diabetes Mellitus. J Am Heart Assoc. 2019;8(24). Open access.

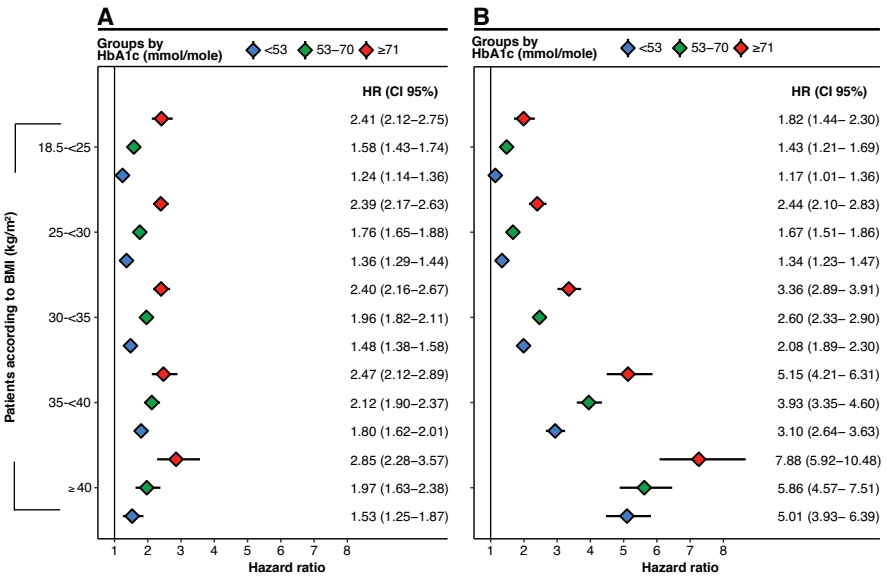

Figure 8. Adjusted HR for AMI and HF according to BMI and HbA1c among patients with type 2 diabetes compared to age- and sex matched controls*

Panel A, AMI; panel B, HF. *Edqvist J, Rawshani A, Adiels M, Björck L, Lind M, Svensson AM, et al. Contrasting Associations of Body Mass Index and Hemoglobin A1c on the Excess Risk of Acute Myocardial Infarction and Heart Failure in Type 2 Diabetes Mellitus. J Am Heart Assoc. 2019;8(24). Open access.

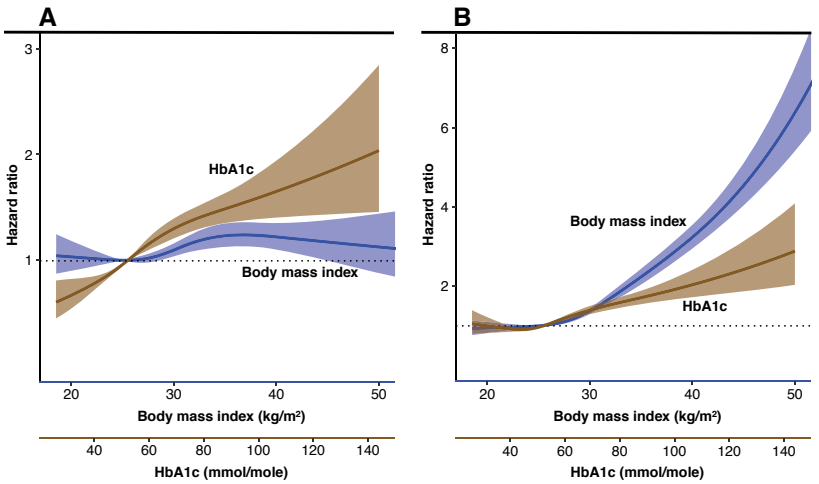

Figure 9. Adjusted HR for AMI and HF according to BMI and HbA1c respectively among patients with type 2 diabetes only, reference level was set to 25 kg/m^2

Panel A, AMI; panel B, HF. *Edqvist J, Rawshani A, Adiels M, Björck L, Lind M, Svensson AM, et al. Contrasting Associations of Body Mass Index and Hemoglobin A1c on the Excess Risk of Acute Myocardial Infarction and Heart Failure in Type 2 Diabetes Mellitus. J Am Heart Assoc. 2019;8(24). Open access.

Study IV

Analyses among 30,005 patients with type 1 diabetes showed trajectories of increased HbA1c levels (~70 mmol/mole) applicable to patients with an age at onset ≤15 years, and aged 18-30 years, HbA1c then declined to ~65 mmol/mole by age in the early 30s. For patients with an onset of type 1 diabetes ≥16 years or older, HbA1c in contrast increased annually from the age of onset beginning approximately at 55 mmol/mole which levelled off at and converged towards a level similar to the patients with an earlier age at onset at ~65 mmol/mole. Thus, patients regardless of the age of onset displayed similar mean HbA1c from approximately the age of 40 with some uncertainty during the last ten years of the observed age span. Patients with an age at onset ≤15 years displayed earlier probability of albuminuria than observed among patients with an onset of type 1 diabetes in adolescence/adulthood. Regarding other risk factors such as LDL cholesterol, blood pressure and BMI, differences between groups by age at onset were small.

Machine learning output showed that regardless of age at onset and sex several risk factors were associated with higher levels of HbA1c such as for instance CVD risk factors in terms of increased blood pressure and lipids, BMI, smoking at baseline, absolute age and kidney function. All machine learning models were similar or superior to analyses performed with linear regression.

DISCUSSION

BMI, mortality and reverse causality in patients type 2 diabetes

Some studies have suggested the possibility of an obesity paradox among patients with type 2 diabetes[31], with a higher BMI seemingly protective against outcomes, or with large spans of minimal mortality risk ranging between overweight to mildly obese[52]. Our analyses showed J- or U-shaped associations with varying nadirs, as high as BMI 35-<40 kg/m^2, with respect to mortality and CVD mortality in the short-term perspective (≤5 years from baseline), whereas long-term follow-up showed that the lowest risk was found in the overweight category, indicating that follow-up time may play a role in in reverse causality by the exclusion of early deaths[48], and that a short follow-up times could potentially contribute to findings consistent with an obesity paradox.

The excess risk of long-term mortality by BMI as well as for CVD mortality was more straightforward, displaying a stepwise increase in excess risks among obese patients with BMI ≥30 kg/m^2 up to a 2-fold risk among patients with BMI ≥40 kg/m^2 for outcomes. Although patients with coexisting conditions such as those with past severe CVD events, cancer and dementia were excluded, we found trends towards increased excess risks among patients with type 2 diabetes and BMI 20-<25. The previously identified increased risks of death among patients with BMI <25 kg/m^2[32] were likewise observed in *Study I*. It cannot, however, be entirely ruled out that our results were influenced by reverse causality since patients within the normal weight range were, for instance, more frequently treated with insulin than patients with higher BMI, therefore suggesting the possibility that this group might contain individuals with LADA or other subgroups of diabetes[53].

Further arguments for reverse causality with respect to mortality may be previous data which have shown a near linear association between BMI and mortality[35], while in the present study we observed attenuated estimates for CVD mortality where patients with 20-<25 did not display any significant increased risk of CVD mortality compared to their matched controls. The very low or non-existent general excess risks of mortality and CVD mortality found in the short-term analyses, may be explained by the short duration of diabetes, where patients newly diagnosed receive regular follow-up by health care institutions, where CVD risk factors are regularly monitored, while the identification and management for e.g. hypertension among controls may not be optimal[54].

BMI, weight change, mortality and CVD outcomes including HF in patients with type 1 diabetes

Type 1 diabetes with intensive insulin therapy is associated with weight gain, however, the weight trends were similar among patients type 1 diabetes in *Study II* to those observed in the Swedish general population[19], with a relatively normal weight pattern. The risks of overweight/obesity on mortality and CVD outcomes including HF, were fairly low, although significant for death, CVD death and HF. Further on,

excessive weight gain seems to predict mortality and HF alike, confirming previous research of increased risks of death[45], Even though weight gain has been observed in Diabetes Clinical Control and Complications Trial (DCCT)[46, 55], in this present study no improved glycemic control was observed among the obese patients, indicating the influence of adverse life style factors could be involved in the acquired weight at baseline. To improve glycemic control among obese patients with type 1 diabetes there is the possibility of benefits of modern medications such as SGLT-2 inhibitors[56], GLP-1 receptor[57] agonists or even bariatric surgery, where recent data has identified benefits such as reduced risk of CVD and improved glycemic control[58], even though the effect from bariatric surgery on blood glucose in type 1 diabetes, has been uncertain in some of the previous research[59]. Hence, with the relatively small differences with respect to BMI and weight change, *Study II* implicates the importance of life style factors in order to avoid obesity but where the concern with respect to weight gain should not hinder efforts towards an effective treatment of blood glucose.

As opposed to *Study I*, *Study II* exhibited no increased risks of death among patients with normal weight at baseline after taking HbA1c, smoking and follow-up time into consideration. Previous research suggested increased risks of mortality in patients with BMI <25 kg/m^2[60] and an acquired BMI <20 kg/m^2. Thus, *Study II* supports recommendations of a healthy life style in patients with type 1 diabetes, including maintaining a healthy weight.

Type 2 diabetes, BMI and associations to HF vs atherosclerotic disease

In diabetes type 2, the association between hyperglycemia and atherosclerotic events are well established, but the link between obesity and coronary heart disease not as extensively investigated. The present study found that, independently of glycemic level, the association between BMI and AMI was almost flat, confirming theories about two different mechanisms between the outcome of atherosclerotic events and incident HF[37]. Patients with obesity exhibited an increased risk of HF as previously reported[36]. The novelty of the findings was the excess risk of several times greater than for the general population, which was worsened by poor glycemic control.

There may be several pathways to explain the association between obesity and HF. Recent data suggests that increased BMI is associated with increased left ventricular mass index as well as increased blood pressure[61], suggesting cardiac remodeling from a young age independent of glycemic levels, with concurrent high risks of HF in obese adolescent men[62]. Obesity is also thought to increase the intravascular volume via sodium retention where the cardiac output increases in order to maintain a larger volume of tissue[37]. In addition, obesity in youth was found to increase risk of CKD, with a proposed link to glomerular hypertension[63]. Our study demonstrates that with coexisting obesity and hyperglycemia[37], risks of HF may increase even further. Clinically, *Study III* underlines the importance of the prevention of HF, perhaps with modern medication such as SGLT-2 inhibitors where risks have been seen to decrease by roughly 30%[64] or with bariatric surgery which has been observed to be an effective intervention for reducing obesity related complications[65], for reducing the risk of HF in obese individuals[66-68], for improving glycemic control and weight in patients with diabetes[69].

Health management in guidelines

The American diabetes association focuses on the importance of health management in both type 1 diabetes and type 2 diabetes particularly with respect to nutritional management and the avoidance of smoking and overweight/obesity in order to improve glycemic levels, blood pressure and lipids, where *Studies I-III* concordantly support these recommendations[70].

Type 1 diabetes and risk factor trajectories by age at onset

High mean values of HbA1c in adolescence/ early adulthood have been identified among persons with type 1 diabetes[71], in *Study IV*, patients with an onset of type 1 diabetes ≤15 years of age displayed similar high means as in the U.S cohort, approximately 70 mmol/mole. However, patients with an age at onset ≥16 years of age exhibited a gradual increase in HbA1c, while, in contrast, among patients with an age at onset <16 years of age, HbA1c declined towards similar mean values i.e, ~65 mmol/mole from early middle age. The high levels of plasma glucose together with earlier onset of albuminuria could potentially contribute to increased excess risks of late complications found in previous research in patients with age at onset ≤15 years[50]. The use of CGM has increased in recent years with an estimated 60% use in 2017, based on data from the NDR, while this study ended in 2012. Still, the data we present are relevant for many middle-aged and older patients, and also for patients in many settings where access to CGM may not be affordable.

Even though we found trajectories for other risk factors such as LDL cholesterol, SBP, DBP, eGFR and BMI to be largely independent of age at onset, earlier treatment of lipids and blood pressure could potentially be discussed since the accumulation of risk factors is an established risk for late complications[43].

Strengths and limitations

The general strength in Swedish epidemiological research lies in the near nationwide coverage of patient cohorts. In this present thesis we had access to large samples of Swedish patients with diabetes where the NDR covers roughly ~90% of the Swedish population with type 2 diabetes and virtually all patients with type 1 diabetes. In studies containing matched controls we were able to obtain 5 age- and sex matched controls per patient with diabetes thus generating nearly 1 million controls in *Study I* and *Study III*. Linking the NDR to the Swedish in-patient registry we received information regarding coexisting conditions and outcomes.

A limitation of the studies on excess risk by BMI compared to the general population was the lack of weight data in controls, although excess risk by BMI should be interpreted as the excess risk compared to mean BMI in the population, approximately ~26 kg/m^2 in adults (22). Whether diabetes would cancel out the risk conferred by obesity in terms of late complications has to be investigated by other means. We also had limited information on smoking status earlier in life as well as limited information about HF diagnoses, where residual confounding and reversed causality may occur, even though these studies have considered several important factors.

CONCLUSION

For the outcomes of mortality and CVD mortality (*Study I*) our study suggested that factors such as coexisting diseases, smoking and follow-up time may influence the relation between BMI and outcomes. Long-term (≥5 years from baseline) analyses showed an increasing risk of death and death from CVD causes from BMI ≥30 kg/m^2. In *Study III*, results suggested different mechanisms of pathophysiology between the outcome of HF and the outcome of AMI. The association between obesity and HF was far greater than for that between obesity and incident AMI, which was seemingly unrelated to BMI. Obesity was however, associated with a multiple-fold risk for HF among the severely obese patients (BMI ≥40 kg/m^2) compared to age- and sex matched controls, further aggravated among patients with poor glycemic control. Tentatively, medications targeted towards HF could be considered for patients with type 2 diabetes and severe obesity, although this concept would warrant rigorous testing, including randomized controlled trials. Hence, *Study I* and *Study III* highlight the importance of weight management as an important aspect of diabetes care in order to reduce mortality and to reduce the incidence of HF.

In *Study II* we found that among patients with type 1 diabetes free from prior CVD, increasing BMI conferred a modestly elevated risk of mortality, CVD mortality, major CVD and HF. For CVD mortality, major CVD and HF we found no suggestion of an obesity paradox suggesting increased risk for patients with BMI ≤25 kg/m^2, nor did we find any increased risk of death when factors such as glycemic control, smoking and short follow-up time were taken into consideration. In contrast to previous conducted research we did not find any evidence of increased risk of mortality or any other of the outcomes in the occurrence of weight loss. Thus, our study supports the pursuit of life style changes to avoid obesity, but the slightly increased risk of late complications among overweight/obese patients should not deter patients and clinicians from striving for good glycemic control or intensive insulin therapy.

In *Study IV* we found that patients with an onset of type 1 diabetes at ≤15 years old had increased HbA1c levels in early adulthood, suggesting an increased glycemic load over a life time concurrent with an increased probability of albuminuria, with the largest differences in mean HbA1c during the first decade of adulthood compared to patients with an onset of type 1 diabetes ≥16 years. Our study suggests attention to the glycemic control in adolescence and early adulthood among patients with an early onset and to slow the gradual increase in HbA1c among patients with an onset in adolescence or adulthood. High baseline HbA1c coexisted with poor control of other CVD risk factors and low education, in support of multifaceted care among patients with type 1 diabetes in order to prevent late complications and to increase survival.

FUTURE PERSPECTIVES

The ongoing increasing rates of obesity worldwide exhibit future challenges for the medical care, where increasing rates of diabetes are to be expected. The research presented in this thesis may highlight the possibility that obesity among patients with type 1 diabetes and type 2 diabetes may further increase the risk of late complications. The largest risk among obese patients with type 2 diabetes may be the substantial increased risk of HF, both within the diabetic group and in relation to the general population. The data presented in this thesis warrants further research, with focus on primary prevention, modern technology and medications that could lessen the risk of HF among patients with an onset of type 2 diabetes. Patients with type 2 diabetes and BMI <25 should be further investigated to why this particular group display increased risks of mortality, whether this may be mediated by frailty, premature aging, vulnerability of particular subgroups of patients with type 2 diabetes or other reasons.

Regarding obesity among patients with type 1 diabetes, however, in the light of previous research and *Study IV* presented in this thesis, there may be more prominent risk factors such as HbA1c and kidney function for clinicians to focus on, even though maintaining a healthy weight could confer other benefits such as better quality of life. Concurrently *Study II* also displayed that a healthy weight is probably not associated with any increased risks for either mortality or CVD complications including HF among patients with type 1 diabetes, although more research is needed on the relationship between intensive insulin therapy and weight gain and potential long-term complications.

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