Body mass index and mortality in patients with new onset type 2 diabetes. A comparison with age- and sex matched controls from the general population.

Running title: Type 2 diabetes, BMI, and mortality

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Abstract

Objective: Type 2 diabetes is strongly associated with obesity, but the mortality risk related to elevated body weight in people with type 2 diabetes compared with people without diabetes has not been established.

Research Design and Methods: We prospectively assessed short- and long-term mortality in people with type 2 diabetes with a recorded diabetes duration ≤5 years identified from the Swedish National Diabetes Registry between 1998 and 2012 and five age- and sex matched controls per study participant from the general population.

Results: Over a median follow-up of 5.5 years there were 17,546 deaths among 149,345 patients with type 2 diabetes (mean age 59.6 years, 40% women) and 68,429 deaths among 743,907 matched controls. Short-term all-cause mortality risk (≤5 years) displayed a U-shaped relationship with BMI, with hazard ratios (HR) ranging from 0.81 (95% CI 0.75–0.88) among patients with diabetes and BMI 30-<35 kg/m^2 to 1.37 (95% CI 1.11–1.71) with BMI ≥40 kg/m^2 compared with controls after multiple adjustments. Long-term, all weight categories showed increased mortality, with a nadir at BMI 25-<30 kg/m^2 and a stepwise increase up to HR 2.00 (95% CI 1.58–2.54) among patients with BMI ≥40 kg/m^2; more pronounced in patients <65 years.

Conclusions: Our findings suggest that the apparent paradoxical findings in other studies in this area may have been affected by reverse causality. Long-term, overweight (BMI 25-<30 kg/m^2) patients with type 2 diabetes had low excess mortality risk compared to controls, whereas risk in those with BMI ≥40 kg/m^2 was substantially increased.

Type 2 diabetes is associated with an increased risk for premature death (1-3), although this may be declining when compared with earlier decades (4, 5). While obesity is a major factor contributing to type 2 diabetes (6), reports on mortality outcomes associated with weight among people with type 2 diabetes are inconsistent. Some studies have reported a linear increase in mortality with increasing body weight (7, 8), while a J- or U-shaped relationship between BMI and mortality has been reported in others (9-11), or an overall J-shaped association between BMI and mortality among most patients, but a direct linear relationship among people who have never smoked (12). An obesity paradox proposes that being overweight, as opposed to a low BMI, might be of benefit in type 2 diabetes (13-16), although more recent reports indicate that any such association could be because of reverse causation (17) or could be confounded by smoking (17-19).

In the current study, we investigated short-term and long-term mortality from cardiovascular disease (CVD) and from all causes at different BMI levels in comparison to age- and sex matched controls from the general population. We also aimed to investigate how the associations between mortality and BMI in comparison to controls are influenced by the time of follow up. The study used a large cohort of people with type 2 diabetes of recent onset (known diabetes duration ≤5 years) from the Swedish National Diabetes Register (NDR) with controls matched for age and sex from the general population. Body weight data were not available for the control group.

Research Design and Methods

Research design

The NDR is estimated to include 90% of all Swedish patients with type 2 diabetes aged ≥18 years. Patient data are continuously reported via electronic records from the clinic, or registered directly online. Thus the registry contains detailed information regarding risk

factors, medication and complications from diabetes. Each patient provides informed consent. The epidemiological definition of type 2 diabetes used was the same as in previous studies: treatment with oral hypoglycemic agents combined with diet or diet only, or individuals aged ≥40 years at the time of diagnosis, treated with oral hypoglycemic agents combined with insulin or insulin only (4, 20). Patients included in the study had at least one registration in the NDR between 1 January 1998 and 31 December 2012 and were followed until 31 December 2013. Entry point for the study was at the first time of registration. Five controls for each patient were randomly selected from the general population of Sweden, matched for age, sex, and county, generating an initial cohort of 457,473 patients and 2,287,365 controls. The ethics review board at the University of Gothenburg approved the study, with informed consent obtained from each patient in NDR.

Data available for patients and controls

To retrieve information regarding coexisting conditions and deaths, data files of patients and controls were linked to the Swedish Inpatient Register and Cause of Death Registries. The Longitudinal Database for Health Insurance and Labor Market studies provided information on individual income, country of birth, marital status, and highest educational level. Country of birth was characterized into Swedish born or foreign born while educational level was stratified into low (compulsory education or lower), intermediate (secondary), and high (university). Marital status was categorized into married/registered partner, single (never married or registered partner), widowed, or divorced. Patients and controls were followed from baseline until death or until 31 December 2013. CVD mortality was defined as any cardiovascular event as the underlying cause of death (Supplementary Table S1). To identify comorbidities such as hospitalizations for heart failure (HF), coronary heart disease (CHD), acute myocardial infarction (AMI), atrial fibrillation (AF), stroke, renal dialysis, and

transplantation, (chronic kidney disease (CKD)) from 1987 onward, codes from the International Classification of Diseases, 9th and 10th revisions, were used.

Data available for patients only

Hba1c was defined in millimoles per mole (mmol/mol) according to International Federation of Clinical Chemistry and Laboratory Medicine and converted into percent according to the Diabetes Control and Complications Trial (21). Microalbuminuria was defined as two positive tests from three samples taken within 1 year, with an albumin/creatinine ratio of 3–30 mg/mmol (~30–300 mg/g) or U-albumin of 20–200 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 calculated using data on weight and height, collected by primary care units and hospital outpatient clinics. Of the patients with diabetes 112,848 (24.7%) had no data on weight or height at the time of their registration in the NDR. Imputation of missing BMI (BMI measured using kg/m^2) was done using the first observed BMI. The imputation was restricted to values occurring within 365 days of the index date, provided that the patient did not suffer any serious event (registration of CHD, AMI, stroke, AF, or CKD) during that period. After imputation and applied exclusion criteria, 22,742 patients (13.2%) had missing data on BMI.

Selection of study group (patients and controls)

Controls were excluded if they had missing vital data, explained by the fact that matching was done by age, sex, county, and year, where some controls died before the patient's first registration in the NDR. There were 4,474 people with type 2 diabetes with a BMI <20 and they were excluded along with their matched controls, as we considered that some of them

might have had other forms of, or secondary, diabetes (patients and controls after exclusion, n=452,999 and n=2,239,239, respectively). Patients with diabetes duration >5 years before registration were excluded along with their matched controls. Duration in NDR means the time between first being diagnosed and the day of registration in the NDR. Patients with a diabetes duration >5 years before registration were excluded along with their matched controls since the majority of patients with longer duration was included early on in the registry and thus were managed in another, earlier era than our selected group of patients with shorter duration. Patients with longer duration may also contribute to a survival bias (patients and controls left after exclusion, n=256,078 and n=1,268,540, respectively). 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). To be able to perform Cox regression analyses for short- and long-term mortality risks, we additionally excluded patients and controls with zero survival time on an individual basis (patients and controls left after exclusion, n=172,087 and n=857,110, respectively). We excluded the entire matched set if the patient had missing BMI after imputation which generated the final cohort of patients and controls, n=149,345 and n=743,907, respectively. (see flow chart in Supplementary Figure S1).

Statistical analysis

Events per 1000 person-years with 95% exact (Poisson) confidence intervals were used to describe crude mortality. Cox regression was used for survival analysis. Patients were stratified into BMI categories: 20-<25, 25-<30, 30-<35, 35-<40, and ≥40 kg/m^2. To fit the Cox regression model, we studied the association between BMI and all-cause death and CVD death in terms of short-term risk for death (defined as death within ≤5 years from baseline), including the entire cohort and where patients and controls that had died during the first time-

period, or were followed less than five years due to end of study, were censored individually. In the second step, we presented the long-term mortality risk (death >5 years from baseline), where patients and controls surviving after 5 years were analyzed within a second time-period, where no reassigning of patients or controls was done (Figure 1 and 2 ,Supplementary Figures S2–S4, Supplementary tables S15-S18, S21 and S22). To further fit the Cox regression model, patients with type 2 diabetes in each BMI category were compared with their matched controls in each BMI group (controls matched for age, sex, and county). We stratified the analysis for age by five equal-sized quintiles resulting in groups of(18-50], (50-57], (57-63], (63-69] and (69- 101) years, and adjusted for years of inclusion by five equal-sized quintiles resulting in groups of (1998-2004], (2004-2007], (2007-2009], (2009-2010] and (2010-2012). As the excess risk decreases with age (4), a five year duration for a young individual is likely different compared to a five year duration for an older individual. Therefore we allowed the effect of duration to be different for different ages. This was implemented as an interaction between duration and age. The models were adjusted for sex, the interaction between duration of diabetes and age, income, education, immigrant status, marital status, and status at baseline with respect to stroke, CHD, AMI, AF, CKD, and HF (Figures 1 and 2, Supplementary Figures S2-S4, Supplementary tables S15-S18, S21 and S22). Variables were stratified into the overall hazard ratio when the assumption of proportional hazards was not fulfilled, where annual income (in Swedish crowns; SEK) was divided into four equal quartiles of SEK 1198, SEK 1198–1732, SEK 1732–2492, and SEK ≥2492. If a BMI group did not fulfill the non-proportional assumption for the long-term analysis, we censored at 12 years in a secondary analysis; however, with no significant change in HR, accordingly, we considered these deviations from non-proportionality as acceptable. We performed sub-group analyses by dividing the cohort into ≤65 years of age and >65 years of age (Figures 1 and 2) and by sex (Supplementary Figures S2 and S3). We

further examined the association between BMI and all-cause mortality and CVD mortality through the exclusion of patients who smoked at baseline (Supplementary Figure S4). We performed additional analyses among patients only, regarding the true difference in BMI (Supplementary tables S15-S18). To investigate any potential difference between the groups of patients with missing and non-missing BMI, we performed Cox regression among patients with missing BMI, using patients with non-missing BMI as reference (Supplementary tables S21 and S22) with crude mortality rates presented in Supplementary tables S19 and S20.

The analyses were performed with R (ver. 3.2.1; R Foundation for Statistical Programming). All tests were two-tailed and a value of 0.05 was considered statistically significant. The assumption of proportional hazards was fulfilled after stratifications.

Results

Study population

A total of 149,345 patients with type 2 diabetes and 743,907 controls were included (Table 1). Median follow-up was 5.5 years, mean age 59.5 years, and 40% were women (Supplementary Table S2). Patients with type 2 diabetes were similar to controls in terms of marital status but had lower income and education and higher baseline prevalence of HF, stroke, CHD, AMI, AF, and CKD. Among patients with type 2 diabetes, age at onset was lowest among those with the highest BMI. Systolic blood pressure, presence of albuminuria, and estimated GFR increased with higher BMI, while mean LDL and mean total cholesterol did not differ markedly between BMI categories.

Mortality

There were 17,546 deaths among patients with type 2 diabetes, of which 7,218 (41.1%) were from CVD. Corresponding figures for controls were 68,429 and 27,854 (40.7%). Crude and

adjusted mortality rates for individuals with diabetes in relation to controls are shown along with the number of events in Table 2. The overall mortality rate for patients was 19.7 (19.4–20.0) for all-cause mortality and 8.09 (7.90–8.27) for CVD mortality. The corresponding rates for controls were 15.2 (15.1–15.3) and 6.17 (6.10–6.25). Event rates, mortality rates, and person-years for Figures 1 and 2 and Supplementary Figures S2–S4 are presented in Supplementary Tables S3–S14.

Short-term mortality at 5 years or fewer from baseline

Figures 1 and 2 show Cox regression models for short-term (within 5 years) and long-term (after 5 years) all-cause and CVD mortality compared with controls by age (<65 and ≥65 years), with all models adjusted or stratified for inclusion by year, age group, duration by age, income, marital status, education, immigrant status, CHD, AMI, HF, AF, and CKD. In the short-term (<5 years) and in patients ≥65 years of age, the association between mortality and BMI was U-shaped (Figure 1), but the only patients with a significantly excess risk for mortality were those with BMI ≥40 with HR 1.37 (95% CI 1.58–2.54) in the overall cohort and 1.79 (95% CI 1.33–2.40) among those aged <65 years. With respect to death occurring within 5 years, the total group of patients and those ≥65 years of age with a BMI 25-<30, 30-<35, or 35-<40 had 19–30% lower short-term risk for death from any cause when compared with controls.

For the overall short-term all-cause and CVD mortality, the association by BMI was also U-shaped, where the majority of BMI groups had a lower risk for death compared with controls. Patients aged ≥65 years in the BMI range 20 up to <40 kg/m^2 had 20–34% lower risk for death from any cause or cardiovascular causes than controls. However, patients with a BMI ≥40 tended to have a higher risk, irrespective of age, but the only significant increase in CVD mortality was found among patients aged <65 years with a BMI ≥40 (HR 1.85, 95%

CI 1.31–2.62) (Figure 2). The reverse linear association that was found short-term, among patients <65 years of age with respect to all-cause mortality (Figure 1), was tested in Supplementary table S17, among patients only, displayed largely the same associations short-term.

Long-term mortality at more than 5 years from baseline

For mortality at more than 5 years from baseline, patients with a BMI ≥30 had increased total and CVD mortality compared with controls. The association was J-shaped and was tested among patients only in Supplementary tables S15 and S16, which displayed a significant increase in mortality from BMI 35 (all-cause mortality) and BMI 30 (CVD mortality). However, among patients aged ≥65 years, a significant excess all-cause mortality was only seen in patients with a BMI 35-<40 (HR 1.21, 95% CI 1.01–1.46) and among the very obese (BMI ≥40) (HR 1.76, 95% CI 1.29–2.40). For CVD mortality among patients aged ≥65 years, only those with a BMI ≥40 had an increased risk (HR 2.31, 95% CI 1.59–3.37) (Figures 1 and 2).

Among younger people, all BMI categories displayed an increased risk for overall and CVD death, with a J-shaped association with a nadir at BMI 25-<30. With increasing BMI, there was a stepwise increase up to a HR 2.06 (95% CI 1.41–3.01) (all-cause mortality) and HR 2.85 (95% CI 1.88–4.43) (CVD mortality) among patients with a BMI ≥40 (Figures 1 and 2). Women had a generally lower mortality compared to controls, than men with respect to both short-term and long-term mortality, with similar associations by BMI as the overall cohort (Supplementary Figures S2 and S3). The results among younger patients only displayed an increase in mortality for death from any cause and CVD causes, and with only a very marginal, or no increase at lower BMI levels (Supplementary tables S17 and S18).

In analyses restricted to non-smoking patients <65 years of age (Supplementary Figure S4), the long-term apparent increase in CVD mortality attenuated to the null among patients with a BMI 20-<25, and was not significantly different from controls with HR 1.07 (95% CI 0.72–1.58).

Missing data

We identified an increased mortality risk among those with missing BMI (22,742/172,090), more pronounced in the short-term perspective.

Conclusions

In this nationwide study of patients with type 2 diabetes of recent onset, overall short-term mortality was slightly lower than that of the general population when grouped by a range of BMI between 20 and <40 kg/m^2. Only patients with a BMI ≥40 showed a significantly excess risk. Long-term risk for patients who survived 5 years after baseline varied by age, such that among individuals aged ≥65 years only the very obese had an excess risk. All BMI categories of patients aged <65 years had higher risks compared with controls. The curve was J-shaped, with the lowest mortality risk among those who were moderately overweight. The substantially increased long-term risk in the obese does not support an alleged influence of reverse causality and, as such, are in opposition to a significant obesity paradox in diabetes.

Earlier studies have shown a U-shaped or J-shaped association between BMI and all-cause mortality among people with type 2 diabetes (9-12); however, a lower risk for mortality with increasing BMI has been reported among people with type 2 diabetes (13-15). Studies on BMI and CVD mortality among people with type 2 diabetes have reported varying results in terms of higher CVD mortality risk (14), lower risk (7), and U-shaped risk (22) in people who are overweight or obese. However, none of these studies compared the risk with

matched controls. In the current study, associations between BMI and mortality varied depending on age and duration of follow-up. A significantly higher risk for mortality among younger patients in the normal weight range was observed in both the short-term and long-term. In older patients, there was only a slight increase in the risk for mortality among patients surviving at least 5 years from baseline but no short-term increased risk.

Among the general population, younger people with a BMI <25 have the lowest mortality (23-25). Our younger (<65 years of age) cohort of patients with type 2 diabetes displayed a J-shaped long-term all-cause and CVD mortality curve. All BMI groups had long-term mortality risks higher than their matched controls, consistent with earlier studies (4, 10), even with good glycemic control (4). For BMI, the short-term mortality risk was similar or lower than that for controls over a BMI range between 25 and <40 kg/m^2. Long-term, the lowest risk for overall and CVD mortality was found among patients with a BMI 25-<30, and a substantially increased risk among the very obese. Our analyses among patients only, displayed however, a near-linear BMI-mortality risk for both death from any cause and CVD causes. These results emphasize the importance of weight control and the avoidance of obesity for younger patients over the long-term, even though the true excess risk by diabetes for obese patients compared to non-diabetic obese persons cannot be quantified, since no data exits BMI for population controls.

Among patients aged ≥65 years, all-cause and CVD mortality risks were lower or similar to that of matched controls, with the exception of long-term risk among patients with a BMI ≥35. Mortality among patients with type 2 diabetes is reported to be lower in older patients (3, 5, 10) compared to that of the general population, perhaps explaining the low short- and long-term increased mortality risks in this age group. Among patients aged ≥65, the very obese (BMI ≥40) had an approximately two-fold increase in long-term mortality risk compared with controls (all-cause and CVD).

In western Europe, obesity has increased, as for many other high-income countries, although the prevalence of obesity is lower in Sweden compared to the high-income English-speaking countries. Since obesity is associated with higher mortality risk from any cause and CVD causes, in the general population (23), the increase in obesity in recent decades will probably contribute to an increased mortality risk and the risk for CVD among our control group. Even though our study population with type 2 diabetes will have had a higher prevalence of obesity (48.3% patients had BMI 30 or above) than the general population and subsequently possibly more CVD, the generally low or lower risk compared to the general population in all age groups, could be explained by the short diabetes duration in our selected cohort. Also patients with new-onset diabetes see health care providers at regular intervals, which could optimize their treatment for e.g. hypertension; whereas management in the general Swedish population is far from optimal (27).

Among patients aged <65 with a BMI 20-<25, both short-term and long-term mortality were higher than that of the general population. A reason for the increased risk among patients with a low weight may be because of a more aggressive phenotype (11, 28), and perhaps even more so among the youngest patients. These patients were more often on insulin compared with the other groups, suggesting that this group might include a proportion of patients with latent autoimmune diabetes in adults or other forms of diabetes (28).

The group with a BMI 20-<25 was large and well-medicated at baseline, although with a higher prevalence of smoking, insulin dependency, AF, and stroke. In many (but not all), lower weight may be an example of reverse causation (17, 29). Because there was no information about these factors in the general population, they could not be adjusted for in the analyses. Given the higher risk at the lower range of BMI, subclinical illness could still be an issue and could be more in the short-term compared with the long-term risk, which we identified among patients aged <65. Current guidelines advocate maintaining a healthy

weight as an important part of diabetes care (30) and our data supports this view, although not among older patients with BMI <35.

Strengths of the study include the very large population of patients with type 2 diabetes and the availability of a non-diabetic control population matched for age and sex. There may have been some patients with diabetes among the controls, as well as a proportion with undiagnosed diabetes, but because of the very high coverage of patients with type 2 diabetes in the NDR, this would have been unlikely to influence our findings more than marginally. Our register-based study provided detailed data on cause of death, socioeconomic status, and risk factors for patients as well as for major comorbidities, which also made it possible to exclude patients and controls with cancer and dementia. Further, we had a uniquely high number of obese participants with excessive BMI, with more than 27,000 patients with a BMI ≥35. We also examined mortality risk at ≤5 years and >5 years, an important consideration given the much higher risk for reverse causality with a shorter follow-up.

This study had some limitations. There were no data on BMI or other individual risk factors among the general population. Thus we cannot draw any conclusions about the excess risk compared to controls with the same BMI. Our conclusions are strictly based on patients versus the average person with approximately BMI 26 kg/m^2 (23), in the general population without diabetes, displaying the excess risk for the type 2 diabetes and BMI combined. Conclusions from previous studies (23, 24), indicate an increased mortality with excess weight among the general population but the true excess risk from type 2 diabetes in obese subjects cannot be estimated in the present study.. Also, 22,742 patients had missing data on BMI. Although causes are unknown, baseline suggests a higher frequency of comorbidities and albuminuria among this group of patients. The increased mortality for patients with missing BMI may have caused a slight bias in the short-term perspective. Even so, we were

able to adjust our analyses with matched controls for a number of other factors such as marital status, immigration, and major diagnoses in all models comprising controls.

In conclusion, in this large population of patients with type 2 diabetes of recent onset the overall short-term excess risk associated with moderately high BMI for death from any cause or from CVD was low, except among the very obese. The association with long-term mortality was J-shaped and the mortality risk increased gradually from BMI 30. Excess all-cause mortality and CVD mortality were markedly higher among younger people, and patients with a BMI ≥40 had an approximately two- to three-fold excess risk, compared to the average non-diabetic person, irrespective of age. A BMI <25 may portend a more complex diabetes panorama, with increased mortality risk from non- CVD causes, potentially indicating reverse causality.

Our findings suggest that the apparent paradoxical findings in other studies in this area may have been affected by reverse causality and that weight management remains an important aspect of care in a large proportion of diabetes patients.

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Conflict of interest

Professor Sattar reports grants and personal fees from Boehringer Ingelheim; personal fees from Janssen, Novonordisk, and Eli Lilly; and grants from AstraZeneca, all outside the submitted work. No other potential conflicts of interest relevant for this article were reported.

Author contributions

J.E., A.Ra., A.Ro., and M.A. developed the study design and concept. J.E., A.Ra., and M.A. performed the statistical analyses. J.E. wrote the draft of the manuscript. J.E., A.Ra., M.A., L.B., M.L., A-M.S., S.G., N.S., and A.Ro. interpreted data and critically revised the manuscript. J.E. and A.Ro. are the guarantors of the presented work, for the integrity of the data, and the accuracy of the data analyses.

Figure legends

Figure 1 Adjusted hazard ratio (HR) for death from any cause by BMI group and time with age- and sex matched controls as reference

White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis was based on Cox regression and adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure, and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, All-cause mortality, HR by BMI group and time. Panel B, All-cause mortality, HR by BMI group and time (age <65 years). Panel C, All-cause mortality, HR by BMI group and time (age ≥65 years).

Figure 2 Adjusted hazard ratio (HR) for death from cardiovascular (CVD) causes by BMI group and time with age- and sex matched controls as reference

White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis was based on Cox regression and adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure, and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, CVD mortality, HR by BMI group and time. Panel B, CVD mortality, HR by BMI group and time (age <65 years). Panel C, CVD mortality, HR by BMI group and time (age ≥65 years).

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Table 1 Baseline characteristics of patients with type 2 diabetes and controls matched for age, sex, and county

	Controls	**Patients, overall**	**20 to <25**	**25 to <30**	**30 to <35**	**35 to <40**	**40 or above**	**Patients with missing BMI**
Individuals, *n*	743907	149345	20297	56943	44266	18766	9073	22742
Age and sex								
Women	297304 (40.0)	59669 (40.0)	8783 (43.3)	19467 (34.2)	17386 (39.3)	9021 (48.1)	5012 (55.2)	9755 (42.9)
Age (years)	59.5 (11.7)	59.6 (11.7)	62.4 (12.7)	61.2 (11.2)	59.0 (11.1)	56.3 (11.4)	52.8 (11.9)	60.8 (13.5)
Socioeconomic status								
Marital status, n (%)								
Divorced	122495 (16.5)	25936 (17.4)	3365 (16.6)	9720 (17.1)	7904 (17.9)	3378 (18.0)	1569 (17.3)	4120 (18.1)
Married	423314 (56.9)	81116 (54.3)	11233 (55.3)	32937 (57.8)	23876 (53.9)	9207 (49.1)	3863 (42.6)	11468 (50.4)
Single	142400 (19.1)	29923 (20.0)	3481 (17.2)	9363 (16.4)	9025 (20.4)	4899 (26.1)	3155 (34.8)	4661 (20.5)
Widowed	55658 (7.5)	12370 (8.3)	2218 (10.9)	4923 (8.6)	3461 (7.8)	1282 (6.8)	486 (5.4)	2493 (11.0)
Education, n (%)								
10 to 12 years	315184 (42.9)	66414 (45.1)	8154 (40.8)	24566 (43.8)	20018 (45.9)	9049 (49.0)	4627 (51.8)	9525 (43.1)
9 years or fewer	219552 (29.9)	54721 (37.2)	7573 (37.9)	21192 (37.7)	16434 (37.7)	6563 (35.5)	2959 (33.2)	8543 (38.7)
College or university	200203 (27.2)	26015 (17.7)	4269 (21.3)	10392 (18.5)	7149 (16.4)	2865 (15.5)	1340 (15.0)	4031 (18.2)
Income (hundreds, SEK*), median [interquartile range]	1775.0 [1214.0, 2543.0]	1543.0 [1133.0, 2232.0]	1455.0 [1083.0, 2143.0]	1576.0 [1144.0, 2277.0]	1564.0 [1148.0, 2261.0]	1538.0 [1138.0, 2193.0]	1466.0 [1106.0, 2107.0]	1437.0 [1075.0, 2119.0]
Swedish born, *n* (%)	647467 (87.0)	120880 (80.9)	16778 (82.7)	46175 (81.1)	35557 (80.3)	15092 (80.4)	7278 (80.2)	17928 (78.8)
Comorbidities								
Atrial fibrillation	20755 (2.8)	7199 (4.8)	1100 (5.4)	2689 (4.7)	2068 (4.7)	882 (4.7)	460 (5.1)	1535 (6.7)
Myocardial infarction	21229 (2.9)	10184 (6.8)	1277 (6.3)	4288 (7.5)	3156 (7.1)	1115 (5.9)	348 (3.8)	1830 (8.0)
Coronary heart disease	41799 (5.6)	18673 (12.5)	2318 (11.4)	7787 (13.7)	5776 (13.0)	2097 (11.2)	695 (7.7)	3310 (14.6)
Stroke	17687 (2.4)	5824 (3.9)	976 (4.8)	2423 (4.3)	1617 (3.7)	567 (3.0)	241 (2.7)	1456 (6.4)
Heart failure	10909 (1.5)	5570 (3.7)	724 (3.6)	1958 (3.4)	1662 (3.8)	808 (4.3)	418 (4.6)	1329 (5.8)
Renal dialysis or transplantation	778 (0.1)	206 (0.1)	60 (0.3)	90 (0.2)	40 (0.1)	9 (0.0)	7 (0.1)	56 (0.2)
Variables from NDR†								
Diabetes duration (years)	NA	1.5 (1.6)	1.6 (1.6)	1.5 (1.6)	1.4 (1.6)	1.4 (1.6)	1.3 (1.5)	1.6 (1.6)
Onset age of diabetes (years)	NA	58.1 (11.7)	60.8 (12.7)	59.6 (11.2)	57.5 (11.0)	55.0 (11.4)	51.5 (11.8)	59.2 (13.4)
HbA1c (%)/(mmol/mol)	NA	7.0 (1.4)/53.3 (15.5)	6.9 (1.5)/52.4 (16.6)	6.9 (1.4)/52.4 (15.1)	7.1 (1.4)/53.6 (15.2)	7.2 (1.4)/54.7 (15.5)	7.3 (1.5)/56.0 (16.3)	53.7 (16.1)
Total cholesterol (mmol/L)	NA	5.2 (1.1)	5.1 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.1 (1.1)	5.1 (1.2)

LDL cholesterol (mmol/L)	NA	3.0 (1.0)	3.0 (1.0)	3.1 (1.0)	3.0 (1.0)	3.0 (0.9)	3.0 (0.9)	3.0 (1.0)
Smokers, n (%)	NA	25429 (18.1)	3979 (20.8)	9419 (17.6)	7311 (17.6)	3145 (17.9)	1575 (18.6)	2816 (18.0)
Body mass index (kg/m^2)	NA	30.6 (5.5)	23.3 (1.3)	27.6 (1.4)	32.2 (1.4)	37.1 (1.4)	44.1 (4.2)	NA
Systolic blood pressure (mmHg)	NA	137.5 (17.5)	135.7 (18.7)	137.3 (17.5)	138.1 (17.2)	138.1 (16.9)	138.1 (16.9)	138.5 (18.3)
Diastolic blood pressure (mmHg)	NA	80.0 (9.8)	77.1 (9.4)	79.4 (9.5)	81.0 (9.8)	81.8 (10.0)	82.6 (10.3)	79.9 (10.0)
Albuminuria, n (%)								
Microalbuminuria	NA	13201 (11.9)	1502 (9.8)	4713 (11.1)	4136 (12.6)	1947 (14.2)	903 (13.9)	1436 (12.3)
Macroalbuminuria	NA	5709 (5.1)	665 (4.3)	2017 (4.7)	1755 (5.4)	843 (6.1)	429 (6.6)	752 (6.4)
eGFR[‡] (mL/min/1.73 m^2)	NA	86.2 (23.0)	85.2 (24.0)	84.7 (22.0)	86.3 (22.7)	88.8 (23.5)	92.3 (25.1)	85.6 (26.0)
Anti-hypertensives, *n* (%)	NA	82810 (59.0)	9077 (47.7)	30566 (57.0)	26328 (63.4)	11462 (65.0)	5377 (63.4)	11610 (57.6)
Statins, *n* (%)	NA	53836 (38.3)	6278 (33.0)	21172 (39.4)	17044 (40.9)	6682 (38.0)	2660 (31.5)	7538 (37.4)
Diabetes treatment, NDR, n (%)								
No pharmacological treatment	NA	65068 (43.6)	9185 (45.3)	25770 (45.3)	19201 (43.4)	7497 (39.9)	3415 (37.6)	9855 (43.3)
Oral agents	NA	65934 (44.1)	7053 (34.7)	24100 (42.3)	20497 (46.3)	9498 (50.6)	4786 (52.7)	9349 (41.1)
Insulin	NA	10116 (6.8)	3156 (15.5)	4129 (7.3)	1957 (4.4)	629 (3.4)	245 (2.7)	1933 (8.5)
Insulin and oral agents	NA	8227 (5.5)	903 (4.4)	2944 (5.2)	2611 (5.9)	1142 (6.1)	627 (6.9)	1605 (7.1)

[*]SEK, Swedish kronor, [†]NDR, Swedish National Diabetes Registry, [‡]eGFR, estimated glomerular filtration rate. Data for continuous variables are mean (standard deviation) with the exception of "Income", which is median [interquartile range]. Data for categorical variables are frequencies (percent). Income is given in hundred SEK.

Table 2 Crude mortality rates per 1 000 person years for all-cause mortality and cardiovascular disease (CVD) mortality among patients with type 2 diabetes and controls in the entire cohort

All-cause mortality			
Category	**Events**	**Person-years**	**Mortality rate**
Patients	17546	892672	19.7 (19.4–20.0)
Control	68429	4511754	15.2 (15.1–15.3)
Patients by BMI			
20 to <25	3499	127131	27.5 (26.6–28.5)
25 to <30	7171	349341	20.5 (20.1–21.0)
30 to <35	4479	261060	17.2 (16.7–17.7)
35 to <40	1665	106075	15.7 (15.0–16.5)
40 or above	732	49065	14.9 (13.9–16.0)
CVD mortality			
Category	**Events**	**Person-years**	**Mortality rate**
Patients	7218	892672	8.09 (7.90–8.27)
Control	27854	4511754	6.17 (6.10–6.25)
Patients by BMI			
20 to <25	1423	127131	11.2 (10.6–11.8)
25 to <30	2966	349341	8.49 (8.19–8.80)
30 to <35	1832	261060	7.02 (6.70–7.35)
35 to <40	700	106075	6.60 (6.12–7.11)
40 or above	297	49065	6.05 (5.38–6.78)

Events and person-years are numbers. Mortality rates are mean (95% CI).

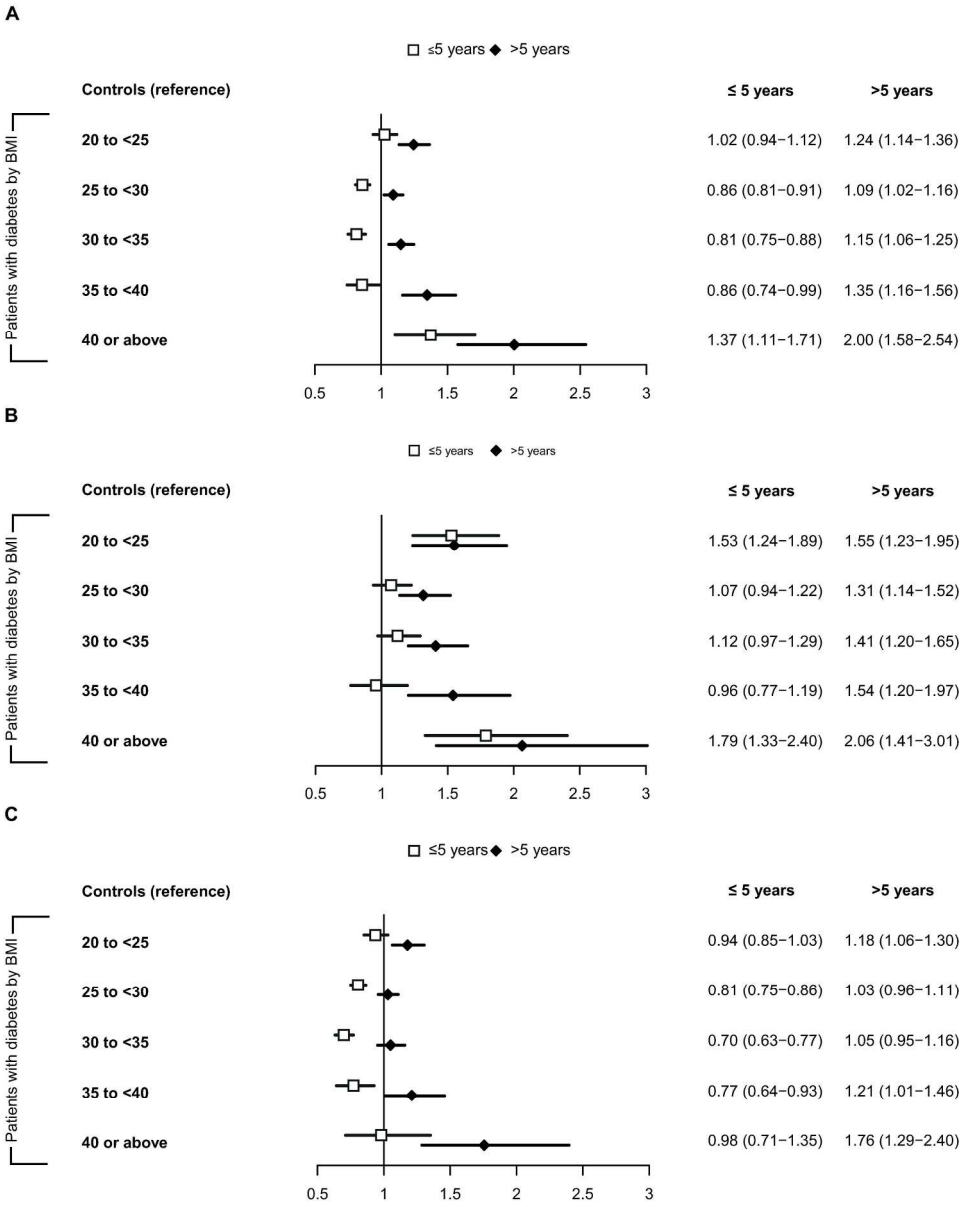

Figure 1 Adjusted hazard ratio (HR) for death from any cause by BMI group and time with age- and sex matched controls as reference

White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis was based on Cox regression and adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure, and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, All-cause mortality, HR by BMI group and time. Panel B, All-cause mortality, HR by BMI group and time (age <65 years). Panel C, All-cause mortality, HR by BMI group and time (age ≥65 years).

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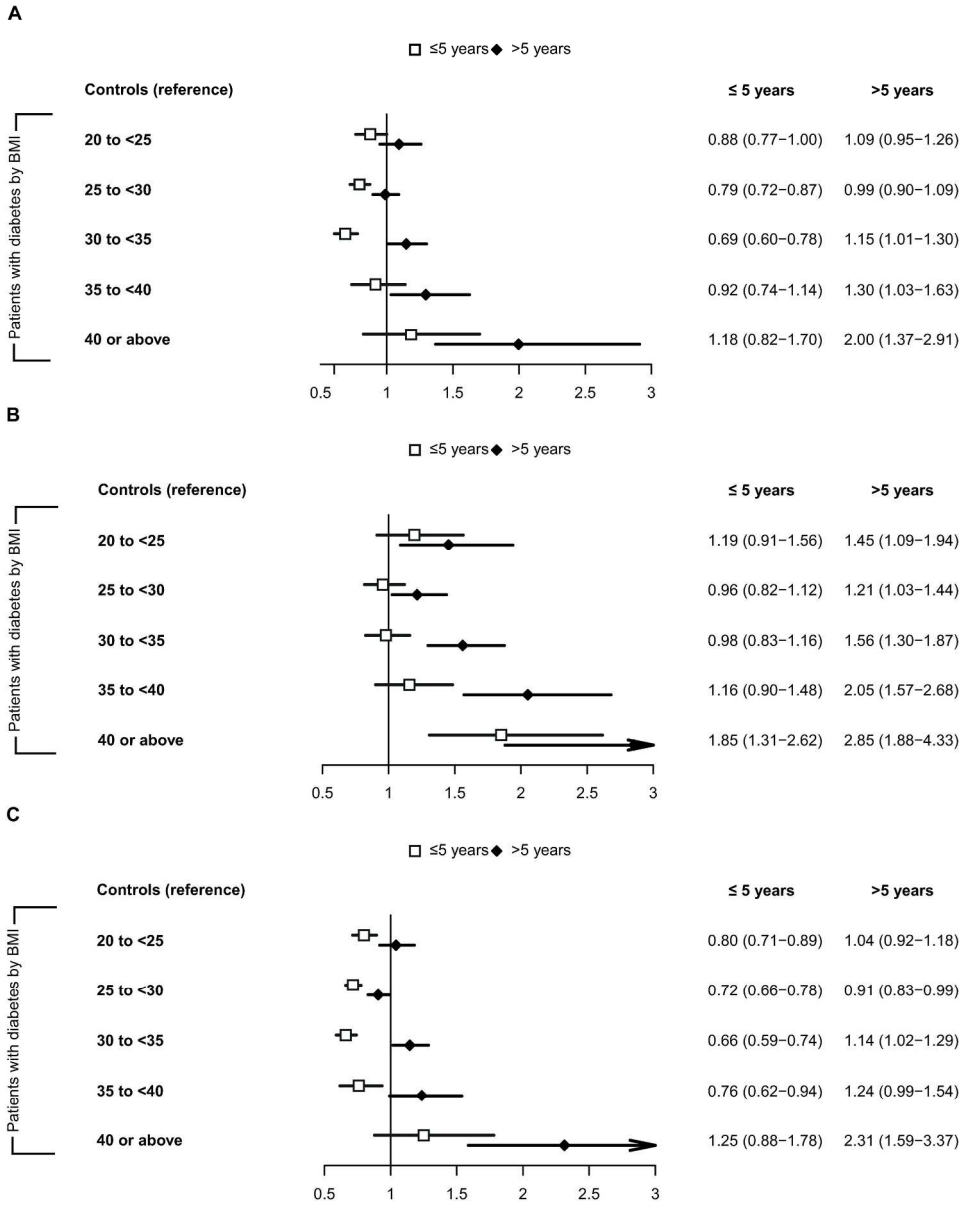

Figure 2 Adjusted hazard ratio (HR) for death from cardiovascular (CVD) causes by BMI group and time with age- and sex matched controls as reference

White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis was based on Cox regression and adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure, and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, CVD mortality, HR by BMI group and time. Panel B, CVD mortality, HR by BMI group and time (age <65 years). Panel C, CVD mortality, HR by BMI group and time (age ≥65 years).

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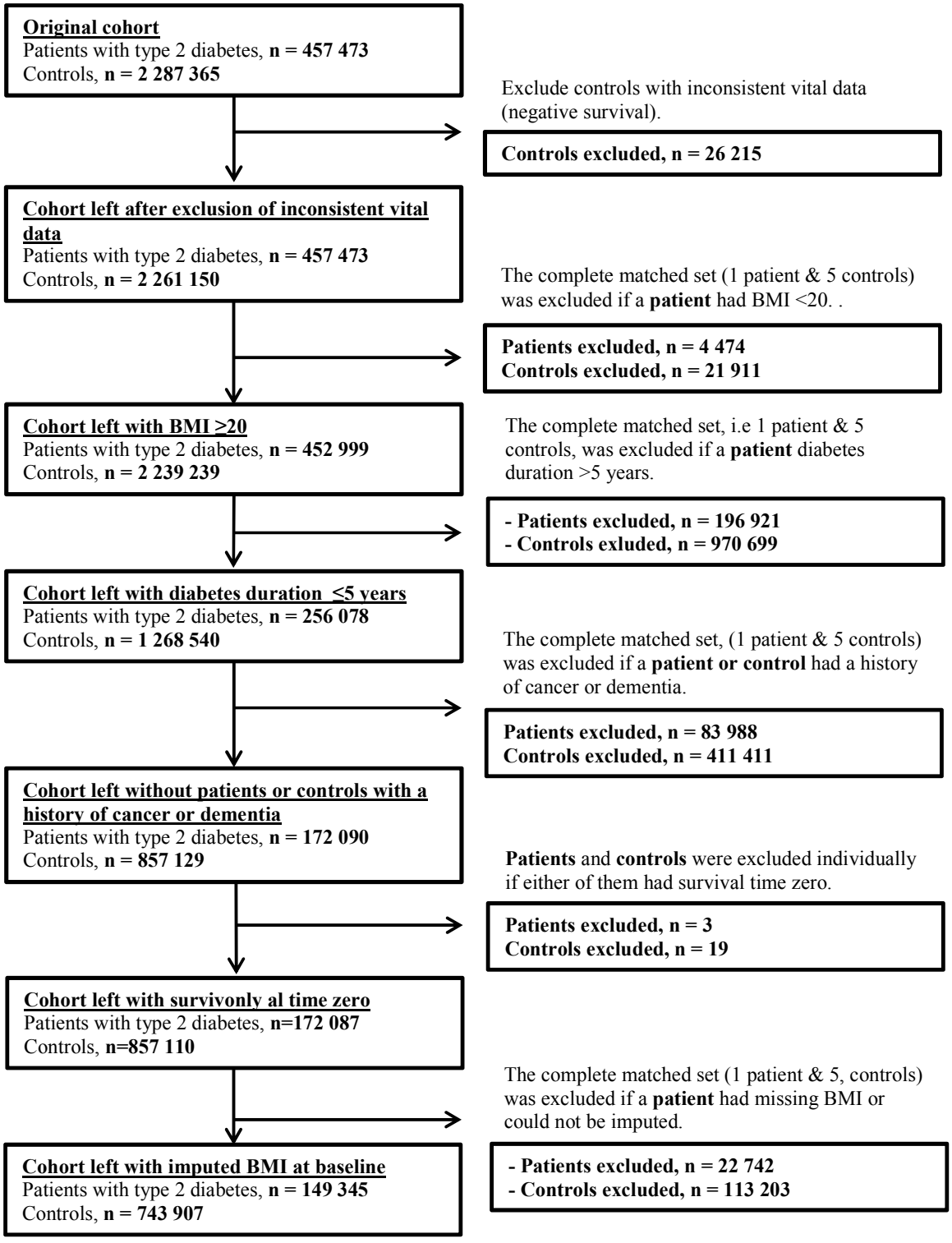
Body mass index and mortality in patients with new onset type 2 diabetes. A comparison with age- and sex matched controls from the general population

Supplementary data

SUPPLEMENTARY DATA

Supplementary Figure S1-Flow chart



Legends: Overview of the study

SUPPLEMENTARY DATA

Supplementary table S1-Descriptions of diagnoses used from the International Classification of Diseases system

Diagnosis	ICD-9	ICD-10
Coronary heart disease	410-414	I20-I25
Acute myocardial infarction	410	I21
Stroke	431, 432X, 433, 434, 436, 437X	I61, I62.9, I63, I64, I67.9
Heart failure	428	I50
Atrial fibrillation	427D	I48
Renal dialysis or transplantation	V42A, V45B, V56A, V56W	Z94.0, Z49, Z99.2
Cancer	140-208	C00-C97
Dementia	-	G30, F00-F03, F05
Cardiovascular mortality	-	I00-I99 as underlying cause of death

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

SUPPLEMENTARY DATA

Supplementary table S2-descriptives	
Median follow-up years	5.46.
Age (Mean)	59.52.
Age (SD)	11.68.
Deaths from any cause (n)	85 975
Cardiovascular deaths (n)	35 072
Heart failure (n)	37 564
Cardiac heart disease (n)	78 870
Stroke (n)	33 608

SUPPLEMENTARY DATA

Supplementary table S3 - Short term (≤5 years) and long term (>5 years) overall crude all-cause mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county

Mortality ≤ 5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	1892	84513	22.39 (21.39-23.42)
Controls	7618	422921	18.01 (17.61-18.42)
25 to <30	3677	237201	15.50 (15.00-16.01)
Controls	16577	1181646	14.03 (13.82-14.24)
30 to <35	2188	181259	12.07 (11.57-12.59)
Controls	9572	904221	10.59 (10.37-10.80)
35 to <40	811	75502	10.74 (10.01-11.51)
Controls	2971	378046	7.86 (7.58- 8.15)
40 or above	389	35892	10.84 (9.79-11.97)
Controls	903	181197	4.98 (4.66- 5.32)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	1607	42618	37.71 (35.89-39.60)
Controls	6180	222906	27.72 (27.04-28.42)
25 to <30	3494	112140	31.16 (30.13-32.21)
Controls	13653	575282	23.73 (23.34-24.13)
30 to <35	2291	79801	28.71 (27.55-29.91)
Controls	7835	413796	18.93 (18.52-19.36)
35 to <40	854	30573	27.93 (26.09-29.87)
Controls	2350	160538	14.64 (14.05-15.24)
40 or above	343	13174	26.04 (23.35-28.94)
Controls	770	71202	10.81 (10.06-11.61)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S4 - Short term (≤5 years) and long term (>5 years) crude mortality rates for patients with type 2 diabetes by BMI aged <65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	413	48029	8.60 (7.79- 9.47)
Controls	1051	242029	4.34 (4.08- 4.61)
25 to <30	982	148884	6.60 (6.19- 7.02)
Controls	3464	746187	4.64 (4.49- 4.80)
30 to <35	827	125407	6.59 (6.15- 7.06)
Controls	2704	628724	4.30 (4.14- 4.47)
35 to <40	350	57422	6.10 (5.47- 6.77)
Controls	1082	287824	3.76 (3.54- 3.99)
40 or above	227	29838	7.61 (6.65- 8.66)
Controls	408	150423	2.71 (2.46- 2.99)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	355	26836	13.23 (11.89-14.68)
Controls	997	138756	7.19 (6.75- 7.65)
25 to <30	938	73569	12.75 (11.95-13.59)
Controls	3064	376534	8.14 (7.85- 8.43)
30 to <35	814	56670	14.36 (13.39-15.39)
Controls	2211	293934	7.52 (7.21- 7.84)
35 to <40	395	23709	16.66 (15.06-18.39)
Controls	823	123401	6.67 (6.22- 7.14)
40 or above	174	11036	15.77 (13.51-18.29)
Controls	291	58279	4.99 (4.44- 5.60)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S5 - Short term (≤5 years) and long term (>5 years) crude all-cause mortality rates for patients with type 2 diabetes by BMI aged ≥65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	1479	36484	40.54 (38.50-42.66)
Controls	6567	180892	36.30 (35.43-37.19)
25 to <30	2695	88317	30.52 (29.37-31.69)
Controls	13113	435458	30.11 (29.60-30.63)
30 to <35	1361	55852	24.37 (23.09-25.70)
Controls	6868	275497	24.93 (24.34-25.53)
35 to <40	461	18080	25.50 (23.22-27.94)
Controls	1889	90222	20.94 (20.00-21.90)
40 or above	162	6053	26.76 (22.80-31.22)
Controls	495	30773	16.09 (14.70-17.57)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	1252	15782	79.33 (75.00-83.85)
Controls	5183	84150	61.59 (59.93-63.29)
25 to <30	2556	38571	66.27 (63.72-68.89)
Controls	10589	198748	53.28 (52.27-54.30)
30 to <35	1477	23131	63.85 (60.64-67.20)
Controls	5624	119862	46.92 (45.70-48.16)
35 to <40	459	6864	66.87 (60.89-73.28)
Controls	1527	37138	41.12 (39.08-43.23)
40 or above	169	2137	79.08 (67.61-91.95)
Controls	479	12924	37.06 (33.82-40.54)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S6 - Short term (≤5 years) and long term (>5 years) crude all-cause mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county among men only

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	1113	47760	23.30 (21.95-24.71)
Controls	4259	239632	17.77 (17.24-18.32)
25 to <30	2436	156269	15.59 (14.98-16.22)
Controls	10649	779290	13.67 (13.41-13.93)
30 to <35	1394	109762	12.70 (12.04-13.38)
Controls	5695	548333	10.39 (10.12-10.66)
35 to <40	474	38863	12.20 (11.12-13.35)
Controls	1572	194957	8.06 (7.67- 8.47)
40 or above	197	15927	12.37 (10.70-14.22)
Controls	411	80525	5.10 (4.62- 5.62)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	854	23829	35.84 (33.48-38.33)
Controls	3330	124843	26.67 (25.78-27.60)
25 to <30	2232	73702	30.28 (29.04-31.57)
Controls	8539	379939	22.47 (22.00-22.96)
30 to <35	1362	47189	28.86 (27.35-30.44)
Controls	4477	247220	18.11 (17.58-18.65)
35 to <40	440	15068	29.20 (26.54-32.06)
Controls	1136	80218	14.16 (13.35-15.01)
40 or above	166	5594	29.67 (25.33-34.55)
Controls	322	30837	10.44 (9.33-11.65)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S7 - Short term (≤5 years) and long term (>5 years) crude all-cause mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county among women only

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	779	36753	21.20 (19.73-22.74)
Controls	3359	183288	18.33 (17.71-18.96)
25 to <30	1241	80932	15.33 (14.49-16.21)
Controls	5928	402356	14.73 (14.36-15.11)
30 to <35	794	71497	11.11 (10.35-11.91)
Controls	3877	355888	10.89 (10.55-11.24)
35 to <40	337	36639	9.20 (8.24-10.23)
Controls	1399	183089	7.64 (7.25- 8.05)
40 or above	192	19965	9.62 (8.30-11.08)
Controls	492	100672	4.89 (4.46- 5.34)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	753	18789	40.08 (37.26-43.04)
Controls	2850	98062	29.06 (28.01-30.15)
25 to <30	1262	38438	32.83 (31.05-34.69)
Controls	5114	195343	26.18 (25.47-26.91)
30 to <35	929	32612	28.49 (26.68-30.38)
Controls	3358	166577	20.16 (19.48-20.85)
35 to <40	414	15504	26.70 (24.19-29.40)
Controls	1214	80321	15.11 (14.28-15.99)
40 or above	177	7580	23.35 (20.04-27.06)
Controls	448	40365	11.10 (10.09-12.18)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S8 - Short term (≤5 years) and long term (>5 years) crude all-cause mortality rates for non-smoking patients with type 2 diabetes by BMI aged <65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortailty rate**
20 to <25	201	32927	6.10 (5.29- 7.01)
Controls	715	165071	4.33 (4.02- 4.66)
25 to <30	560	109810	5.10 (4.69- 5.54)
Controls	2578	548344	4.70 (4.52- 4.89)
30 to <35	488	92712	5.26 (4.81- 5.75)
Controls	2016	463523	4.35 (4.16- 4.54)
35 to <40	211	42458	4.97 (4.32- 5.69)
Controls	804	212261	3.79 (3.53- 4.06)
40 or above	140	22082	6.34 (5.33- 7.48)
Controls	326	110941	2.94 (2.63- 3.28)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortailty rate**
20 to <25	170	18902	8.99 (7.69-10.45)
Controls	690	95367	7.24 (6.71- 7.80)
25 to <30	591	55461	10.66 (9.81-11.55)
Controls	2331	279758	8.33 (8.00- 8.68)
30 to <35	515	42496	12.12 (11.09-13.21)
Controls	1675	217109	7.72 (7.35- 8.09)
35 to <40	263	17972	14.63 (12.92-16.51)
Controls	624	92349	6.76 (6.24- 7.31)
40 or above	117	8331	14.04 (11.61-16.83)
Controls	218	43487	5.01 (4.37- 5.72)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S9 - Short term (≤5 years) and long term (>5 years) overall crude CVD mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county

Mortality ≤5			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	776	84513	9.18 (8.55- 9.85)
Controls	3393	422921	8.02 (7.76- 8.30)
25 to <30	1522	237201	6.42 (6.10- 6.75)
Controls	6945	1181646	5.88 (5.74- 6.02)
30 to <35	858	181259	4.73 (4.42- 5.06)
Controls	3865	904221	4.27 (4.14- 4.41)
35 to <40	330	75502	4.37 (3.91- 4.87)
Controls	1062	378046	2.81 (2.64- 2.98)
40 or above	152	35892	4.23 (3.59- 4.96)
Controls	314	181197	1.73 (1.55- 1.94)
Mortality >5			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	647	42618	15.18 (14.03-16.40)
Controls	2603	222906	11.68 (11.23-12.13)
25 to <30	1444	112140	12.88 (12.22-13.56)
Controls	5571	575282	9.68 (9.43- 9.94)
30 to <35	974	79801	12.21 (11.45-13.00)
Controls	2986	413796	7.22 (6.96- 7.48)
35 to <40	370	30573	12.10 (10.90-13.40)
Controls	865	160538	5.39 (5.03- 5.76)
40 or above	145	13174	11.01 (9.29-12.95)
Controls	250	71202	3.51 (3.09- 3.97)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

SUPPLEMENTARY DATA

Supplementary table S10 - Short term (≤5 years) and long term (>5 years) crude CVD mortality rates for patients with type 2 diabetes by BMI aged <65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	103	48029	2.14 (1.75-2.60)
Controls	319	242029	1.32 (1.18-1.47)
25 to <30	309	148884	2.08 (1.85-2.32)
Controls	1079	746187	1.45 (1.36-1.53)
30 to <35	266	125407	2.12 (1.87-2.39)
Controls	869	628724	1.38 (1.29-1.48)
35 to <40	131	57422	2.28 (1.91-2.71)
Controls	318	287824	1.10 (0.99-1.23)
40 or above	82	29838	2.75 (2.19-3.41)
Controls	119	150423	0.79 (0.66-0.95)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	100	26836	3.73 (3.03-4.53)
Controls	286	138756	2.06 (1.83-2.31)
25 to <30	323	73569	4.39 (3.92-4.90)
Controls	892	376534	2.37 (2.22-2.53)
30 to <35	281	56670	4.96 (4.40-5.57)
Controls	634	293934	2.16 (1.99-2.33)
35 to <40	151	23709	6.37 (5.39-7.47)
Controls	234	123401	1.90 (1.66-2.16)
40 or above	73	11036	6.61 (5.18-8.32)
Controls	68	58279	1.17 (0.91-1.48)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S11 - Short term (≤5 years) and long term (>5 years) crude CVD mortality rates for patients with type 2 diabetes by BMI aged ≥65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	673	36484	18.45 (17.08-19.89)
Controls	3074	180892	16.99 (16.40-17.61)
25 to <30	1213	88317	13.73 (12.97-14.53)
Controls	5866	435458	13.47 (13.13-13.82)
30 to <35	592	55852	10.60 (9.76-11.49)
Controls	2996	275497	10.87 (10.49-11.27)
35 to <40	199	18080	11.01 (9.53-12.65)
Controls	744	90222	8.25 (7.66- 8.86)
40 or above	70	6053	11.56 (9.02-14.61)
Controls	195	30773	6.34 (5.48- 7.29)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	547	15782	34.66 (31.82-37.69)
Controls	2317	84150	27.53 (26.42-28.68)
25 to <30	1121	38571	29.06 (27.39-30.82)
Controls	4679	198748	23.54 (22.87-24.23)
30 to <35	693	23131	29.96 (27.77-32.28)
Controls	2352	119862	19.62 (18.84-20.43)
35 to <40	219	6864	31.91 (27.82-36.42)
Controls	631	37138	16.99 (15.69-18.37)
40 or above	72	2137	33.69 (26.36-42.43)
Controls	182	12924	14.08 (12.11-16.28)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S12 - Short term (≤5 years) and long term (>5 years) crude CVD mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county among men only

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	460	47760	9.63 (8.77-10.55)
Controls	1896	239632	7.91 (7.56- 8.28)
25 to <30	1014	156269	6.49 (6.10- 6.90)
Controls	4414	779290	5.66 (5.50- 5.83)
30 to <35	557	109762	5.07 (4.66- 5.51)
Controls	2326	548333	4.24 (4.07- 4.42)
35 to <40	200	38863	5.15 (4.46- 5.91)
Controls	559	194957	2.87 (2.63- 3.12)
40 or above	85	15927	5.34 (4.26- 6.60)
Controls	164	80525	2.04 (1.74- 2.37)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	340	23829	14.27 (12.79-15.87)
Controls	1369	124843	10.97 (10.39-11.56)
25 to <30	909	73702	12.33 (11.54-13.16)
Controls	3405	379939	8.96 (8.66- 9.27)
30 to <35	575	47189	12.19 (11.21-13.22)
Controls	1678	247220	6.79 (6.47- 7.12)
35 to <40	196	15068	13.01 (11.25-14.96)
Controls	412	80218	5.14 (4.65- 5.66)
40 or above	74	5594	13.23 (10.39-16.61)
Controls	102	30837	3.31 (2.70- 4.02)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S13 - Short term (≤5 years) and long term (>5 years) crude CVD mortality rates for patients with type 2 diabetes by BMI and controls matched to BMI group by age, sex and county among women only

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	316	36753	8.60 (7.68- 9.60)
Controls	1497	183288	8.17 (7.76- 8.59)
25 to <30	508	80932	6.28 (5.74- 6.85)
Controls	2531	402356	6.29 (6.05- 6.54)
30 to <35	301	71497	4.21 (3.75- 4.71)
Controls	1539	355888	4.32 (4.11- 4.55)
35 to <40	130	36639	3.55 (2.96- 4.21)
Controls	503	183089	2.75 (2.51- 3.00)
40 or above	67	19965	3.36 (2.60- 4.26)
Controls	150	100672	1.49 (1.26- 1.75)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortality rate**
20 to <25	307	18789	16.34 (14.56-18.27)
Controls	1234	98062	12.58 (11.89-13.31)
25 to <30	535	38438	13.92 (12.76-15.15)
Controls	2166	195343	11.09 (10.63-11.57)
30 to <35	399	32612	12.23 (11.06-13.50)
Controls	1308	166577	7.85 (7.43- 8.29)
35 to <40	174	15504	11.22 (9.62-13.02)
Controls	453	80321	5.64 (5.13- 6.18)
40 or above	71	7580	9.37 (7.32-11.81)
Controls	148	40365	3.67 (3.10- 4.31)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S14 - Short term (≤5 years) and long term (>5 years) crude CVD mortality rates for non-smoking patients with type 2 diabetes by BMI aged <65 years of age and controls matched to BMI group by age, sex and county

Mortality ≤5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortailty rate**
20 to <25	54	32927	1.64 (1.23-2.14)
Controls	210	165071	1.27 (1.11-1.46)
25 to <30	159	109810	1.45 (1.23-1.69)
Controls	804	548344	1.47 (1.37-1.57)
30 to <35	151	92712	1.63 (1.38-1.91)
Controls	652	463523	1.41 (1.30-1.52)
35 to <40	74	42458	1.74 (1.37-2.19)
Controls	229	212261	1.08 (0.94-1.23)
40 or above	53	22082	2.40 (1.80-3.14)
Controls	98	110941	0.88 (0.72-1.08)
Mortality >5 years			
Patients by BMI and matched controls	**Events**	**Person years**	**Mortailty rate**
20 to <25	50	18902	2.65 (1.96-3.49)
Controls	212	95367	2.22 (1.93-2.54)
25 to <30	205	55461	3.70 (3.21-4.24)
Controls	671	279758	2.40 (2.22-2.59)
30 to <35	170	42496	4.00 (3.42-4.65)
Controls	476	217109	2.19 (2.00-2.40)
35 to <40	100	17972	5.56 (4.53-6.77)
Controls	174	92349	1.88 (1.61-2.19)
40 or above	49	8331	5.88 (4.35-7.78)
Controls	50	43487	1.15 (0.85-1.52)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S15 - Adjusted hazard ratio (HR) for death from any cause by BMI group and time, among patients only. Patients with BMI 25 to <30 used as reference.

Mortality ≤5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.31	1.21	1.41
25 to <30 (Ref)	1	1	1
30 to <35	0.91	1.84	0.98
35 to <40	0.93	0.83	1.03
40 and above	1.14	0.99	1.33
Mortality >5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.17	1.09	1.27
25 to <30 (Ref)	1	1	1
30 to <35	1.04	0.97	1.11
35 to <40	1.13	1.02	1.25
40 and above	1.34	1.15	1.55

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

Supplementary table S16 - Adjusted hazard ratio (HR) for death from CVD causes by BMI group and time, among patients only. Patients with BMI 25 to <30 used as reference.

Mortality ≤5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.25	1.14	1.36
25 to <30 (Ref)	1	1	1
30 to <35	0.87	0.80	0.94
35 to <40	0.95	0.84	1.08
40 and above	1.17	0.98	1.39
Mortality >5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.13	1.03	1.24
25 to <30 (Ref)	1	1	1
30 to <35	1.10	1.01	1.19
35 to <40	1.36	1.21	1.53
40 and above	1.59	1.33	1.89

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

Supplementary data

Supplementary table S17 - Adjusted hazard ratio (HR) for death from any cause by BMI group and time, among patients only aged <65 years. Patients with BMI 25 to <30 used as reference.

Mortality ≤5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.41	1.26	1.59
25 to <30 (Ref)	1	1	1
30 to <35	1.02	0.93	1.12
35 to <40	1.01	0.89	1.14
40 and above	1.37	1.18	1.59
Mortality >5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.13	1.00	1.28
25 to <30 (Ref)	1	1	1
30 to <35	1.15	1.04	1.26
35 to <40	1.41	1.26	1.59
40 and above	1.49	1.26	1.76

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

Supplementary table S18 - Adjusted hazard ratio (HR) for death from CVD causes by BMI group and time, among patients only aged <65 years. Patients with BMI 25 to <30 used as reference.

Mortality ≤5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	1.14	0.91	1.43
25 to <30 (Ref)	1	1	1
30 to <35	1.03	0.87	1.21
35 to <40	1.19	0.97	1.47
40 and above	1.58	1.23	2.03
Mortality >5 years			
BMI group	**HR estimate**	**Lower CI 95%**	**Upper CI 95%**
20 to <25	0.98	0.78	1.22
25 to <30 (Ref)	1	1	1
30 to <35	1.14	0.97	1.34
35 to <40	1.55	1.27	1.87
40 and above	1.86	1.44	2.41

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

Supplementary data

Supplementary table S19 - Crude mortality rates for all-cause mortality among patients with missing/non-missing BMI

Group	Missing/non-missing BMI among patients	Mortality by time period	Events	Person years	Mortality rate/1000 person years
Overall	Missing BMI	≤5 years	2210	91302	24.21 (23.21-25.24)
	Non-missing BMI	≤5 years	8957	614367	14.58 (14.28-14.88)
	Missing BMI	>5 years	1632	41755	39.09 (37.21-41.03)
	Non-missing BMI	>5 years	8589	278305	30.86 (30.21-31.52)
<65	Missing BMI	≤5 years	539	56618	9.52 (8.73-10.36)
	Non-missing BMI	≤5 years	2799	409580	6.83 (6.58- 7.09)
	Missing BMI	>5 years	466	27609	16.88 (15.38-18.48)
	Non-missing BMI	>5 years	2676	191821	13.95 (13.43-14.49)
>65	Missing BMI	≤5 years	1671	34684	48.18 (45.90-50.54)
	Non-missing BMI	≤5 years	6158	204787	30.07 (29.32-30.83)
	Missing BMI	>5 years	1166	14146	82.43 (77.76-87.30)
	Non-missing BMI	>5 years	5913	86484	68.37 (66.64-70.14)
Men	Missing BMI	≤5 years	1207	52318	23.07 (21.79-24.41)
	Non-missing BMI	≤5 years	5614	368581	15.23 (14.84-15.64)
	Missing BMI	>5 years	851	23819	35.73 (33.37-38.21)
	Non-missing BMI	>5 years	5054	165382	30.56 (29.72-31.41)
Women	Missing BMI	≤5 years	1003	38984	25.73 (24.16-27.37)
	Non-missing BMI	≤5 years	3343	245786	13.60 (13.14-14.07)
	Missing BMI	>5 years	781	17936	43.54 (40.54-46.71)
	Non-missing BMI	>5 years	3535	112923	31.30 (30.28-32.35)
Non-smokers	Missing BMI	≤5 years	255	29212	8.73 (7.69- 9.87)
	Non-missing BMI	≤5 years	1600	299990	5.33 (5.08- 5.60)
	Missing BMI	>5 years	304	17202	17.67 (15.74-19.77)
	Non-missing BMI	>5 years	1656	143163	11.57 (11.02-12.14)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S20 - Crude mortality rates for CVD mortality among patients with missing/non-missing BMI

Group	Missing/non-missing BMI	Mortality by time period	Events	Person years	Mortality rate/1000 person years
Overall	Missing BMI	≤5 years	1028	91302	11.26 (10.58-11.97)
	BMI measured	≤5 years	3638	614367	5.92 (5.73- 6.12)
	Missing BMI	>5 years	695	41755	16.64 (15.43-17.93)
	BMI measured	>5 years	3580	278305	12.86 (12.45-13.29)
<65	Missing BMI	≤5 years	200	56618	3.53 (3.06-4.06)
	BMI measured	≤5 years	891	409580	2.18 (2.03-2.32)
	Missing BMI	>5 years	161	27609	5.83 (4.97-6.81)
	BMI measured	>5 years	928	191821	4.84 (4.53-5.16)
>65	Missing BMI	≤5 years	828	34684	23.87 (22.27-25.56)
	BMI measured	≤5 years	2747	204787	13.41 (12.92-13.93)
	Missing BMI	>5 years	534	14146	37.75 (34.61-41.09)
	BMI measured	>5 years	2652	86484	30.66 (29.51-31.85)
Men	Missing BMI	≤5 years	555	52318	10.61 (9.74-11.53)
	BMI measured	≤5 years	2316	368581	6.28 (6.03- 6.54)
	Missing BMI	>5 years	370	23819	15.53 (13.99-17.20)
	BMI measured	>5 years	2094	165382	12.66 (12.13-13.22)
Women	Missing BMI	≤5 years	473	38984	12.13 (11.06-13.28)
	BMI measured	≤5 years	1322	245786	5.38 (5.09- 5.68)
	Missing BMI	>5 years	325	17936	18.12 (16.20-20.20)
	BMI measured	>5 years	1486	112923	13.16 (12.50-13.85)
Non-smokers	Missing BMI	≤5 years	96	29212	3.29 (2.66-4.01)
	BMI measured	≤5 years	106	17202	6.16 (5.05-7.45)
	Missing BMI	>5 years	491	299990	1.64 (1.50-1.79)
	BMI measured	>5 years	574	143163	4.01 (3.69-4.35)

Legends: Events and person years are presented as numbers. Incidence rate is presented as mean (CI 95%)

Supplementary data

Supplementary table S21 - Fully adjusted hazard ratio (HR) for death from any cause by BMI group and time, among patients only with missing BMI. Patients with non-missing BMI used as reference.

Group	Mortality by time period	HR estimate	Lower CI 95%	Upper CI 95%
Overall	≤5 years	1.41	1.32	1.50
	>5 years	1.14	1.06	1.22
<65 years	≤5 years	1.32	1.20	1.44
	>5 years	1.16	1.05	1.29
≥65 years	≤5 years	1.44	1.34	1.55
	>5 years	1.14	1.05	1.23
Men	≤5 years	1.30	1.18	1.42
	>5 years	1.06	0.95	1.17
Women	≤5 years	1.48	1.38	1.59
	>5 years	1.17	1.08	1.27
Non-smokers	≤5 years	1.45	1.27	1.66
	>5 years	1.39	1.23	1.57

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

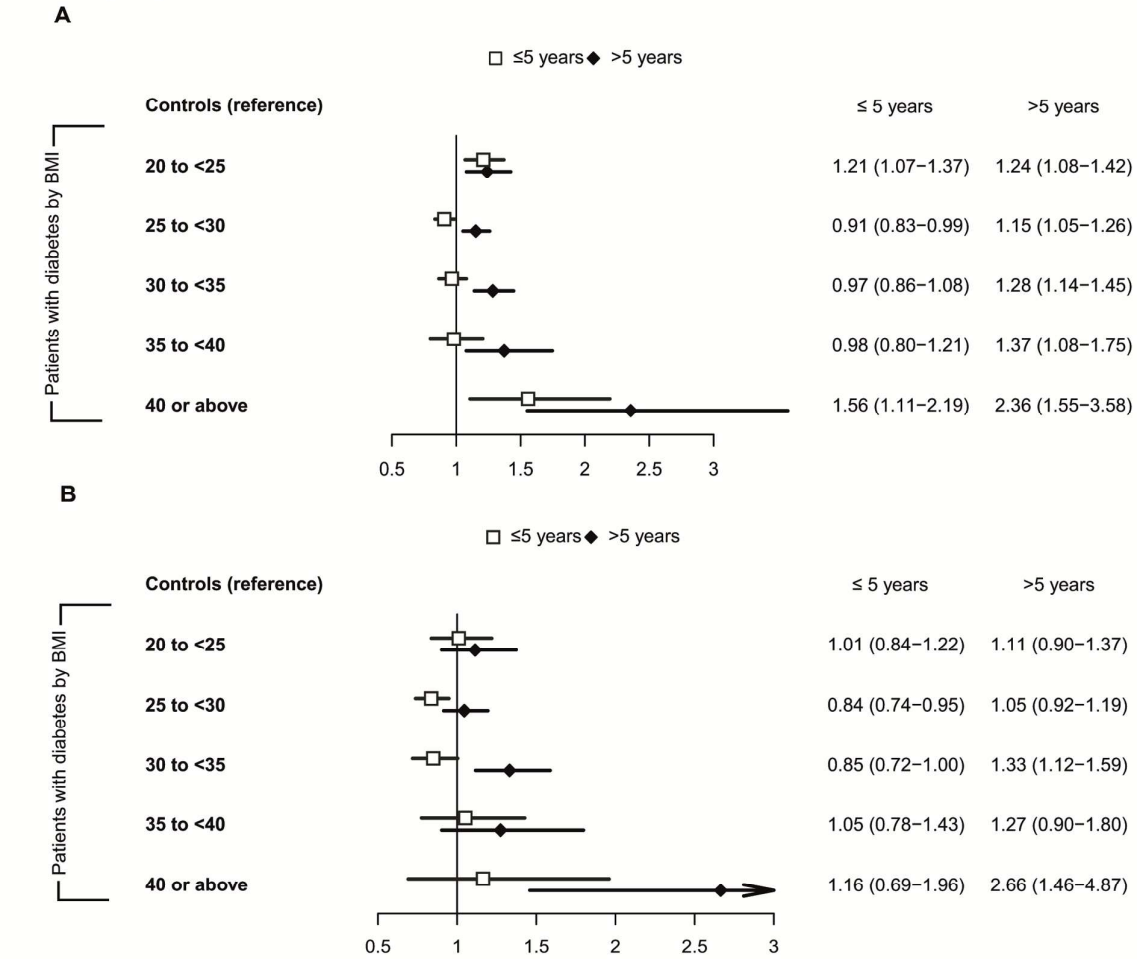
Supplementary table S22 – Fully adjusted hazard ratio (HR) for death from CVD causes by BMI group and time, among patients only with missing BMI. Patients with non-missing BMI used as reference.

Group	Mortality by time period	HR estimate	Lower CI 95%	Upper CI 95%
Overall	≤5 years	1.47	1.37	1.58
	>5 years	1.07	0.98	1.16
<65 years	≤5 years	1.31	1.03	1.65
	>5 years	1.10	0.86	1.40
≥65 years	≤5 years	1.49	1.37	1.61
	>5 years	1.04	0.94	1.14
Men	≤5 years	1.39	1.27	1.53
	>5 years	1.04	0.93	1.16
Women	≤5 years	1.61	1.44	1.80
	>5 years	1.10	0.97	1.25
Non-smokers	≤5 years	1.64	1.31	2.07
	>5 years	1.41	1.14	1.74

Legends: The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio.

SUPPLEMENTARY DATA

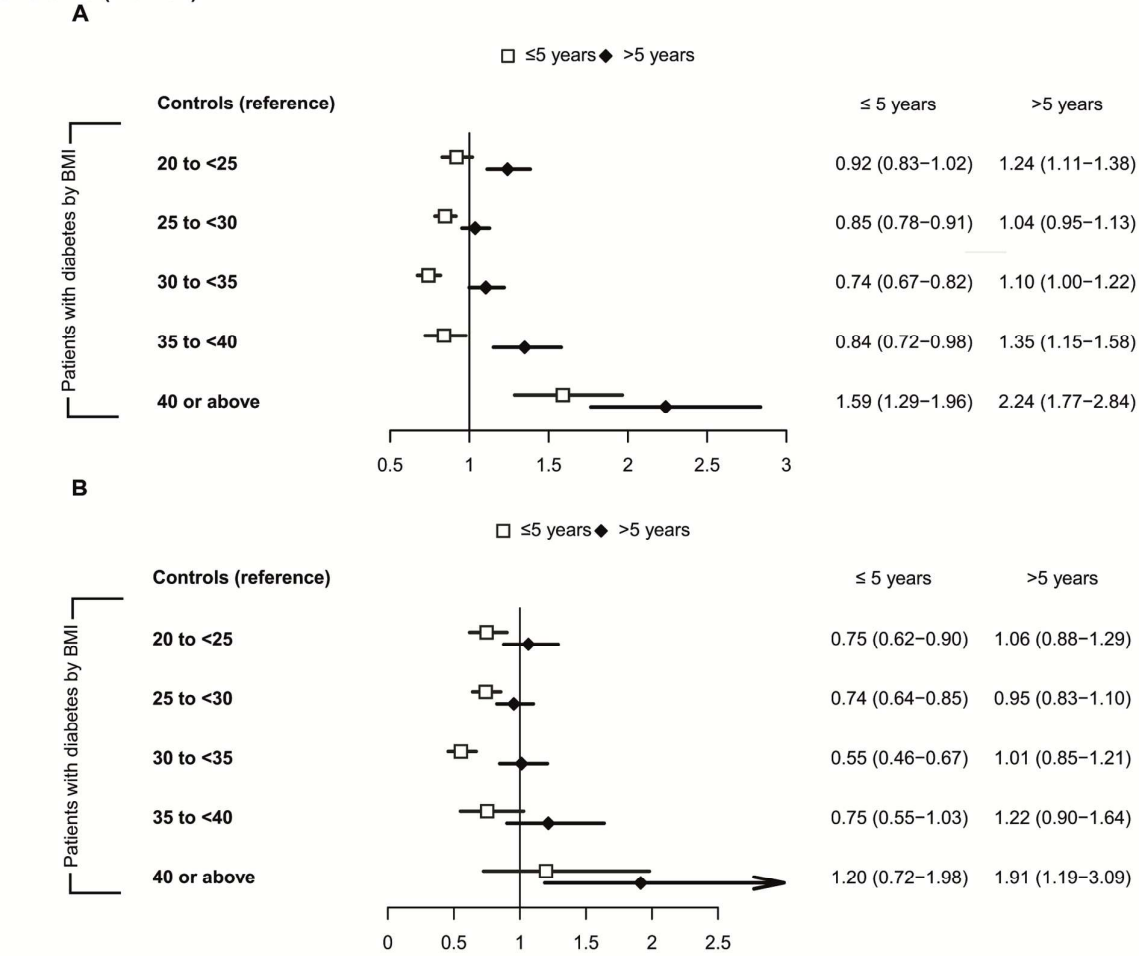
Supplementary figure S2 - hazard ratio (HR) for death from any cause and CVD causes by BMI group and time (men)



Legends: White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis based on cox regression was adjusted for age group, year of inclusion, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, All-cause mortality, HR by BMI group and time (men only). Panel B, CVD mortality, HR by BMI group and time (men only).

SUPPLEMENTARY DATA

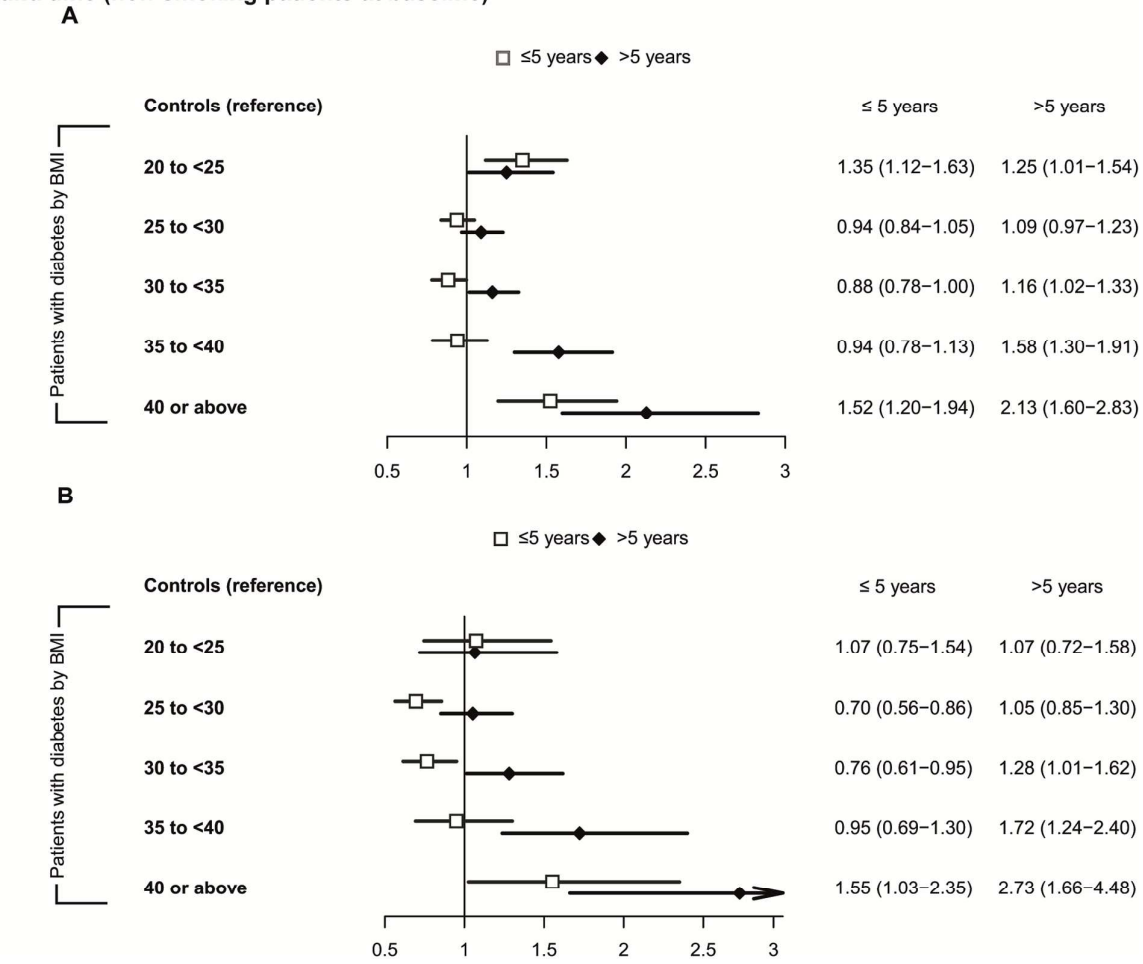
Supplementary figure S3 - hazard ratio (HR) for death from any cause and CVD causes by BMI group and time (women)



Legends: White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis based on cox regression was adjusted for age group, year of inclusion, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A, All-cause mortality, HR by BMI group and time (women only). Panel B, CVD mortality, HR by BMI group and time (women only).

SUPPLEMENTARY DATA

Supplementary figure S4 - hazard ratio (HR) for death from any cause and CVD causes by BMI group and time (non-smoking patients at baseline)



Legends: White squares = mortality ≤5 years; black diamonds = mortality >5 years. The analysis based on cox regression was adjusted for age group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and chronic kidney disease. Variables that were non-proportional were adjusted for by stratification into the overall hazard ratio. Panel A (All-cause mortality, HR by BMI group and time (age <65 years, non-smoking patients). Panel B CVD mortality, HR by BMI group and time (age <65 years, non-smoking patients).