Obesity in diabetes
Cardiovascular outcomes and risk factor trajectories

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Sahlgrenska universitetssjukhuset/lokal Arvid Carlsson, Medicinaregatan 3, Göteborg den 15 april 2021 kl 09.00, deltagande via länk.

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Avhandlingen baseras på följande delarbeten

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.
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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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