BMI and Mortality in Patients With New-Onset Type 2 Diabetes: A Comparison With Age- and Sex-Matched Control Subjects From the General Population

Jon Edqvist,[1,2] Araz Rawshani,[1] Martin Adiels,[3] Lena Björck,[1,2] Marcus Lind,[1,4] Ann-Marie Svensson,[5] Sofia Gudbjörnsdottir,[5] Naveed Sattar,[6] and Annika Rosengren[1,2]

Diabetes Care 2018;41:485–493 | https://doi.org/10.2337/dc17-1309

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 Register (NDR) between 1998 and 2012 and five age- and sex-matched control subjects 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 control subjects. Short-term all-cause mortality risk (≤5 years) displayed a U-shaped relationship with BMI, with hazard ratios (HRs) ranging from 0.81 (95% CI 0.75–0.88) among patients with diabetes and BMI 30 to <35 kg/m^2 to 1.37 (95% CI 1.11–1.71) with BMI ≥40 kg/m^2 compared with control subjects after multiple adjustments. Long-term, all weight categories showed increased mortality, with a nadir at BMI 25 to <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, that was more pronounced in patients <65 years old.

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 to <30 kg/m^2) patients with type 2 diabetes had low excess mortality risk compared with control subjects, 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 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

[1]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[2]Sahlgrenska University Hospital/Östra, Gothenburg, Sweden
[3]Health Metrics Unit, Sahlgrenska Academy, Gothenburg, Sweden
[4]NU Hospital Organisation, Uddevalla, Sweden
[5]Swedish National Diabetes Register, Centre of Registers, Gothenburg, Sweden
[6]BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.

Corresponding author: Jon Edqvist, jon.edqvist@gu.se.

Received 30 June 2017 and accepted 4 December 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1309/-/DC1.

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 with age- and sex matched control subjects from the general population. We also aimed to investigate how the associations between mortality and BMI in comparison with control subjects 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 control subjects 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 and 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. The entry point for the study was at the first time of registration. Five control subjects 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 control subjects. 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 Control Subjects

For retrieval of information regarding coexisting conditions and deaths, data files of patients and control subjects 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 as Swedish born or foreign born, while educational level was stratified into categories of low (compulsory education or lower), intermediate (secondary), and high (university). Marital status was categorized as married/registered partner, single (never married or registered partner), widowed, or divorced. Patients and control subjects 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 1). For identification of 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 ICD-9 and ICD-10 were used.

Data Available for Patients Only

Hba_{1c} was defined in millimoles per mole according to the International Federation of Clinical Chemistry and Laboratory Medicine and converted into percent according to the methodology of the Diabetes Control and Complications Trial (DCCT) (21). Microalbuminuria was defined as two positive tests from three samples taken within 1 year, with an albumin-to-creatinine ratio of 3–30 mg/mmol (~30–300 mg/g) or urinary albumin of 20–200 μg/min (20–300 mg/L), and macroalbuminuria as albumin-to-creatinine ratio >30 mg/mmol (approximately >300 mg/g) or urinary 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 registration in the NDR. Imputation of missing BMI (BMI measured weight in kilogram divided by the square of height in meters) 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 Control Subjects)

Control subjects were excluded if they had missing vital data, explained by the fact that matching was done by age, sex, county, and year, where some control subjects died before the patient's first registration in the NDR. There were 4,474 people with type 2 diabetes with a BMI <20 kg/m^2, and they were excluded along with their matched control subjects, as we considered that some of them might have had other forms of, or secondary, diabetes (patients and control subjects 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 control subjects. 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 control subjects, since the majority of patients with longer duration were 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 control subjects left after exclusion, n = 256,078 and n = 1,268,540, respectively). Patients and control subjects were excluded along with their matched set if there was a history of cancer or dementia at baseline (patients and control subjects 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 control subjects with zero survival time on an individual basis (patients and control subjects 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 control subjects, n = 149,345 and n = 743,907, respectively. (See flowchart in Supplementary Fig. 1).

Statistical Analysis

Events per 1,000 person-years with 95% exact (Poisson) CIs were used to describe crude mortality. Cox regression was used for survival analysis. Patients were stratified into BMI categories: 20 to <25, 25 to <30, 30 to <35, 35 to <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 control subjects that had died during the first time period, or were followed <5 years owing 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 control subjects surviving after 5 years were analyzed within a second time period, where no reassigning of patients or control subjects was done (Figs. 1 and 2, Supplementary Figs. 2–4, and Supplementary Tables 15–18, 21, and 22). To further fit the Cox regression model, we compared patients with type 2 diabetes in each BMI category with their matched control subjects in each BMI group (control subjects matched for age, sex, and county). We stratified the analysis for age by five equal-sized quintiles, resulting in age-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 5-year duration for a young individual is likely different compared with a 5-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 (Figs. 1 and 2, Supplementary Figs. 2–4, and Supplementary Tables 15–18, 21, and 22). Variables were stratified into the overall hazard ratio (HR) when the assumption of proportional hazards was not fulfilled, where annual income (in Swedish crowns [SEK]) was divided into four equal quartiles of SEK 1,198, SEK 1,198–1,732, SEK 1,732–2,492, and SEK ≥2,492. If a BMI group did not fulfill the nonproportional 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 nonproportionality as acceptable. We performed subgroup analyses by dividing the cohort into ≤65 years of age and >65 years of age (Figs. 1 and 2) and by sex (Supplementary Fig. 2 and 3). We further examined the association between BMI and all-cause mortality and CVD mortality through the exclusion of patients who smoked at baseline (Supplementary Fig. 4). We performed additional analyses among patients only regarding the true difference in BMI (Supplementary Tables 15–18). To investigate any potential difference between the groups of patients with missing and nonmissing BMI, we performed Cox regression among patients with missing BMI, using patients with nonmissing BMI as reference (Supplementary Tables 21 and 22), with crude mortality rates presented in Supplementary Tables 19 and 20.

The analyses were performed with R (ver. 3.2.1; R Foundation for Statistical Programming). All tests were two tailed,

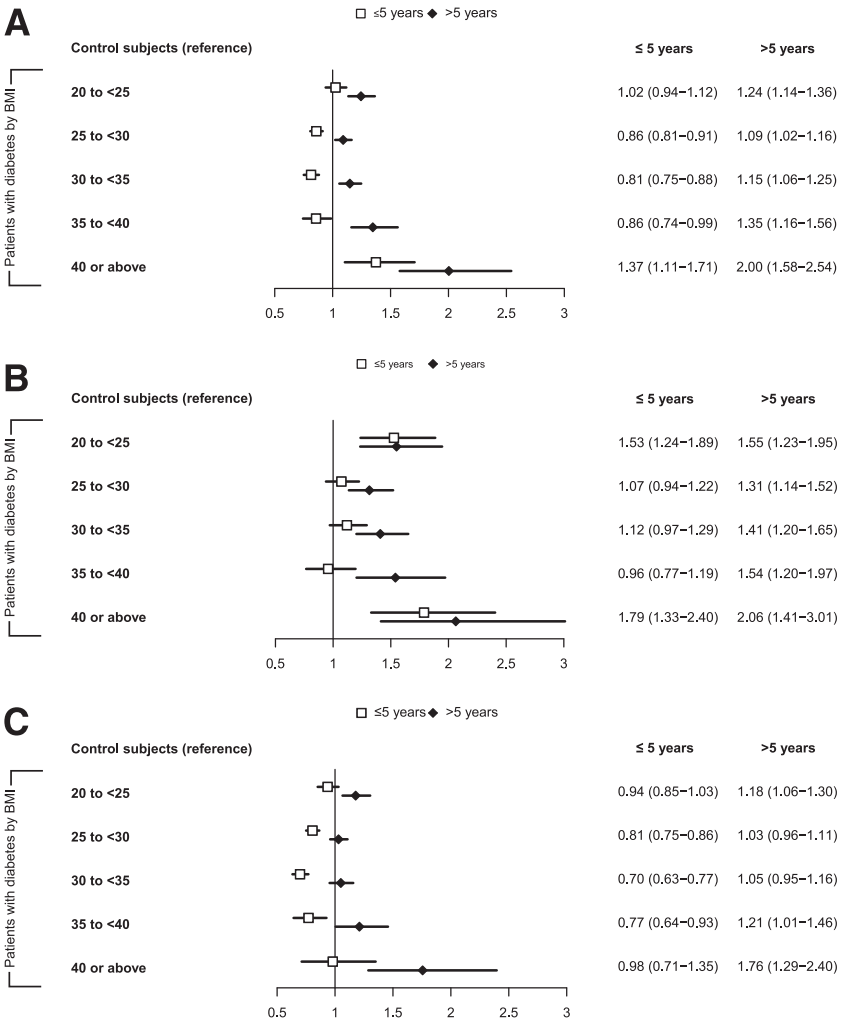

Figure 1—Adjusted HR for death from any cause by BMI group and time with age- and sex-matched control subjects as reference. □, mortality in ≤5 years; ◆, mortality in >5 years. The analysis was based on Cox regression and adjusted for age-group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, CHD, AMI, stroke, AF, HF, and CKD. Variables that were nonproportional were adjusted for by stratification into the overall HR. *A*: All-cause mortality HR by BMI group and time. *B*: All-cause mortality HR by BMI group and time (age <65 years). *C*: All-cause mortality HR by BMI group and time (age ≥65 years).

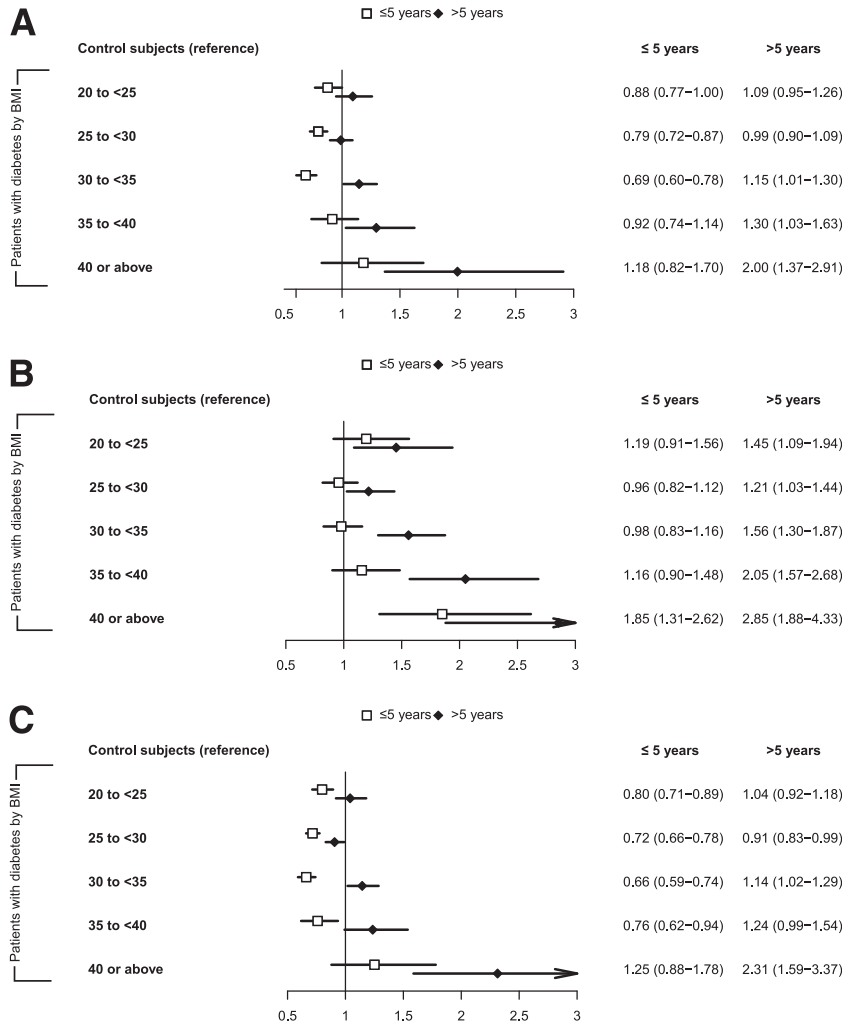

Figure 2—Adjusted HR for death from cardiovascular (CVD) causes by BMI group and time with age- and sex-matched control subjects as reference. □, mortality in ≤5 years; ◆, mortality in >5 years. The analysis was based on Cox regression and adjusted for age-group, year of inclusion, sex, the interaction between duration of diabetes and age, income, education, marital status, immigrant status, CHD, AMI, stroke, AF, HF, and CKD. Variables that were nonproportional were adjusted for by stratification into the overall HR. *A*: CVD mortality HR by BMI group and time. *B*: CVD mortality HR by BMI group and time (age <65 years). *C*: CVD mortality HR by BMI group and time (age ≥65 years).

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 control subjects were included (Table 1). Median follow-up was 5.5 years, mean age was 59.5 years, and 40% were women (Table 1 and Supplementary Table 2). Patients with type 2 diabetes were similar to control subjects in terms of marital status but had lower income, less 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 glomerular filtration rate 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 control subjects were 68,429 and 27,854 (40.7%). Crude and adjusted mortality rates for individuals with diabetes in relation to control subjects are shown along with the number of events in Table 2. The overall mean mortality rate for patients was 19.7 (95% CI 19.4–20.0) for all-cause mortality and 8.09 (7.90–8.27) for CVD mortality. The corresponding rates for control subjects were 15.2 (15.1–15.3) and 6.17 (6.10–6.25). Event rates, mortality rates, and person-years for Figs. 1 and 2 and Supplementary Figs. 2–4 are presented in Supplementary Tables 3–14.

Short-term Mortality at ≤5 Years 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 control subjects by age (<65 and ≥65 years), with all models adjusted or stratified for inclusion by year, age-group, sex, duration by age, income, marital status, education, immigrant status, CHD, AMI, stroke, 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 (Fig. 1), but the only patients with significantly excess risk for mortality were those with BMI ≥40 kg/m^2 with HR 1.37 (95% CI 1.11–1.71) 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 to <30, 30 to <35, or 35 to <40 kg/m^2 had 19–30% lower short-term risk for death from any cause compared with control subjects.

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 control subjects. Patients aged ≥65 years in the BMI range of 20 up to <40 kg/m^2 had 20–34% lower risk for death from any cause or cardiovascular causes than control subjects. However, patients with a BMI ≥40 kg/m^2 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]) (Fig. 2). The reverse linear association that was found short-term, among patients <65 years of age with respect to all-cause mortality (Fig. 1), was tested (Supplementary Table 17) and, among patients only, displayed largely the same associations short-term.

Long-term Mortality at >5 Years From Baseline

For mortality at >5 years from baseline, patients with a BMI ≥30 kg/m^2 had

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

	Control subjects	Patients (overall)	BMI 20 to <25 kg/m^2	BMI 25 to <30 kg/m^2	BMI 30 to <35 kg/m^2	BMI 35 to <40 kg/m^2	BMI ≥40 kg/m^2	Patients with missing BMI
Individuals, *n*	743,907	149,345	20,297	56,943	44,266	18,766	9,073	22,742
Age and sex								
Women, *n* (%)	297,304 (40.0)	59,669 (40.0)	8,783 (43.3)	19,467 (34.2)	17,386 (39.3)	9,021 (48.1)	5,012 (55.2)	9,755 (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	122,495 (16.5)	25,936 (17.4)	3,365 (16.6)	9,720 (17.1)	7,904 (17.9)	3,378 (18.0)	1,569 (17.3)	4,120 (18.1)
Married	423,314 (56.9)	81,116 (54.3)	11,233 (55.3)	32,937 (57.8)	23,876 (53.9)	9,207 (49.1)	3,863 (42.6)	11,468 (50.4)
Single	142,400 (19.1)	29,923 (20.0)	3,481 (17.2)	9,363 (16.4)	9,025 (20.4)	4,899 (26.1)	3,155 (34.8)	4,661 (20.5)
Widowed	55,658 (7.5)	12,370 (8.3)	2,218 (10.9)	4,923 (8.6)	3,461 (7.8)	1,282 (6.8)	486 (5.4)	2,493 (11.0)
Education, *n* (%)								
10–12 years	315,184 (42.9)	66,414 (45.1)	8,154 (40.8)	24,566 (43.8)	20,018 (45.9)	9,049 (49.0)	4,627 (51.8)	9,525 (43.1)
≤9 years	219,552 (29.9)	54,721 (37.2)	7,573 (37.9)	21,192 (37.7)	16,434 (37.7)	6,563 (35.5)	2,959 (33.2)	8,543 (38.7)
College or university	200,203 (27.2)	26,015 (17.7)	4,269 (21.3)	10,392 (18.5)	7,149 (16.4)	2,865 (15.5)	1,340 (15.0)	4,031 (18.2)
Income (hundred SEK)	1,775.0 (1,214.0, 2,543.0)	1,543.0 (1,133.0, 2,232.0)	1,455.0 (1,083.0, 2,143.0)	1,576.0 (1,144.0, 2,277.0)	1,564.0 (1,148.0, 2,261.0)	1,538.0 (1,138.0, 2,193.0)	1,466.0 (1,106.0, 2,107.0)	1,437.0 (1,075.0, 2,119.0)
Swedish born, *n* (%)	647,467 (87.0)	120,880 (80.9)	16,778 (82.7)	46,175 (81.1)	35,557 (80.3)	15,092 (80.4)	7,278 (80.2)	17,928 (78.8)
Comorbidities								
AF	20,755 (2.8)	7,199 (4.8)	1,100 (5.4)	2,689 (4.7)	2,068 (4.7)	882 (4.7)	460 (5.1)	1,535 (6.7)
Myocardial infarction	21,229 (2.9)	10,184 (6.8)	1,277 (6.3)	4,288 (7.5)	3,156 (7.1)	1,115 (5.9)	348 (3.8)	1,830 (8.0)
CHD	41,799 (5.6)	18,673 (12.5)	2,318 (11.4)	7,787 (13.7)	5,776 (13.0)	2,097 (11.2)	695 (7.7)	3,310 (14.6)
Stroke	17,687 (2.4)	5,824 (3.9)	976 (4.8)	2,423 (4.3)	1,617 (3.7)	567 (3.0)	241 (2.7)	1,456 (6.4)
HF	10,909 (1.5)	5,570 (3.7)	724 (3.6)	1,958 (3.4)	1,662 (3.8)	808 (4.3)	418 (4.6)	1,329 (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)
Age at diabetes onset (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)
HbA_{1c}, %, 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)	7.1 (1.5), 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	25,429 (18.1)	3,979 (20.8)	9,419 (17.6)	7,311 (17.6)	3,145 (17.9)	1,575 (18.6)	2,816 (18.0)
BMI (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)

Continued on p. 490

Table 1—Continued

	Control subjects	Patients (overall)	BMI 20 to <25 kg/m^2	BMI 25 to <30 kg/m^2	BMI 30 to <35 kg/m^2	BMI 35 to <40 kg/m^2	BMI ≥40 kg/m^2	Patients with missing BMI
Albuminuria, *n* (%)								
Microalbuminuria	NA	13,201 (11.9)	1,502 (9.8)	4,713 (11.1)	4,136 (12.6)	1,947 (14.2)	903 (13.9)	1,436 (12.3)
Macroalbuminuria	NA	5,709 (5.1)	665 (4.3)	2,017 (4.7)	1,755 (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)
Antihypertensives, *n* (%)	NA	82,810 (59.0)	9,077 (47.7)	30,566 (57.0)	26,328 (63.4)	11,462 (65.0)	5,377 (63.4)	11,610 (57.6)
Statins, *n* (%)	NA	53,836 (38.3)	6,278 (33.0)	21,172 (39.4)	17,044 (40.9)	6,682 (38.0)	2,660 (31.5)	7,538 (37.4)
Diabetes treatment, *n* (%)								
No pharmacological treatment	NA	65,068 (43.6)	9,185 (45.3)	25,770 (45.3)	19,201 (43.4)	7,497 (39.9)	3,415 (37.6)	9,855 (43.3)
Oral agents	NA	65,934 (44.1)	7,053 (34.7)	24,100 (42.3)	20,497 (46.3)	9,498 (50.6)	4,786 (52.7)	9,349 (41.1)
Insulin	NA	10,116 (6.8)	3,156 (15.5)	4,129 (7.3)	1,957 (4.4)	629 (3.4)	245 (2.7)	1,933 (8.5)
Insulin and oral agents	NA	8,227 (5.5)	903 (4.4)	2,944 (5.2)	2,611 (5.9)	1,142 (6.1)	627 (6.9)	1,605 (7.1)

Data for continuous variables are mean (SD), with the exception of income, which is median (interquartile range). Data for categorical variables are *n* (%), and individuals are given as *n*, as noted. eGFR, estimated glomerular filtration rate; NA, not available.

increased total and CVD mortality compared with control subjects. The association was J shaped and was tested among patients only (Supplementary Tables 15 and 16), who displayed a significant increase in mortality from BMI 35 kg/m^2 (all-cause mortality) and BMI 30 kg/m^2 (CVD mortality). However, among patients aged ≥65 years, a significant excess all-cause mortality was only seen in patients with a BMI 35 to <40 (HR 1.21 [95% CI 1.01–1.46]) and among the very obese (BMI ≥40 kg/m^2) (HR 1.76 [95% CI 1.29–2.40]). For CVD mortality among patients aged ≥65 years, only those with a BMI ≥40 kg/m^2 had an increased risk (HR 2.31 [95% CI 1.59–3.37]) (Figs. 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 to <30 kg/m^2. With increasing BMI, there was a stepwise increase up to an HR 2.06 (95% CI 1.41–3.01) (all-cause mortality) and HR 2.85 (95% CI 1.88–4.33) (CVD mortality) among patients with a BMI ≥40 kg/m^2 (Figs. 1 and 2). Women had a generally lower mortality compared with control subjects than men did with respect to both short-term and long-term mortality, with similar associations by BMI as the overall cohort (Supplementary Figs. 2 and 3). 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 increase, or no increase, at lower BMI levels (Supplementary Tables 17 and 18).

In analyses restricted to nonsmoking patients <65 years of age (Supplementary Fig. 4), the long-term apparent increase in CVD mortality attenuated to the null among patients with a BMI 20 to <25 kg/m^2 and was not significantly different from control subjects 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 of 172,090), which was 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

Table 2—Crude mortality rates per 1,000 person-years for all-cause mortality and CVD mortality among patients with type 2 diabetes and control subjects in the entire cohort

Category	Events	Person-years	Mortality rate
All-cause mortality			
Patients	17,546	892,672	19.7 (19.4–20.0)
Control subjects	68,429	4,511,754	15.2 (15.1–15.3)
Patients by BMI			
20 to <25 kg/m^2	3,499	127,131	27.5 (26.6–28.5)
25 to <30 kg/m^2	7,171	349,341	20.5 (20.1–21.0)
30 to <35 kg/m^2	4,479	261,060	17.2 (16.7–17.7)
35 to <40 kg/m^2	1,665	106,075	15.7 (15.0–16.5)
≥40 kg/m^2	732	49,065	14.9 (13.9–16.0)
CVD mortality			
Patients	7,218	892,672	8.09 (7.90–8.27)
Control subjects	27,854	4,511,754	6.17 (6.10–6.25)
Patients by BMI			
20 to <25 kg/m^2	1,423	127,131	11.2 (10.6–11.8)
25 to <30 kg/m^2	2,966	349,341	8.49 (8.19–8.80)
30 to <35 kg/m^2	1,832	261,060	7.02 (6.70–7.35)
35 to <40 kg/m^2	700	106,075	6.60 (6.12–7.11)
≥40 kg/m^2	297	49,065	6.05 (5.38–6.78)

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

BMI ≥40 kg/m^2 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 control subjects. 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, is 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 that of matched control subjects. 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 kg/m^2 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 those of their matched control subjects, consistent with earlier studies (4,10), even with good glycemic control (4). For BMI, the short-term mortality risk was similar to or lower than that for control subjects 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 to <30 kg/m^2 and a substantially increased risk was found 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 with obese persons without diabetes cannot be quantified, since no data exist for BMI for population control subjects.

Among patients aged ≥65 years, all-cause and CVD mortality risks were lower or similar to those of matched control subjects, with the exception of long-term risk among patients with a BMI ≥35 kg/m^2. Mortality among patients with type 2 diabetes is reported to be lower in older patients (3,5,10) compared with that of the general population, perhaps explaining the low short- and long-term increased mortality risks in this age-group. Among patients aged ≥65 years, the very obese (BMI ≥40 kg/m^2) had an approximately twofold increase in long-term mortality risk compared with control subjects (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 with the high-income English-speaking countries (26). 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 kg/m^2) than the general population and subsequently possibly more CVD, the generally low or lower risk compared with 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, for example, hypertension, whereas management in the general Swedish population is far from optimal (27).

Among patients aged <65 years with a BMI 20 to <25 kg/m^2, both short-term and long-term mortality were higher than those 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 to <25 kg/m^2 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 so in the short-term compared with the long-term risk that we identified among patients aged <65 years. Current guidelines advocate maintaining a healthy weight as an important part of diabetes care (30), and our data support this view, although not among older patients with BMI <35 kg/m^2.

Strengths of the study include the very large population of patients with type 2 diabetes and the availability of a control population without diabetes matched for age and sex. There may have been some patients with diabetes among the control subjects, 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 control subjects with cancer and dementia. Further, we had a uniquely high number of obese participants with excessive BMI, with >27,000 patients with a BMI ≥35 kg/m^2. 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 with control subjects with the same BMI. Our conclusions are strictly based on patients versus the average person with BMI of ~26 kg/m^2 (23), in the general population without diabetes, and so display the excess risk for 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 current study. Also, 22,742 patients had missing data on BMI. Although causes are unknown, baseline data suggest a higher frequency of comorbidities and albuminuria among patients with missing BMI. 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 control subjects for a number of other factors such as marital status, immigration, and major diagnoses in all models comprising control subjects.

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, but the overall short-term excess risk was high among the very obese. The association with long-term mortality was J shaped, and the mortality risk increased gradually from BMI 30 kg/m^2. Excess all-cause mortality and CVD mortality were markedly higher among younger people, and patients with a BMI ≥40 kg/m^2 had an approximately two- to threefold excess risk compared with the average person without diabetes, irrespective of age. A BMI <25 kg/m^2 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 patients with diabetes.

Acknowledgments. The authors thank the regional NDR coordinators as well as the contributing nurses, physicians, and patients.

Funding. This study received grants from the Swedish State under the Agreement Concerning Research and Education of Doctors (ALFGBG-427301), the Swedish Heart and Lung Foundation (2015-0438), the Swedish Research Council (2013-4236), the Swedish Diabetes Foundation (2013-5187), and the Swedish Council for Health, Working Life and Welfare (FORTE) (2013-0325). The Swedish Diabetes Association and the Swedish Society of Diabetology support the NDR. The Swedish Association of Local Authorities and Regions funds the NDR.

Duality of Interest. N.S. reports grants and personal fees from Boehringer Ingelheim; personal fees from Janssen, Novo Nordisk, and Eli Lilly; and grants from AstraZeneca, all of which were outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.E., A.Ra., M.A., and A.Ro. 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 this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Sarwar N, Gao P, Seshasai SR, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–2222
2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364:829–841
3. Koskinen SV, Reunanen AR, Martelin TP, Valkonen T. Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. Am J Public Health 1998;88:765–770
4. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732
5. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia 2013;56:2601–2608
6. Hu Y, Bhupathiraju SN, de Koning L, Hu FB. Duration of obesity and overweight and risk of type 2 diabetes among US women. Obesity (Silver Spring) 2014;22:2267–2273
7. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. 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
8. Katzmarzyk PT, Hu G, Cefalu WT, Mire E, Bouchard C. The importance of waist circumference and BMI for mortality risk in diabetic adults. Diabetes Care 2013;36:3128–3130
9. Zhao W, Katzmarzyk PT, Horswell R, et al. Body mass index and the risk of all-cause mortality among patients with type 2 diabetes mellitus. Circulation 2014;130:2143–2151
10. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the UK. Diabet Med 2006;23:516–521
11. Logue J, Walker JJ, Leese G, et al.; Scottish Diabetes Research Network Epidemiology Group. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. Diabetes Care 2013;36:887–893
12. Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med 2014;370:233–244
13. Thomas G, Khunti K, Curcin V, et al. Obesity paradox in people newly diagnosed with type 2 diabetes with and without prior cardiovascular disease. Diabetes Obes Metab 2014;16:317–325
14. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. JAMA 2012;308: 581–590
15. Jackson CL, Yeh HC, Szklo M, et al. Body-mass index and all-cause mortality in US adults with and without diabetes. J Gen Intern Med 2014; 29:25–33
16. Perotto M, Panero F, Gruden G, et al. Obesity is associated with lower mortality risk in elderly diabetic subjects: the Casale Monferrato study. Acta Diabetol 2013;50:563–568

17. Tobias DK, Hu FB. Does being overweight really reduce mortality? Obesity (Silver Spring) 2013;21:1746–1749
18. Stokes A, Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. Obesity (Silver Spring) 2015;23:2485–2490
19. Lawlor DA, Hart CL, Hole DJ, Davey Smith G. Reverse causality and confounding and the associations of overweight and obesity with mortality. Obesity (Silver Spring) 2006;14:2294–2304
20. Eliasson B, Gudbjörnsdottir S. Diabetes care–improvement through measurement. Diabetes Res Clin Pract 2014;106(Suppl. 2):S291–S294
21. Hoelzel W, Weykamp C, Jeppsson JO, et al.; IFCC Working Group on HbA1c Standardization. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166–174
22. Khalangot M, Tronko M, Kravchenko V, Kulchinska J, Hu G. Body mass index and the risk of total and cardiovascular mortality among patients with type 2 diabetes: a large prospective study in Ukraine. Heart 2009;95:454–460
23. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097–1105
24. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211–2219
25. Whitlock G, Lewington S, Sherliker P, et al.; Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083–1096
26. 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 2016;387:1377–1396
27. Palafox B, McKee M, Balabanova D, et al. Wealth and cardiovascular health: a cross-sectional study of wealth-related inequalities in the awareness, treatment and control of hypertension in high-, middle- and low-income countries. Int J Equity Health 2016;15:199
28. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet 2014;383:1084–1094
29. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? Circulation 2017;135:2369–2372
30. American Diabetes Association. Standards of medical care in diabetes–2012. Diabetes Care 2012;35(Suppl. 1):S11–S63