ORIGINAL RESEARCH

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

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***Background*—**Body mass index (BMI) may be a stronger risk factor for heart failure than for coronary heart disease in type 2 diabetes mellitus, but prior studies have not been powered to investigate the relative and absolute risks for acute myocardial infarction and heart failure in type 2 diabetes mellitus by BMI and glycemic level combined as compared with age- and sex-matched general population comparators.

***Methods and Results*—**We identified 181 045 patients from The Swedish National Diabetes Registry, registered during 1998 to 2012 and 1538 434 general population comparators without diabetes mellitus, matched for age, sex, and county, all without prior major cardiovascular disease. Cases and comparators were followed with respect to the outcomes through linkage to the Swedish Inpatient Registry. Over a median follow-up time of 5.7 years, there were 28 855 acute myocardial infarction and 33 060 heart failure cases among patients and comparators. Excess risk (above that of comparators in whom no data on hemoglobin A1c and BMI was available), incidence rates and hazard ratios for heart failure were substantially higher among the obese patients compared with those with low BMI, where very obese patients (BMI $\geq$40 kg/m^2) who also had poor glycemic control, suffered a 7-fold risk of heart failure versus comparators (reference level). By contrast, for acute myocardial infarction, the highest absolute and relative risks were found among patients with poor glycemic control, with no additional risk conferred by increasing BMI.

***Conclusions*—**BMI is a strong independent risk factor for heart failure but not for acute myocardial infarction among patients with type 2 diabetes mellitus. **(*J Am Heart Assoc*. 2019;8:e013871. DOI: 10.1161/JAHA.119.013871.)**

Key Words: body mass index • glucose • heart failure • myocardial infarction • type 2 diabetes mellitus

People with type 2 diabetes mellitus are at increased risk of cardiovascular disease, heart failure and death, as compared with the general population. Studies show that the excess risks associated with diabetes mellitus are mediated primarily by hyperglycemia[1,2] and overall poor risk factor control.[3] Effective treatment of traditional cardiovascular risk factors has reduced the excess risk of atherosclerotic cardiovascular disease (CVD), such as acute myocardial infarction (AMI) and stroke in people with type 2 diabetes mellitus.[4] However, the incidence of heart failure has not declined to the same extent as that of CVD,[4] and recent studies suggest that heart failure may be more common than previously believed,[5,6] and at least as common as AMI as an initial "vascular" complication of type 2 diabetes mellitus. This highlights the importance of thinking beyond atherosclerotic CVD to include heart failure as a diabetes mellitus complication.

Heart failure is thought to have other underlying mechanisms in part propelled by obesity, which leads to an increased volume load and consequently a glomerular and hemodynamic stress which is believed to increase the risk of heart failure.[7] Studies also suggest that both obesity and hyperglycemia may independently be causal in the development of heart failure in people with type 2 diabetes

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Accompanying Tables S1 through S5 and Figures S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013871

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Clinical Perspective

What Is New?

- In patients with type 2 diabetes mellitus poor glycemic control was associated with future risk of both myocardial infarction and heart failure.
- By contrast, overweight and obesity was at most only weakly associated with myocardial infarction whereas there was a strong and direct association between increasing body mass index and heart failure.
- Patients with type 2 diabetes mellitus who were severely obese, with body mass index ≥40 kg/m^2, demonstrated a 5-fold risk for heart failure, compared with normal weight, even if they were well controlled, but a nearly 8-fold increased risk among those with poor glycemic control.

What Are the Clinical Implications?

- These findings indicate that the pathophysiological links between obesity and acute myocardial infarction and those between obesity and heart failure may differ markedly.
- Additionally, the strong relationship between elevated body weight and heart failure supports the goal of maintaining a healthy weight in type 2 diabetes mellitus.

mellitus.[2,8,9] Both these risk factors are also often invoked as important in the risk of coronary heart disease (CHD), CVD, and mortality, although the relevant weightings of such risks are rarely considered. We therefore studied the excess risk of AMI, and heart failure in relation to body mass index (BMI) and hemoglobin A1c (HbA1c) among individuals with type 2 diabetes mellitus compared with population comparators from the Swedish general population matched by age and sex. Our hypothesis was that while metabolic control is probably important as a predictor for both conditions, higher BMI may be more strongly associated with incident heart failure hospitalization but much less a strong predictor of AMI.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the NDR (Swedish National Diabetes Registry).[10]

The NDR includes ≈90% of all patients aged ≥18 years diagnosed with type 2 diabetes mellitus in Sweden. Healthcare providers report continuously directly to the NDR or via electronic patient records from routine clinical practice.[11,12] For the purpose of this report, we identified all patients with type 2 diabetes mellitus using previously validated criteria: (1) patients aged ≥40 years at the time of diagnosis and treated with insulin only; (2) regardless of age, patients treated with diet only or oral hypoglycemic agents combined with diet; (3) regardless of age, patients treated with insulin combined with oral hypoglycemic agents.[1,11] For each patient selected for this study, 5 population comparators without diabetes mellitus, matched by age, sex, and county, were randomly selected from the Swedish Total Population registry. Each patient in NDR has given informed consent and the study is approved by the ethics review board at the University of Gothenburg.

Baseline and Outcome Data in Patients and Population Comparators

Patients and comparators were registered from January 1, 1998, until December 31, 2012 and followed until December 31, 2013, the event of interest or death. Patients and comparators were linked to the Swedish Inpatient and Cause of Death Registers through their personal identification number[13,14] to obtain information about coexisting conditions such as stroke, AMI, CHD, hospitalization for heart failure, atrial fibrillation (AF), renal dialysis/transplantation (chronic kidney disease), cancer and dementia. Codes from the *International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10)*, were used from 1987 and onwards (Table S1).

For the outcomes of AMI and heart failure (Table S1), we similarly used the Swedish Inpatient and Cause of Death Registers, where AMI was defined as the principal or contributory diagnosis at the first identified case of either hospitalization or death in AMI (I21). The outcome of heart failure was defined as either the principal or contributory diagnosis at the first identified case of a hospitalization for heart failure (I50). The Longitudinal Database for Health Insurance and Labor Market studies provided information about socioeconomic variables, marital status (divided into single, married, divorced, and widowed), education level (divided into compulsory education or lower, intermediate, ie, upper secondary, and high, ie, university) and country of birth (Swedish/other).

Patient Data

BMI was calculated from data on height and weight measured by the reporting unit (primary care units or hospital outpatient diabetes mellitus clinics) as weight (kg)/height (meters).[2] HbA1c was initially measured as percent (mono-s) and converted into mmol/mole per mole (IFCC [International Federation of Clinical Chemistry]) (10). Microalbuminuria was defined as 2 positive tests from 3 samples taken within 1 year, with an albumin/creatinine ratio of 3–30 mg/mmol (≈30–300 mg/g) or U-albumin of 20 to 200 µg/min (20–300 mg/L), and macroalbuminuria as albumin/creatinine

ratio >30 mg/mmol (≈ >300 mg/g) or U-albumin >200 μg/min (>300 mg/L). BMI was measured as kg/m^2 and imputed by using first observation carried backward if missing. We only imputed BMI if values were available within 365 days and provided that no intervening major cardiovascular event occurred (stroke, AMI, CHD, AF, or chronic kidney disease). Before imputation, 112 848 (24.7%) patients had missing BMI, which decreased to 81 721 (17.9%) after imputation.

Selection of Study Group

See flowchart in Figure S1. The original cohort consisted of 457 473 patients and 2 287 365 comparators from the general population. Patients and comparators were excluded if they had inconsistent survival data, which are usually explained by reuse of the unique Swedish personal identification number. We additionally excluded patients and comparators with survival time of 0; after these exclusions 457 453 individuals with type 2 diabetes mellitus and 2 260 994 matched-population comparators remained. We excluded the complete matched set (1 patient along with 5 comparators) if any of the following conditions were fulfilled: a patient or control had a previous diagnosis of AMI, stroke, CHD, or heart failure (patients and comparators left after exclusion, n=216 183 and n=1 077 471, respectively); if the patient had BMI <18.5 (patients and comparators left after exclusion, n=215 590 and n=1 074 521, respectively) or if the patient had missing BMI after imputation (13.4%; patients and comparators left after exclusion, n=181 045 and n=902 302, respectively).

Statistical Analyses

Patients were divided into 5 BMI categories; 18.5 to <25, 25 to <30, 30 to <35, 35 to <40 and ≥40 kg/m^2. Each BMI group was further divided into HbA1c categories; <53 mmol/mole, 53 to 70 mmol/mole, and ≥71 mmol/mole. Age-adjusted incidence rates were calculated as events per 1000 person-years with 95% exact (Poisson) CIs. To present the excess risk for patients with type 2 diabetes mellitus versus the average age- and sex-matched comparators, we performed Cox regression analyses, adjusted for age, sex, duration of diabetes mellitus, socioeconomic status, and comorbidities at baseline (AF and chronic kidney disease) additionally performed with the outcome of heart failure as the principal diagnosis. Comparators served as the reference group for each Cox regression performed separately by each presented HbA1c group (<53, 53–70, and ≥71 mmol/mole), to demonstrate the effect from BMI and HbA1c compared with the general population comparators with a presumed normal HbA1c and population mean BMI with a similar design as previously published research from NDR.[1,2,4] Duration of diabetes mellitus was centered around the grand mean, while the duration for comparators was set to 0 days. Thus, the excess risk for patients represents the excess risk after a diabetes mellitus duration of 4.3 years.

To determine the risk association within the group of patients with type 2 diabetes mellitus for AMI and heart failure by BMI and HbA1c, respectively, we performed analyses without comparators from the general population to present the differences within the group of type 2 diabetes mellitus, adjusted for variables not available for comparators. These analyses were adjusted for age, sex, diabetes mellitus duration, education, marital status, income, immigrant status, and additionally risk factors; low-density lipoprotein (LDL) cholesterol, systolic blood pressure, and smoking. BMI and risk factors were modeled using restricted cubic splines with 4 equally distanced knots. We performed analyses separately for each outcome and risk factor, and additionally modeled an interaction term with HbA1c groups and BMI. We noted that there was no significant interaction between HbA1c and BMI. Since AMI is an established mediator for heart failure, we performed a time updated Cox regression with the outcome of heart failure, where we adjusted for AMI during follow-up, BMI with an added interaction term between AMI during follow-up and BMI. Of the 8622 patients who were diagnosed with heart failure, 2210 (25.6%) patients were diagnosed with AMI earlier during follow-up, or at the same day as the diagnosis of heart failure. In the cases where incident AMI and heart failure occurred at the same day, we added 1 day to the follow-up time of heart failure. The proportional hazards assumption was checked with Schoenfeldt residuals and there were no significant deviations from the assumption. The analyses were 2-tailed where a value of 0.05 was considered statistically significant. We used R (ver. 3.2.1; R Foundation for Statistical Programming).

Results

Baseline Characteristics

For this study, we identified 181 045 patients with type 2 diabetes mellitus and 902 302 age- and sex-matched population comparators. Mean age for both cases and comparators were 58.3 years, and 50.0% were women. Fewer patients (18.8%) than population comparators (28.8%) had a college/university degree. In terms of coexisting conditions at baseline, patients with type 2 diabetes mellitus had more frequently AF. Among patients with type 2 diabetes mellitus increasing body weight was associated with successively younger age, a higher proportion of women, and a lower proportion with college or university education. Similarly, there were associations between increasing body weight and lower age at onset of diabetes mellitus, shorter diabetes

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Table. Baseline Characteristics Among Age- and Sex-Matched General Population Comparators and Patients With Type 2 Diabetes Mellitus Stratified for Body Mass Index

	Comparators	Patients, Overall	18.5 to <25 y	25 to <30 y	30 to <35 y	35 to <40 y	≥40 y
Individuals, n	902 302	181 045	26 958	67 166	52 404	23 125	11 392
Women, n (%)	451 282 (50.0)	90 549 (50.0)	14 362 (53.3)	29 522 (44.0)	26 046 (49.7)	13 334 (57.7)	7285 (63.9)
Age (y)	58.3 (11.1)	58.3 (11.1)	60.0 (12.1)	59.6 (10.6)	58.1 (10.6)	55.9 (11.1)	52.6 (11.6)
Socioeconomic status							
Marital status—n (%)							
Divorced	152 785 (16.9)	31 701 (17.5)	4640 (17.2)	11 702 (17.4)	9232 (17.6)	4099 (17.7)	2028 (17.8)
Married	513 004 (56.9)	98 600 (54.5)	14 743 (54.7)	38 754 (57.7)	28 637 (54.6)	11 563 (50.0)	4903 (43.0)
Single	173 757 (19.3)	36 304 (20.1)	4878 (18.1)	11 265 (16.8)	10 493 (20.0)	5839 (25.2)	3829 (33.6)
Widowed	62 701 (6.9)	14 440 (8.0)	2697 (10.0)	5445 (8.1)	4042 (7.7)	1624 (7.0)	632 (5.5)
Education—n (%)							
9 y	248 184 (27.8)	63 553 (35.7)	9532 (35.9)	23 806 (36.0)	18 690 (36.3)	7865 (34.7)	3660 (32.8)
10 to 12 y	387 251 (43.4)	80 997 (45.5)	11 027 (41.5)	29 362 (44.4)	23 777 (46.2)	11 080 (48.9)	5751 (51.5)
College or university	256 727 (28.8)	33 404 (18.8)	5984 (22.5)	12 940 (19.6)	8991 (17.5)	3732 (16.5)	1757 (15.7)
Income (hundreds, SEK)—median (IQR)	1772.0 [1207.0, 2521.0]	1516.0 [1103.0, 2192.0]	1452.0 [1062.2, 2105.0]	1562.0 [1119.0, 2250.0]	1526.0 [1111.0, 2206.2]	1488.0 [1100.0, 2142.0]	1436.0 [1078.0, 2056.0]
Swedish born, n (%)	781 300 (86.6)	143 288 (79.1)	21 750 (80.7)	53 160 (79.1)	41 092 (78.4)	18 275 (79.0)	9011 (79.1)
Comorbidities, n (%)							
Atrial fibrillation	12 953 (1.4)	3853 (2.1)	534 (2.0)	1400 (2.1)	1124 (2.1)	513 (2.2)	282 (2.5)
Renal dialysis or transplantation	654 (0.1)	262 (0.1)	69 (0.3)	118 (0.2)	50 (0.1)	17 (0.1)	8 (0.1)
Variables from the Swedish National Diabetes registry							
Diabetes mellitus duration, y	NA	4.3 (5.7)	5.4 (6.9)	4.6 (5.9)	4.0 (5.3)	3.6 (4.9)	3.1 (4.6)
Debut age of diabetes mellitus, y	NA	54.1 (11.4)	54.6 (13.1)	55.1 (11.0)	54.1 (10.8)	52.5 (10.9)	49.8 (11.2)
HbA1c (mmol/mole)	NA	55.0 (15.9)	54.5 (16.8)	54.3 (15.5)	55.2 (15.6)	56.0 (16.0)	57.0 (16.5)
LDL cholesterol, mmol/L	NA	3.1 (1.0)	3.0 (1.0)	3.1 (1.0)	3.1 (1.0)	3.1 (0.9)	3.0 (0.9)
Total cholesterol, mmol/L	NA	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.1 (1.0)
Smokers, n (%)	NA	31 710 (18.8)	5669 (22.6)	11 660 (18.6)	8736 (17.9)	3798 (17.8)	1847 (17.7)
Body mass index, kg/m^2	NA	30.5 (5.7)	23.1 (1.5)	27.6 (1.4)	32.2 (1.4)	37.1 (1.4)	44.2 (4.2)
	NA	138.1 (17.6)	135.7 (18.6)	138.0 (17.5)	139.0 (17.3)	139.1 (17.0)	138.7 (16.8)

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Table. Continued

	Comparators	Patients, Overall	18.5 to <25 y	25 to <30 y	30 to <35 y	35 to <40 y	≥40 y
Systolic blood pressure, mm Hg							
Diastolic blood pressure, mm Hg	NA	80.1 (9.7)	77.2 (9.3)	79.6 (9.4)	81.1 (9.6)	81.8 (9.9)	82.4 (10.2)
Albuminuria, n (%)							
No albuminuria	NA	112 015 (82.5)	17 777 (86.0)	42 487 (83.4)	31 800 (81.5)	13 533 (79.1)	6418 (78.9)
Microalbuminuria	NA	16 723 (12.3)	2033 (9.8)	5941 (11.7)	5073 (13.0)	2467 (14.4)	1209 (14.9)
Macroalbuminuria	NA	7120 (5.2)	858 (4.2)	2490 (4.9)	2165 (5.5)	1098 (6.4)	509 (6.3)
eGFR, mL/min per 1.73 m^2	NA	87.3 (23.1)	87.0 (23.9)	86.1 (22.2)	87.1 (23.0)	88.8 (23.6)	92.5 (25.4)
Antihypertensives, n (%)	NA	93 065 (54.6)	10 559 (41.7)	33 154 (52.4)	29 276 (59.4)	13 541 (62.2)	6535 (61.2)
Statins, n (%)	NA	58 735 (34.5)	7490 (29.5)	22 497 (35.5)	18 166 (36.8)	7451 (34.4)	3131 (29.4)
Diabetes mellitus treatment, n (%)							
No pharmacologic treatment	NA	66 759 (36.9)	10 085 (37.4)	25 036 (37.3)	19 306 (36.8)	8303 (35.9)	4029 (35.4)
Oral agents	NA	82 891 (45.8)	9986 (37.0)	30 226 (45.0)	25 145 (48.0)	11 593 (50.1)	5941 (52.2)
Insulin	NA	16 166 (8.9)	5254 (19.5)	6443 (9.6)	3070 (5.9)	1014 (4.4)	385 (3.4)
Insulin+oral agents	NA	15 229 (8.4)	1633 (6.1)	5461 (8.1)	4883 (9.3)	2215 (9.6)	1037 (9.1)

Categorical variables are presented as n (%). Continuous variables are presented as the mean (SD), unless noted otherwise. eGFR indicates estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; LDL, low-density lipoprotein; NA, not available; SEK, Swedish kronor.

mellitus duration, more albuminuria, higher eGFR, and more treatment with statins and antihypertensives. (Table). Baseline characteristics for the patients with missing BMI at study entry after imputation, are presented in Table S2.

Incidence Rates

Over a median follow-up time of 5.7 years, there were a total number of 33 060 cases of AMI and 28 855 hospitalizations for heart failure (Table S3, with *ICD*-code presented in Table S1). Age-adjusted incidence rates, shown in Figure 1 (exact crude- and age-adjusted rates presented in Tables S4 and S5), were higher among patients with type 2 diabetes mellitus for all outcomes and poor glycemic control was associated with increased incidence rates. With respect to AMI, comparators displayed similar age-adjusted incidence rate of 4.0 to 4.6 cases per 1000 person-years. Since comparators worked as reference to Cox regression analyses stratified separately by each HbA1c group, the similar incidence rates between the matched comparators strengthened our matching process. Among individuals with diabetes mellitus, those with higher HbA1c had higher incidence rates, but there was no clear association between BMI and risk of AMI. For heart failure, we observed a strong association for both HbA1c and BMI, with an incidence of heart failure for individuals who were both poorly controlled and severely obese of 21.4 (17.9–25.5) per 1000 person-years, compared with 4.6 (4.2–5.1) per 1000 person-years among patients with optimal glycemic control and BMI 18.5 to <25 kg/m^2 and ≈3.0 to 3.8 cases of heart failure per 1000 person-years among matched-population comparators.

Hazard Ratios

Patterns for hazard ratios for AMI and heart failure were in line with those noted for incidence rates (Figure 2). Glycemic control beyond target level of 52 mmol/mole was associated with increased risks of both outcomes. There were no clear

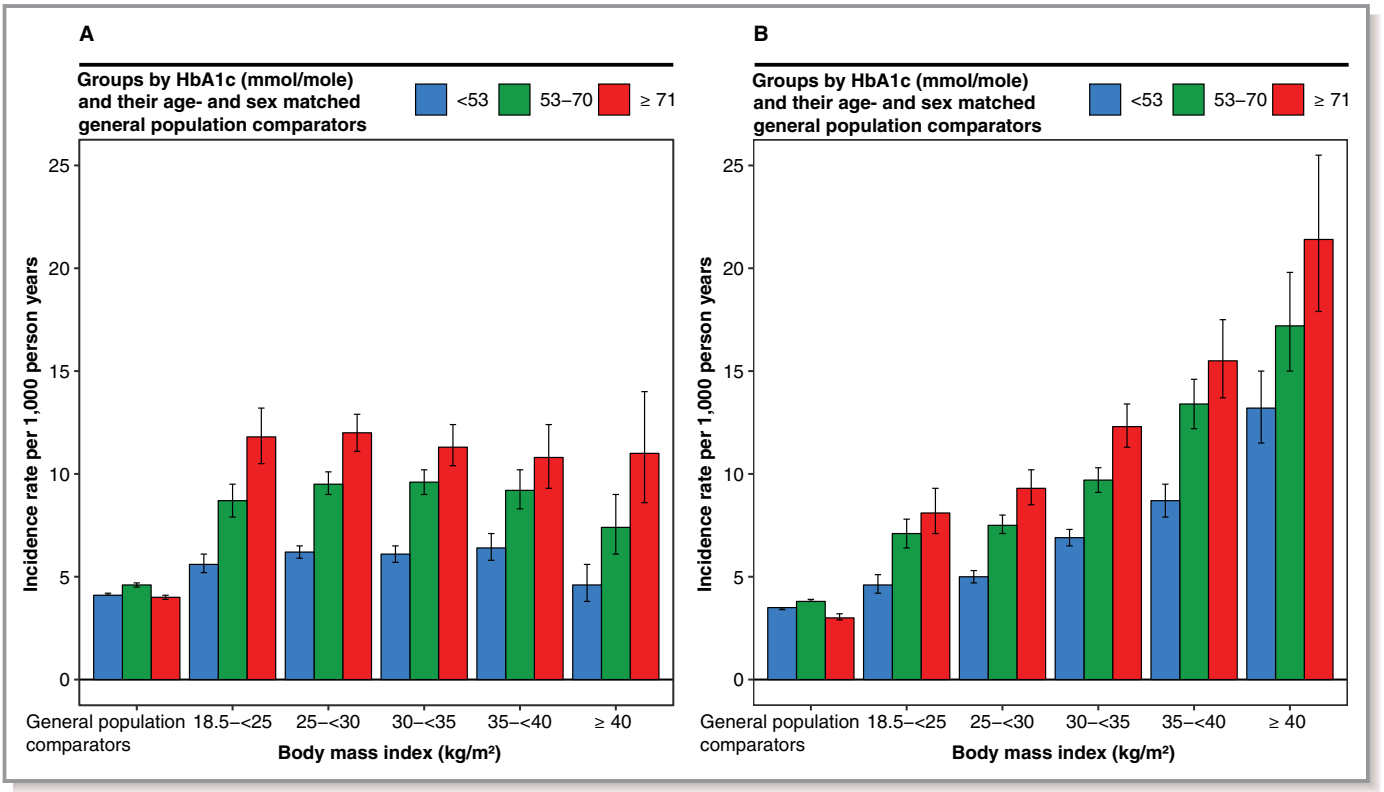

Figure 1. Age-adjusted* incidence rates per 1000 person-years for the risk of acute myocardial infarction and hospitalization for heart failure among patients with type 2 diabetes mellitus by body mass index (kg/m^2) group stratified by hemoglobin A1c (mmol/mole) and the age- and sex matched general population comparators with a presumed mean body mass index and normal hemoglobin A1c. Figure 1 describes age-adjusted incidence rates for acute myocardial infarction (**A**) and hospitalization for heart failure (**B**). Each step by body mass index or control subjects, consists of 3 hemoglobin A1c groups. Since incidence rates were performed separately stratified by hemoglobin A1c level, the control subjects are also represented by each hemoglobin A1c group. Colors blue (<53 mmol/mole), green (53–70 mmol/mole), and red (≥71 mmol/mole) define patients with type 2 diabetes mellitus stratified by the hemoglobin A1c group and their respective age and sex comparators with a presumed mean body mass index and normal hemoglobin A1c. BMI indicates body mass index; HbA1c, hemoglobin A1c. *Age standardization by direct method with exact CIs.

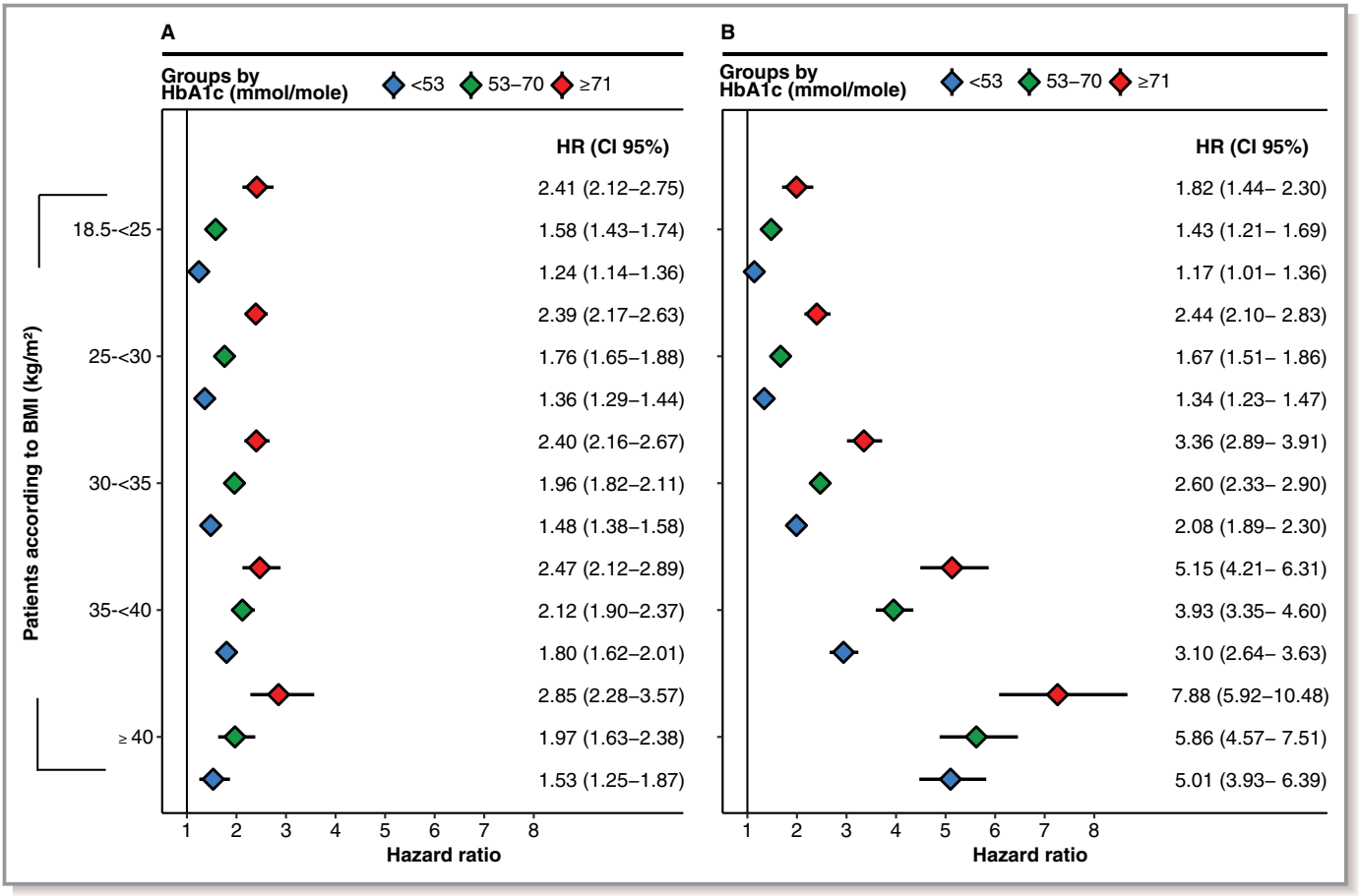

Figure 2. Hazard ratios for the risk of acute myocardial infarction and hospitalization for heart failure in type 2 diabetes mellitus by BMI (kg/m^2) stratified for hemoglobin A1c (mmol/mole) vs age- and sex-matched general population comparators with a presumed mean BMI and normal hemoglobin A1c. The analyses based on Cox regression analyses adjusted for age, sex, duration of diabetes mellitus, marital status, education, immigrant status, income, atrial fibrillation, and chronic kidney disease. Models were performed stratified by each HbA1c level, respectively groups. **A**, hazard ratios for the risk of acute myocardial infarction in type 2 diabetes mellitus by BMI and HbA1c vs age- and sex-matched general population comparators. **B**, hazard ratios for the risk of hospitalization for heart failure by BMI and HbA1c vs age- and sex-matched comparators (reference). BMI indicates body mass index; HR, hazard ratio.

associations between higher BMI and risk of AMI at any level of glycemic control. In contrast, there was a distinct almost linear increase in excess risk of heart failure with increasing BMI at all levels of glycemic control which was substantial among the very obese compared with comparators. In sensitivity analyses using heart failure registered as the principal diagnosis (about half of all heart failure cases; Figure S2) findings with respect to excess risk for BMI and glycemic control among patients with type 2 diabetes mellitus were similar to those for heart failure in any diagnostic position. Separate analyses in men and women displayed similar associations (Figure S3 and S4) as the main analyses. Women, compared with men, had somewhat higher excess risks for AMI, however, with respect to heart failure men and women displayed more or less similar excess risks.

Among analyses restricted to patients with type 2 diabetes mellitus (Figure 3), additionally adjusted for LDL cholesterol, systolic blood pressure, smoking status, and BMI/HbA1c (depending on the exposure), which was not possible to adjust for in analyses comparing with the population comparators, BMI was a stronger independent risk factor for heart failure than HbA1c, whereas for AMI, the risk increased linearly by HbA1c, but associations between BMI and risk were essentially flat when compared with the reference level of 25 kg/m^2. The analyses modeled as an interaction between HbA1c and BMI (Figure S5) showed similar results as analyses versus comparators, with higher estimates among the poorly controlled patients and a strong link of heart failure to increasing BMI. Our sensitivity analysis (Figure S6) suggested largely the same risk trajectory for the risk of heart failure as in the main analysis (Figure 3), regardless of incident AMI.

Discussion

This nationwide study containing 181 045 patients with type 2 diabetes mellitus, we found BMI to be much more strongly

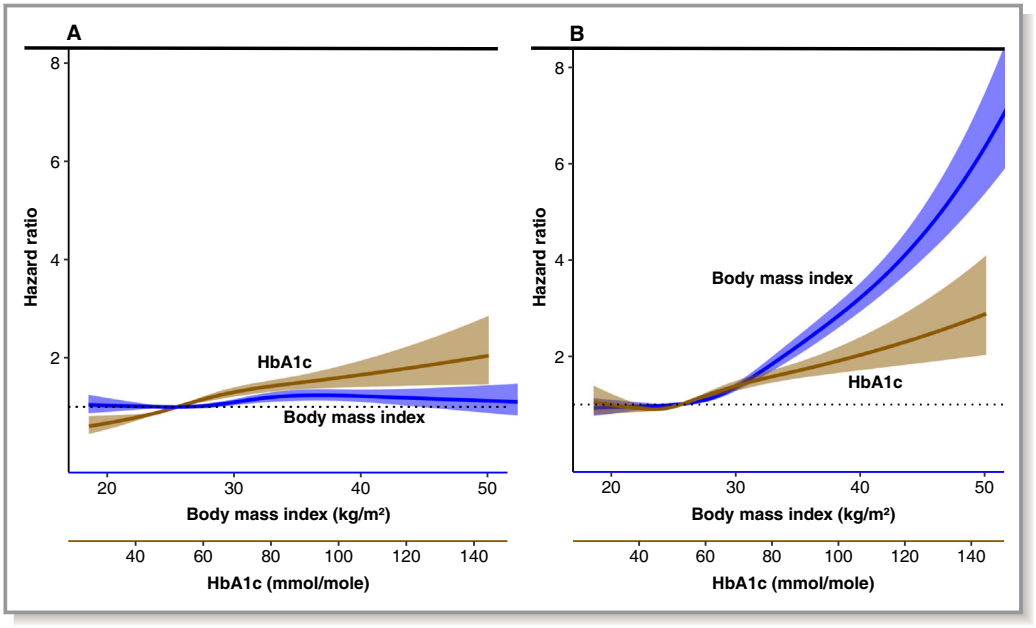

Figure 3. Associations between body mass index (kg/m^2), HbA1c and the risk of acute myocardial infarction and heart failure in patients with type 2 diabetes mellitus. The analyses were based on separate Cox regression models with predicted hazard ratios. Continuous variables were modeled as cubic splines. All 4 models were performed separately for each exposure and outcome, where the *y*-axis was cut at hazard ratio 8 (affecting 1041 patients with body mass index >50 kg/m^2, while the complete scale of hemoglobin A1c is shown). All models were adjusted for age, sex, duration of diabetes mellitus, income, education, marital status, immigrant status, atrial fibrillation, chronic kidney disease, low-density lipoprotein cholesterol, systolic blood pressure, and smoking status at baseline. Acute myocardial infarction (**A**): blue color describes hazard ratio for the risk of acute myocardial infarction according to body mass index, additionally adjusted for hemoglobin A1c; yellow color describes hazard ratio for the risk of acute myocardial infarction according to hemoglobin A1c, additionally adjusted for body mass index. Hospitalization for heart failure (**B**): blue color describes hazard ratio for the risk of hospitalization for heart failure according to body mass index, additionally adjusted for hemoglobin A1c; brown color describes hazard ratio for the risk of hospitalization for heart failure according to HbA1c, additionally adjusted for body mass index. Reference levels for body mass index and HbA1c were 25 kg/m^2 and 52 mmol/mole, respectively. Shaded area denotates CI 95%. HbA1c indicates hemoglobin A1c; LDL, low-density lipoprotein cholesterol.

associated with risk for heart failure than for AMI, where both excess risk and absolute risk associated with high BMI substantially more pronounced for heart failure than for AMI. In analyses against population comparators in whom normal BMI and HbA1c was assumed and who had the lowest absolute risks of all groups in our study, patients with type 2 diabetes mellitus having BMI ≥40 kg/m^2 experienced a substantial 5- to 7-fold excess risk of heart failure. Collectively, these findings highlight obesity as a particularly strong risk factor for heart failure in the setting of type 2 diabetes mellitus.

The excess risk of atherosclerotic events, as well as the risk of heart failure among patients with type 2 diabetes mellitus, compared with the general population, are well known. Findings with respect to obesity and CHD have been less consistent, whereas a strong link between obesity and heart failure has been established in people with, as well as without, diabetes mellitus. For AMI associations with BMI were essentially flat irrespective of glycemic control. In contrast, severely obese patients displayed up to an 8-fold risk of heart failure, compared with normal weight. This further supports a hypothesis of differential underlying pathogenetic mechanisms for atherosclerotic CVD outcomes versus heart failure among patients with type 2 diabetes mellitus.[7]

If our findings are true, what might be the mechanisms for a stronger BMI to heart failure link and what are the clinical implications, if any? In terms of mechanisms, we have shown previously that obesity is more strongly linked to heart failure than it is to AMI in young men conscripts.[15] Linked to this, higher BMI was recently reported to be associated with higher blood pressure and left ventricular mass index among young men and women aged 18 years.[16] These 2 observations suggest obesity starts to promote cardiac remodeling independent of dysglycemia from a young age. We also know that

obesity leads to an increase in intravascular volume expansion, partially via greater sodium retention, and that cardiac output has to be higher to supply a greater volume of tissue. Obesity is also a well-established risk factor for chronic kidney disease,[17] perhaps by linked mechanisms feeding through glomerular hypertension. Thus, several pathways seem to link obesity to heart failure risk. We recently proposed such perturbances might worsen when frank hyperglycemia manifests, and so risks for heart failure should be exaggerated when both hyperglycemia and obesity are prevalent.[7] Our current findings support this contention.

In terms of clinical management, our work highlights further the importance of heart failure risks in diabetes mellitus per se, but also that such relative (and absolute) risks are significantly greater when glucose control is poor and, critically, when BMI levels are high. Of note, we now have access to a class of drugs, the SGLT2 (sodium-glucose transport protein 2) inhibitors which consistently lessen risks for heart failure (by ~30%) seemingly through hemodynamic mechanisms.[18] The SGLT2 inhibitor class also aids weight loss, which is helpful to patients who are obese, and lessens blood pressure. Whether other forms of weight loss in diabetes mellitus decrease the risk for heart failure is currently unproven but the current GLP-1RA (glucagon-like peptide-1 receptor agonist) trials do not seem to show reductions in heart failure risk.[19]

Sweden is not exempt from the current obesity epidemic.[20] The global increase in obesity may confer an increased incidence of heart failure, which has already been proven to be true for the Swedish younger population,[21] which could imply a future increasing impact on healthcare resources.[22] To date, medical interventions have not been demonstrated to be effective, and the only treatment for severe obesity is bariatric surgery proven to reduce weight and obesity related cardiovascular complications.[23] However, for financial and other reasons surgical intervention is out of reach for the majority of the obese with type 2 diabetes mellitus globally, who may already be struggling to obtain medical care,[24] highlighting the need for primary prevention.

Considering BMI as an independent risk factor for mortality, and the common risks with obesity in type 2 diabetes mellitus, findings from previous research among patients with type 2 diabetes mellitus and low weight have been diverging, debating over a potential obesity paradox for mortality.[25–27] In this present study obesity was demonstrated to increase the risk of heart failure regardless of glycemic control. We also found no sign of reverse causality among the leanest patients, even though our normal weight patients (BMI 18.5 to <25) displayed a higher insulin use than other groups which might potentially imply a more aggressive form of diabetes mellitus such as Late Autoimmune Diabetes in Adults,[28] however, there was no increased risk of AMI compared with overweight patients, and the leanest patients in our study did not display any increased risk, which might support current recommendations for weight management for type 2 diabetes mellitus.[29] Weight loss can reverse diabetes mellitus, as recently shown in the DiRECT (Diabetes Remission Clinical Trial)[30] whereas gain of fat mass was associated with left ventricular concentric remodeling and impairment of systolic and diastolic function parameters.[31] Further research to prevent heart failure among patients with type 2 diabetes mellitus is needed, since heart failure is associated with worse functional status and prognosis,[32] and where the present study may implicate weight management as a preventative strategy for the development of heart failure.

There are several strengths of the study, foremost, using nationwide registers to include data from a large number of patients seen in routine clinical practice and implementing a controlled study design that sought to limit different sources of bias. NDR has a wide national coverage of patients diagnosed with type 2 diabetes mellitus, with measured BMI and the possibility to use the in-patient registry to identify all hospitalizations, including heart failure. Furthermore, we were able to adjust for multiple comorbidities and exclude patients with severe heart-related conditions which could generate biased analyses with respect to BMI.[33] The size of the cohort made it possible to stratify for both glycemic control and for body weight categories. The availability of population-based comparators made it possible to identify not only absolute and relative risks among the population with diabetes mellitus, but also the excess risk in relationship to non-diabetic mellitus population comparators.

Our study also has some limitations, foremost, the lack of data on BMI among population comparators. Therefore, we were not able to quantify the excess risk by BMI only, that is, to which extent the excess risk among the obese with diabetes mellitus was dependent on their weight and how much on their diabetes mellitus as such. Hence, the interpretation of "excess risk" by BMI and glycemic control should be compared with the general population with average BMI estimated at ≈25 to 26 kg/m^2[34] and a presumed normal HbA1c. A further limitation is that milder cases of heart failure may be missed, however, hospitalization for heart failure in the in-patient registry is a validated and specific outcome,[12,35] and hazard ratio did not change substantially with the outcome of heart failure was limited to heart failure as the principal diagnosis of hospitalization.

Conclusions

We found an excess risk of heart failure among all age groups and HbA1c categories, that increased stepwise by BMI with an additionally worsened prognosis conferred by poor glycemic control. In contrast, for AMI, even a very high BMI

provided only limited extra risk over and above the risk conferred by glycemic control, indicating different pathophysiological mechanisms for atherosclerotic disease and for heart failure. Other than the overall goal of maintaining a healthy weight, specific pharmacological therapies proven to lessen heart failure risks and lower BMI might be considered in obese/very obese patients with type 2 diabetes mellitus, although further study is clearly needed.

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References

1. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. *The New England journal of medicine*. 2015;373:1720–1732.
2. Rosengren A, Edqvist J, Rawshani A, Sattar N, Franzen S, Adiels M, Svensson AM, Lind M, Gudbjornsdottir S. Excess risk of hospitalisation for heart failure among people with type 2 diabetes. *Diabetologia*. 2018;61:2300–2309.
3. Rawshani A, Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjornsdottir S. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *The New England journal of medicine*. 2018;379:633–644.
4. Rawshani A, Rawshani A, Franzen S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjornsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *The New England journal of medicine*. 2017;376:1407–1418.
5. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *The lancet Diabetes & endocrinology*. 2016;4:537–547.
6. Dinesh Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of a wide range of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet (London, England)*. 2015;385 (suppl 1):S86.
7. Sattar N, McGuire DK. Pathways to cardiorenal complications in type 2 diabetes mellitus: a need to rethink. *Circulation*. 2018;138:7–9.
8. Glogner S, Rosengren A, Olsson M, Gudbjornsdottir S, Svensson AM, Lind M. The association between BMI and hospitalization for heart failure in 83,021 persons with Type 2 diabetes: a population-based study from the Swedish National Diabetes Registry. *Diabetic*. 2014;31:586–594.
9. Li W, Katzmarzyk PT, Horswell R, Zhang Y, Wang Y, Johnson J, Hu G. Body mass index and heart failure among patients with type 2 diabetes mellitus. *Circulation Heart failure*. 2015;8:455–463.
10. Forskning. Nationella diabetesregistret. Available at: https://www.ndr.nu/#/forskning. Accessed September 1, 2019.
11. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Nunez L, Gudbjornsdottir S, Eliasson B. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia*. 2009;52:65–73.
12. Eliasson B, Gudbjornsdottir S. Diabetes care–improvement through measurement. *Diabetes Res Clin Pract*. 2014;106(suppl 2):291–294.
13. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659–667.
15. Rosengren A, Aberg M, Robertson J, Waern M, Schaufelberger M, Kuhn G, Aberg D, Schioler L, Toren K. Body weight in adolescence and long-term risk of early heart failure in adulthood among men in Sweden. *Eur Heart J*. 2017;38:1926–1933.
16. Wade KH, Chiesa ST, Hughes AD, Chaturvedi N, Charakida M, Rapala A, Muthurangu V, Khan T, Finer N, Sattar N, Howe LD, Fraser A, Lawlor DA, Davey Smith G, Deanfield JE, Timpson NJ. Assessing the causal role of body mass index on cardiovascular health in young adults: mendelian randomization and recall-by-genotype analyses. *Circulation*. 2018;138:2187–2201.
17. Silverwood RJ, Pierce M, Hardy R, Thomas C, Ferro C, Savage C, Sattar N, Kuh D, Nitsch D. Early-life overweight trajectory and CKD in the 1946 British birth cohort study. *Am J Kidney Dis*. 2013;62:276–284.
18. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet (London, England)*. 2019;393:31–39.
19. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, Meeran K. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319:1580–1591.
20. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet (London, England)*. 2016;387:1377–1396.
21. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J*. 2014;35:25–32.
22. Paren P, Schaufelberger M, Bjorck L, Lappas G, Fu M, Rosengren A. Trends in prevalence from 1990 to 2007 of patients hospitalized with heart failure in Sweden. *Eur J Heart Fail*. 2014;16:737–742.
23. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273:219–234.
24. Chow CK, Ramasundarahettige C, Hu W, AlHabib KF, Avezum A Jr, Cheng X, Chifamba J, Dagenais G, Dans A, Egbujie BA, Gupta R, Iqbal R, Ismail N, Keskinler MV, Khatib R, Kruger L, Kumar R, Lanas F, Lear S, Lopez-Jaramillo P, McKee M, Mohammadifard N, Mohan V, Mony P, Orlandini A, Rosengren A, Vijayakumar K, Wei L, Yeates K, Yusoff K, Yusuf R, Yusufali A, Zatonska K, Zhou Y, Islam S, Corsi D, Rangarajan S, Teo K, Gerstein HC, Yusuf S. Availability and affordability of essential medicines for diabetes across high-income, middle-income, and low-income countries: a prospective epidemiological study. *The lancet Diabetes & endocrinology*. 2018;6:798–808.

25. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, Manson JE, Hu FB. Body-mass index and mortality among adults with incident type 2 diabetes. *The New England journal of medicine*. 2014;370:233–244.
26. Jackson CL, Yeh HC, Szklo M, Hu FB, Wang NY, Dray-Spira R, Brancati FL. Body-mass index and all-cause mortality in us adults with and without diabetes. *J Gen Intern Med*. 2014;29:25–33.
27. Edqvist J, Rawshani A, Adiels M, Bjorck L, Lind M, Svensson AM, Gudbjornsdottir S, Sattar N, Rosengren A. 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.
28. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet (London, England)*. 2014;383:1084–1094.
29. American Diabetes Association. 4. Lifestyle management: standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41:38–50.
30. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, Ross HM, McIlvenna Y, Stefanetti R, Trenell M, Welsh P, Kean S, Ford I, McConnachie A, Sattar N, Taylor R. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet (London, England)*. 2018;391:541–551.
31. Markus MR, Werner N, Schipf S, Siewert-Markus U, Bahls M, Baumeister SE, Volzke H, Felix SB, Ittermann T, Dorr M. Changes in body weight and composition are associated with changes in left ventricular geometry and function in the general population: SHIP (study of health in pomerania). *Circulation Cardiovascular imaging*. 2017;10:e005544.
32. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *The lancet Diabetes & endocrinology*. 2014;2:843–851.
33. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? *Circulation*. 2017;135:2369–2372.
34. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults. *The New England journal of medicine*. 2010;363:2211–2219.
35. Ingelsson E, Arnlov J, Sundstrom J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail*. 2005;7:787–791.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics for the final cohort vs cohort with missing body mass index after applied exclusion criteria.

	Patients, overall	**Patients, missing BMI**
Individuals - n	181045	34545
Females – n (%)	90549 (50.0)	18224 (52.8)
Age (years)	58.3 (11.1)	57.4 (13.3)
Socioeconomic status		
Marital status - n (%)		
Divorced	31701 (17.5)	6338 (18.3)
Married	98600 (54.5)	17134 (49.6)
Single	36304 (20.1)	8095 (23.4)
Widowed	14440 (8.0)	2978 (8.6)
Education - n (%)		
10 to 12 years	80997 (45.5)	14815 (44.2)
9 years or less	63553 (35.7)	11611 (34.7)
College or university	33404 (18.8)	7071 (21.1)
Income (hundreds, SEK[*]) - median (IQR[†])	1516.0 [1103.0, 2192.0]	1456.0 [1068.0, 2140.0]
Swedish born - n (%)	143288 (79.1)	26140 (75.7)
Comorbidities - n (%)		
Atrial fibrillation	3853 (2.1)	874 (2.5)
Renal dialysis or transplantation	262 (0.1)	130 (0.4)
Variables from the Swedish national Diabetes registry		
Diabetes duration (years)	4.3 (5.7)	6.3 (8.7)
Debut age of diabetes (years)	54.1 (11.4)	51.0 (16.0)
HbA1c[‡] (mmol/mole)	55.0 (15.9)	55.1 (16.6)
LDL[§] cholesterol (mmol/L)	3.1 (1.0)	3.1 (1.0)
Total cholesterol (mmol/L)	5.2 (1.1)	5.2 (1.1)
Smokers - n (%)	31710 (18.8)	3966 (20.0)
Body Mass Index (kg/m^2)	30.5 (5.7)	NA[#]
Systolic blood pressure (mmHg)	138.1 (17.6)	138.4 (18.4)
Diastolic blood pressure (mmHg)	80.1 (9.7)	80.0 (10.0)
Albuminuria - n (%)		
No albuminuria	112015 (82.5)	12996 (80.9)
Microalbuminuria	16723 (12.3)	2130 (13.3)
Macroalbuminuria	7120 (5.2)	944 (5.9)
eGFR[‖] ($mL/min/m^{1.73}$)	87.3 (23.1)	88.0 (26.1)
Antihypertensives - n (%)	93065 (54.6)	15094 (48.7)
Statins - n (%)	58735 (34.5)	9639 (31.1)
Diabetes treatment - n (%)		
No pharmacologic treatment	66759 (36.9)	16187 (46.9)
Oral agents	82891 (45.8)	13340 (38.6)
Insulin	16166 (8.9)	2467 (7.1)
Insulin + oral agents	15229 (8.4)	2551 (7.4)

Categorical variables are presented as n (%). Continuous variables are presented as the mean (SD), unless noted otherwise. [*]SEK, Swedish kronor. [†]IQR, interquartile range, [‡]HbA1c, hemoglobin A1c, [§]LDL, low-density lipoprotein, [‖]eGFR, estimated glomerular filtration rate, [#]NA, not available

Table S2. Follow-up descriptive.

Median follow up years Acute myocardial infarction	5.7
Median follow up years Hospitalization for heart failure	5.7
Age - mean	58.3
Age - SD	11.1
Total number of events for patients and comparators, acute myocardial infarction - n	33,060
Total number of events for patients and comparators, hospitalization for heart failure - n	28,855
Number of events, hospitalization for heart failure, defined as the principal diagnosis, overall - n	12,821
Number of events, Acute myocardial infarction, patients - n	8,735
Number of events, hospitalization for heart failure, patients - n	8,622
Number of events, hospitalization for heart failure, defined as the principal diagnosis, overall - n	4,231

Diagnosis	ICD-9, pre-existing condition	ICD-10, pre-existing condition	Definition of outcomes (ICD-10)
Acute myocardial infarction	410	I21	The first occurrence of I21 as the principal- or contributory diagnosis in either a registered hospitalization or a registered cause of death
Heart failure	428	I50	The first occurrence of I50 as the principal- or contributory diagnosis in a registered hospitalization
Heart failure (First diagnostic position)	428	I50	The first occurrence of I50 as the principal diagnosis in a registered hospitalization
Coronary heart disease	410-414	I20-I25	
Stroke	431, 432X, 433, 434, 436, 437X	I61, I62.9, I63, I64, I67.9	
Atrial fibrillation	427D	I48	
Renal dialysis or transplantation	V42A, V45B, V56A, V56W	Z94.0, Z49, Z99.2	

Table S3. Descriptions of diagnoses for pre-existing conditions and outcomes used from the International Classification of Diseases system.

Diagnosis used from the inpatient registry according to the International Classification of Diseases (ICD) system, 9th revision and 10th revision.

Table S4. Crude and age standardized incidence rates per 1,000 person years for acute myocardial infarction among patients with type 2 diabetes stratified by HbA1c[*] (mmol/mole) and BMI[†] (kg/m^2) and age- and sex matched general population comparators.

Category	Events	Person years	Crude rate (CI 95%)	Age adjusted Rate (CI 95%)
HbA1c <53 mmol/mole				
Comparators	12357	2987515	4.1 (4.1-4.2)	4.1 (4.1-4.2)
Patients BMI (kg/m^2)				
18.5-<25	593	96064	6.2 (5.7-6.7)	5.6 (5.2-6.1)
25-<30	1505	232092	6.5 (6.2-6.8)	6.2 (5.9-6.5)
30-<35	982	164843	6.0 (5.6-6.3)	6.1 (5.7-6.5)
35-<40	386	67650	5.7 (5.2-6.3)	6.4 (5.8-7.1)
≥40	119	30489	3.9 (3.2-4.7)	4.6 (3.8-5.6)
HbA1c 53-70 mmol/mole				
Comparators	8403	1834580	4.6 (4.5-4.7)	4.6 (4.5-4.7)
Patients by BMI (kg/m^2)				
18.5-<25	502	53417	9.4 (8.6-10.3)	8.7 (7.9-9.5)
25-<30	1335	134954	9.9 (9.4-10.4)	9.5 (9.0-10.1)
30-<35	963	102671	9.4 (8.8-10.0)	9.6 (9.0-10.2)
35-<40	365	43836	8.3 (7.5-9.2)	9.2 (8.3-10.2)
≥40	120	20500	5.9 (4.9-7.0)	7.4 (6.1-9.0)
***HbA1c* ≥71 mmol/mole**				
Comparators	3248	811103	4.0 (3.9-4.1)	4.0 (3.9-4.1)
Patients by BMI (kg/m^2)				
18.5-<25	288	23673	12.2 (10.8-13.7)	11.8 (10.5-13.2)
25-<30	643	52179	12.3 (11.4-13.3)	12.0 (11.1-12.9)
30-<35	499	44448	11.2 (10.3-12.3)	11.3 (10.4-12.4)
35-<40	201	20904	9.6 (8.3-11.0)	10.8 (9.3-12.4)
≥40	87	10898	8.0 (6.4-9.8)	11.0 (8.6-14.0)

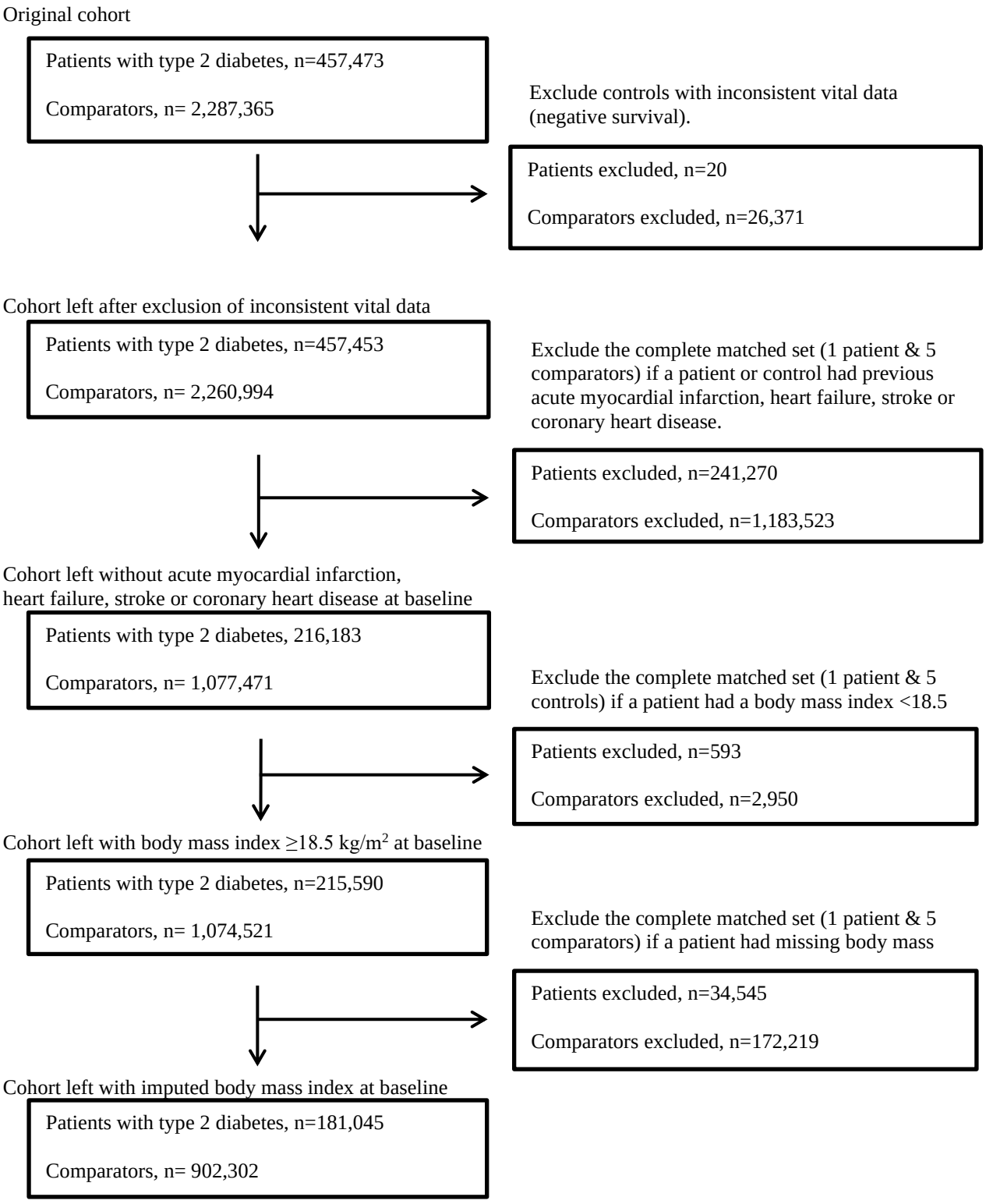
[*]HbA1c, hemoglobin A1c, [†]BMI, body mass index

Table S5. Crude- and age standardized incidence rates per 1,000 person years for hospitalization for heart failure among patients with type 2 diabetes stratified by HbA1c[*] (mmol/mole) and BMI[†] (kg/m^2) and age- and sex matched general population comparators.

Category	Events	Person years	Crude rate (CI 95%)	Age adjusted Rate (CI 95%)
HbA1c < 53 mmol/mole				
Comparators	10415	2996275	3.5 (3.4-3.5)	3.5 (3.4-3.5)
Patients by BMI (kg/m^2)				
18.5-<25	515	96344	5.3 (4.9-5.8)	4.6 (4.2-5.1)
25-<30	1255	233550	5.4 (5.1-5.7)	5.0 (4.7-5.3)
30-<35	1088	164884	6.6 (6.2-7.0)	6.9 (6.5-7.3)
35-<40	485	67388	7.2 (6.6-7.9)	8.7 (7.9-9.5)
≥40	262	29950	8.7 (7.7-9.9)	13.2 (11.5-15.0)
HbA1c 53-70 mmol/mole				
Comparators	7096	1840784	3.9 (3.8-3.9)	3.8 (3.8-3.9)
Patients by BMI (kg/m^2)				
18.5-<25	424	53860	7.9 (7.1-8.7)	7.1 (6.4-7.8)
25-<30	1075	136201	7.9 (7.4-8.4)	7.5 (7.1-8.0)
30-<35	956	103006	9.3 (8.7-9.9)	9.7 (9.1-10.3)
35-<40	506	43444	11.6 (10.7-12.7)	13.4 (12.2-14.6)
≥40	245	20073	12.2 (10.7-13.8)	17.2 (15.0-19.8)
HbA1c ≥71 mmol/mole				
Comparators	2487	814373	3.1 (2.9-3.2)	3.0 (2.9-3.2)
Patients by BMI (kg/m^2)				
18.5-<25	207	24021	8.6 (7.5-9.9)	8.1 (7.1-9.3)
25-<30	506	52634	9.6 (8.8-10.5)	9.3 (8.5-10.2)
30-<35	529	44316	11.9 (10.9-13.0)	12.3 (11.3-13.4)
35-<40	279	20616	13.5 (12.0-15.2)	15.5 (13.7-17.5)
≥40	157	10631	14.8 (12.5-17.3)	21.4 (17.9-25.5)

[*]HbA1c, hemoglobin A1c, [†]BMI, body mass index

Figure S1. Flow chart for the final cohort containing patients with type 2 diabetes and age- and sex matched general population comparators.



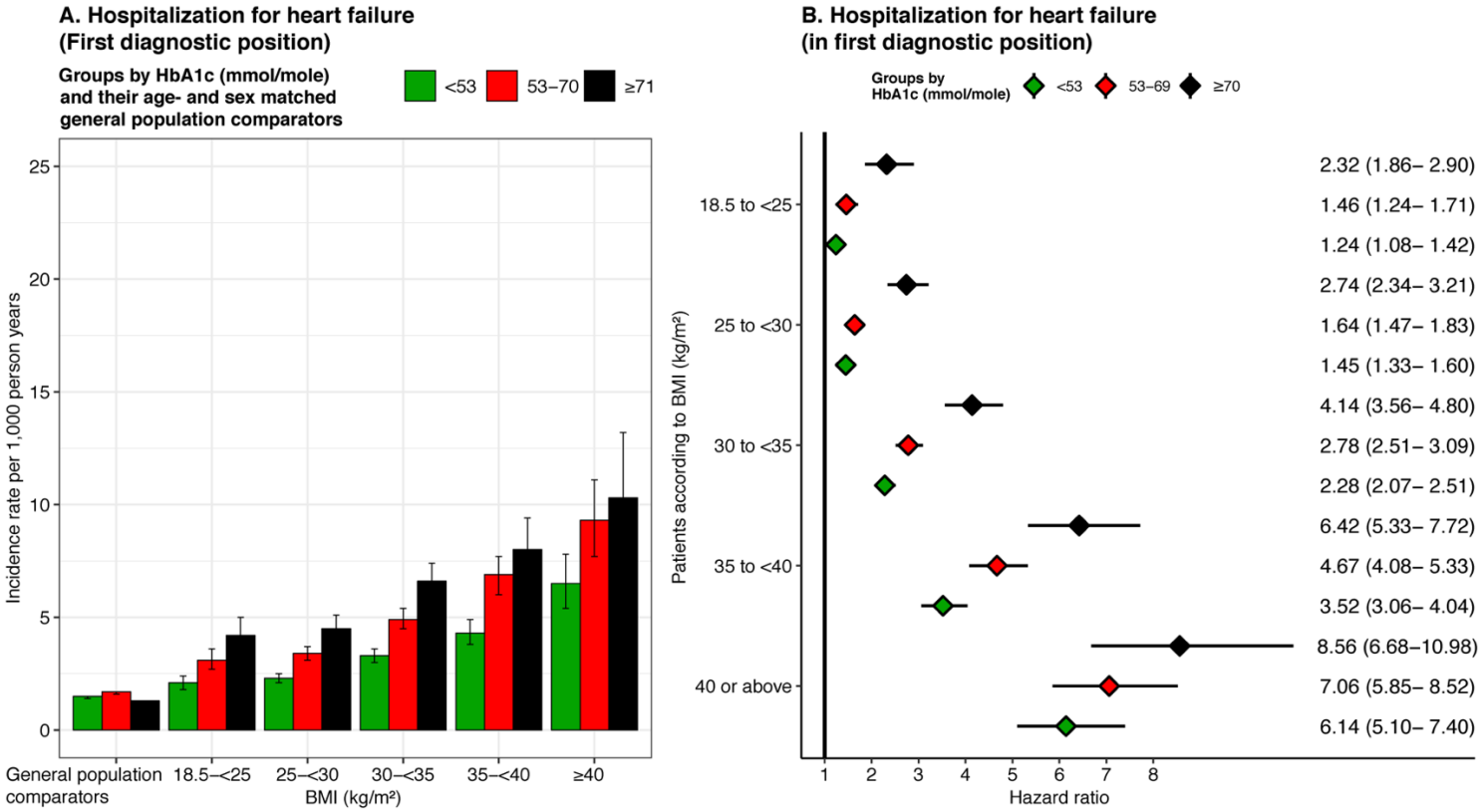


Figure S2. Age adjusted[*] incidence rates per 1000 person years and hazard ratios for the risk of hospitalization for heart failure defined as the principal diagnosis among patients with type 2 diabetes stratified for HbA1c (mmol/mole) and body mass index (kg/m^2) vs age- and sex matched population comparators.

The analyses based on Cox regression adjusted for age, duration of diabetes, marital status, education, immigrant status, income, atrial fibrillation and chronic kidney disease. Panel A, age adjusted incidence rates for hospitalization for heart failure. Each step by body mass index or control subjects, consists of three HbA1c groups. Since incidence rates were performed separately stratified by HbA1c level, the control subjects are also represented by each HbA1c group. Panel B, hazard ratios for the risk of hospitalization for heart failure defined as the principal diagnosis by BMI and HbA1c vs age- and sex matched population comparators (reference), among women only. BMI, body mass index, HbA1c, Hemoglobin A1c, CI, confidence interval. [*]Age standardization by Direct Method with exact confidence intervals.

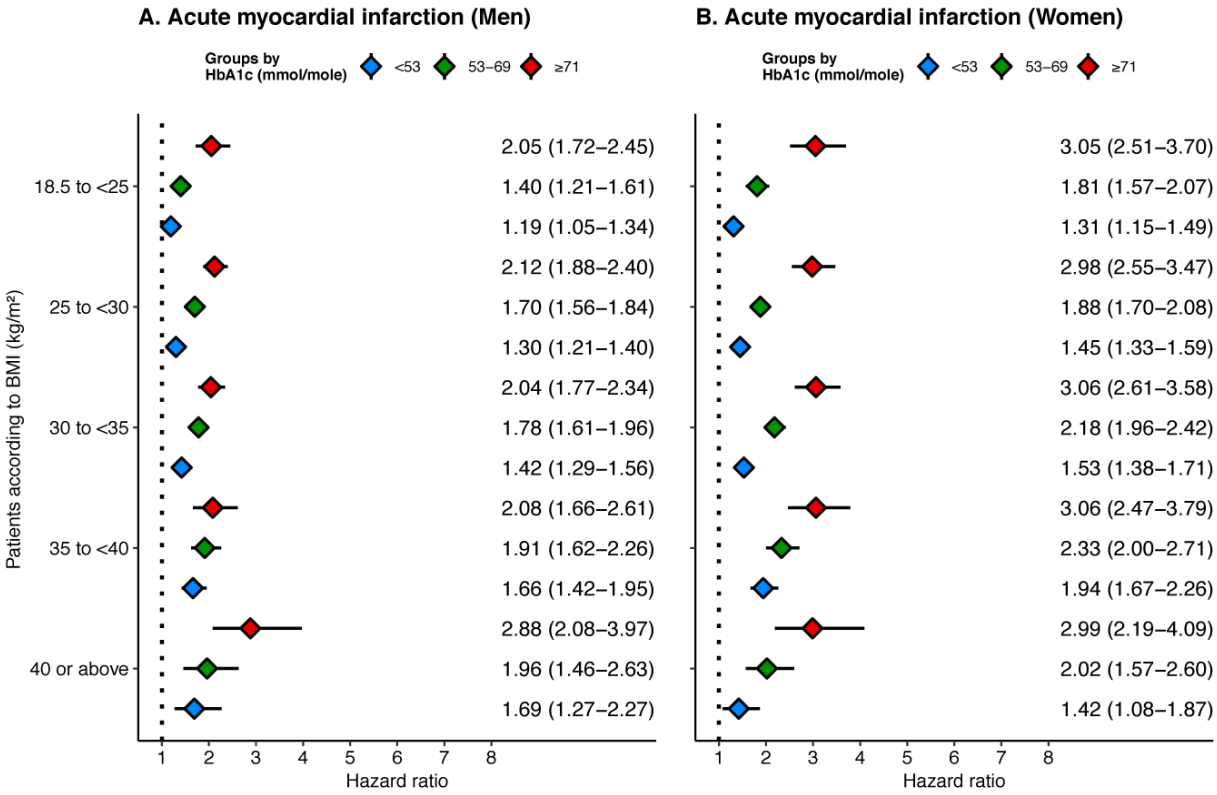


Figure S3. Sex-specific hazard ratios for the risk of acute myocardial infarction among patients with type 2 diabetes stratified for HbA1c (mmol/mole) and BMI (kg/m^2) vs age- and sex matched population comparators.

The analyses based on Cox regression adjusted for age, duration of diabetes, marital status, education, immigrant status, income, atrial fibrillation and chronic kidney disease. Panel A, hazard ratios for the risk of acute myocardial infarction in type 2 diabetes by BMI and HbA1c vs age- and sex matched population comparators (reference), among men only. Panel B, hazard ratios for the risk of acute myocardial infarction by BMI and Hemoglobin A1c vs age- and sex matched controls (reference), among women only. BMI, body mass index, HbA1c, Hemoglobin A1c, CI, confidence interval.

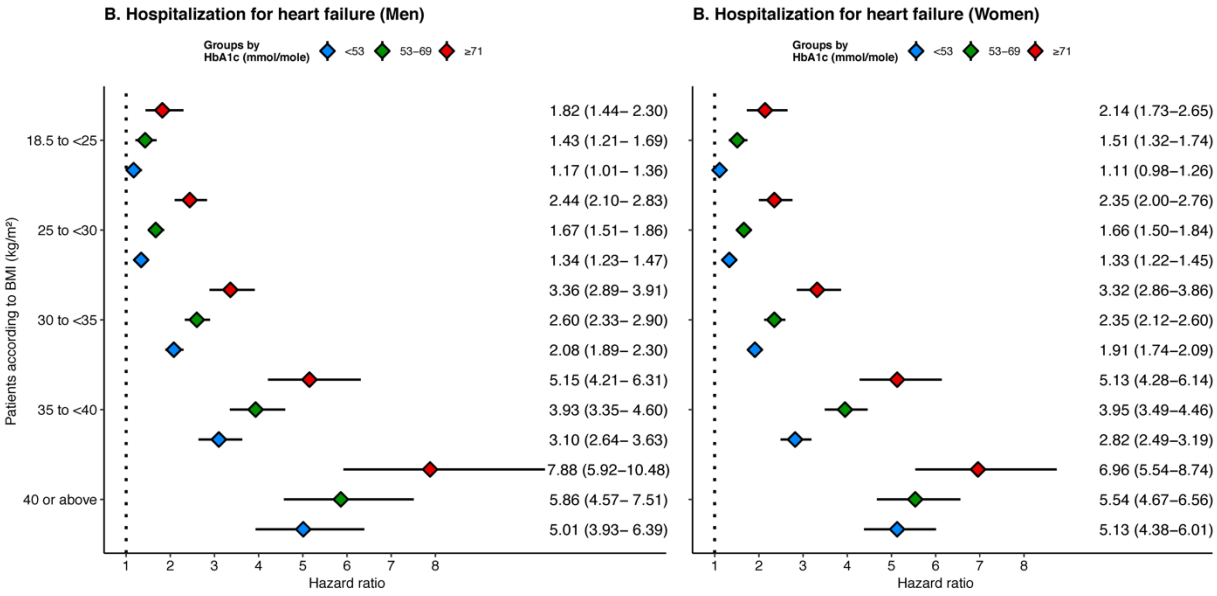


Figure S4. Sex-specific hazard ratios for the risk of hospitalization for heart failure among patients with type 2 diabetes stratified for HbA1c (mmol/mole) and BMI (kg/m^2) vs age- and sex matched population comparators.

The analyses based on Cox regression adjusted for age, duration of diabetes, marital status, education, immigrant status, income, atrial fibrillation and chronic kidney disease. Panel A, hazard ratios for the risk of hospitalization for heart failure in type 2 diabetes by BMI and HbA1c vs age- and sex matched population comparators (reference), among men only. Panel B, hazard ratios for the risk of hospitalization for heart failure by BMI and HbA1c vs age- and sex matched population comparators (reference), among women only. BMI, body mass index, HbA1c, Hemoglobin A1c, CI, confidence interval.

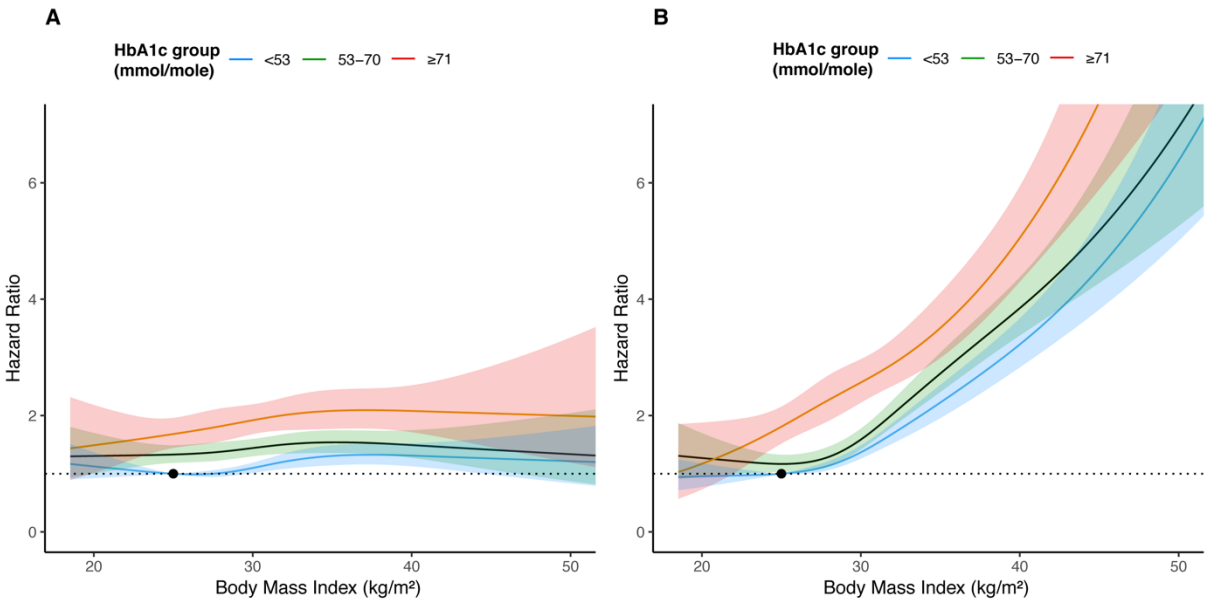


Figure S5. Adjusted hazard ratio for all outcomes, restricted to type 2 diabetes by BMI (kg/m^2) with interaction terms BMI*HbA1c.

The analysis based on cox regression was adjusted for age, sex, duration of diabetes, income, education, marital status, immigrant status, atrial fibrillation, chronic kidney disease, HbA1c, LDL-cholesterol, systolic blood pressure and smoking status at baseline. Hazard ratios for the risk of acute myocardial infarction according to BMI; p-value for the interaction term body mass index*HbA1c=0.7 (Panel A). Hazard ratios for the risk of hospitalization for heart failure according to BMI; p-value for the interaction term body mass index*HbA1c=0.3 (Panel B). Reference level was set to body mass index 25 kg/m^2, in the group with HbA1c <53 mmol/mole. Shaded area denotates confidence intervals 95%. BMI=body mass index, HbA1c=Hemoglobin A1c, LDL=low density lipoprotein cholesterol.

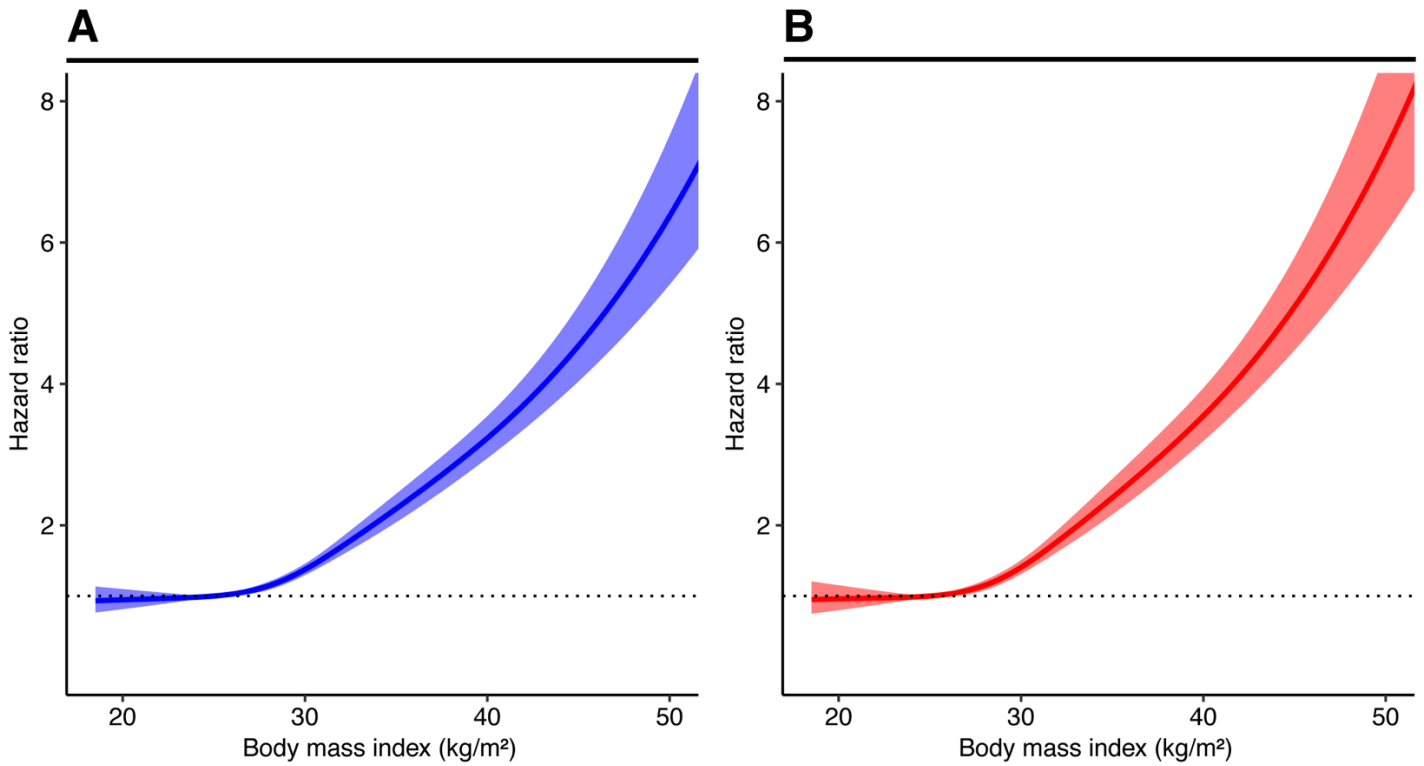


Figure S6. Associations between BMI (kg/m^2) and the risk of heart failure, original model vs time updated model for incident acute myocardial infarction during follow up in patients with type 2 diabetes.

The analyses were based on time updated Cox regression with predicted hazard ratios. Continuous variables were modelled as cubic splines. The model was adjusted for age, sex, duration of diabetes, income, education, marital status, immigrant status, atrial fibrillation, chronic kidney disease, HbA1c, LDL-cholesterol, systolic blood pressure, smoking status at baseline. Original model presenting the risk of hospitalization for heart failure by body mass index (Panel A). The risk of hospitalization for heart failure by body mass index, additionally adjusted for the interaction between body mass index and acute myocardial infarction during follow-up (Panel B); p-value for acute myocardial infarction during follow-up (Panel B) <0.0001; p-value for the interaction term BMI*acute myocardial infarction (Panel B) <0.0001. Reference level was set to body mass index 25 kg/m^2. BMI, body mass index, HbA1c, Hemoglobin A1c, LDL, low density lipoprotein cholesterol.