

Association Between BMI Measured Within a Year After Diagnosis of Type 2 Diabetes and Mortality

JENNIFER LOGUE, MD¹
 JEREMY J. WALKER, PHD²
 GRAHAM LEESE, MD³
 ROBERT LINDSAY, PHD¹
 JOHN MCKNIGHT, MD⁴
 ANDREW MORRIS, MD³

SAM PHILIP, MD⁵
 SARAH WILD, FRCP²
 NAVEED SATTAR, FRCP¹
 ON BEHALF OF THE SCOTTISH DIABETES
 RESEARCH NETWORK EPIDEMIOLOGY
 GROUP*

OBJECTIVE—To describe the association of BMI with mortality in patients diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Using records of 106,640 patients in Scotland, we investigated the association between BMI recorded around the diagnosis of type 2 diabetes mellitus (T2DM) and mortality using Cox proportional hazards regression adjusted for age and smoking status, with BMI 25 to <30 kg/m² as a referent group. Deaths within 2 years of BMI determination were excluded. Mean follow-up to death or the end of 2007 was 4.7 years.

RESULTS—A total of 9,631 deaths occurred between 2001 and 2007. Compared with the reference group, mortality risk was higher in patients with BMI 20 to <25 kg/m² (hazard ratio 1.22 [95% CI 1.13–1.32] in men, 1.32 [1.22–1.44] in women) and patients with BMI ≥35 kg/m² (for example, 1.70 [1.24–2.34] in men and 1.81 [1.46–2.24] in women for BMI 45 to <50 kg/m²). Vascular mortality was higher for each 5-kg/m² increase in BMI >30 kg/m² by 24% (15–35%) in men and 23% (14–32%) in women, but was lower below this threshold. The results were similar after further adjustment for HbA_{1c}, year of diagnosis, lipids, blood pressure, and socioeconomic status.

CONCLUSIONS—Patients categorized as normal weight or obese with T2DM within a year of diagnosis of T2DM exhibit variably higher mortality outcomes compared with the overweight group, confirming a U-shaped association of BMI with mortality. Whether weight loss interventions reduce mortality in all T2DM patients requires study.

Diabetes Care 36:887–893, 2013

Compared with normal weight, obesity is associated with increased all-cause mortality in the general population, as well as increased cardiovascular and cancer mortality (excluding smoking-related cancers) (1–3). However, the findings in patients with type 2 diabetes mellitus (T2DM) have been variable, with some studies reporting an increase in all-cause mortality with

increasing body mass (4–6), but many studies finding no relationship (7–10) or a decrease in mortality with higher BMI (11). This may be due to limited power, as those studies describing no association all included <1,000 individuals (7–10) and limitations of the analytical approaches. In the general population, the relationship between BMI and mortality is U-shaped (1) with excess mortality

seen at BMI <22.5 kg/m² compared with 22.5–25 kg/m². Consequently, if the lowest BMI group is used as the reference group, excess mortality in the obese range compared with the BMI group with the lowest mortality (i.e., the low normal range) is not always apparent. There is also the potential for reverse causality as a consequence of another medical condition causing both weight loss and death and confounding by smoking, which can lead to smokers having a lower BMI than nonsmokers yet a high risk of smoking-related disease. Higher BMI is associated with increased risk of coronary heart disease and cardiovascular mortality among people with T2DM (6,12), in keeping with results from the general population. As these studies (4–11) represent cross-sections of populations with established T2DM, there is the potential that diabetes control, treatment, and duration will have influenced BMI. These complexities and conflicting results have in some way deflected attention from the potential importance of weight reduction in patients with diabetes.

The aim of the present work, based on data from the Scottish Care Information Diabetes Collaboration (SCI-DC) database, was to examine the relationship between BMI within a year after diagnosis of T2DM and all-cause, cardiovascular, cancer, and respiratory mortality in the medium term. The use of a large contemporary database has allowed closer examination of any graded association between obesity and mortality than among smaller studies. The availability of BMI recorded within a year after diagnosis limits the potential effects that diabetes treatment and glycemic control can have on BMI.

RESEARCH DESIGN AND METHODS

Data collection

Data were drawn from a 2008 extract of the SCI-DC dataset, a dynamic clinical database that was started on a national basis in 2000 and included retrospective data collation where available. Completeness increased up to 2004, after which we

From the ¹Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; the ²Centre for Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom; the ³School of Medicine, University of Dundee, Dundee, United Kingdom; the ⁴Western General Hospital, Edinburgh, United Kingdom; and the ⁵Aberdeen Royal Infirmary, Aberdeen, United Kingdom.

Corresponding author: Jennifer Logue, jennifer.logue@glasgow.ac.uk.

Received 15 May 2012 and accepted 9 September 2012.

DOI: 10.2337/dc12-0944

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0944/-/DC1>.

*A complete list of the Scottish Diabetes Research Network Epidemiology Group can be found in the Supplementary Data online.

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

estimate that that data were derived from all hospitals, and all except 5 of ~1,000 general practitioners are downloaded to SCI-DC on a daily basis, representing data from >99% of people with diagnosed diabetes in Scotland. Generation of the linked dataset was approved by the SCI-DC steering committee, the Scottish Multicenter Research ethics committee, the Privacy Advisory Committee of National Health Service (NHS) National Services Scotland, and data protection guardians of all Health Boards in Scotland. The research database is pseudonymized. Inclusion criteria for this analysis included a diagnosis of T2DM, a measurement of BMI recorded within 1 year after diagnosis of diabetes, and data available for year of birth and sex. Patients with BMI recorded after the study end point (31 December 2007) were excluded, as were those aged <30 years when diagnosed with diabetes. Completeness of BMI data has increased over time from 40% in 2001 to 85% in 2007 (13). Other characteristics recorded within 1 year of diagnosis of diabetes that were investigated included total cholesterol, HDL, HbA_{1c}, blood pressure, smoking status, and an area-based measure of socioeconomic status (quintiles of the Scottish Index of Multiple Deprivation [SIMD]). The SIMD combines 38 indicators across seven domains, namely: income, employment, health, education, skills and training, housing, geographic access, and crime and provides a relative measure of deprivation that can be used to compare data zones by providing a relative ranking from most deprived to least deprived (14). Where multiple measurements were recorded within 1 year after diagnosis of T2DM, the chronologically earliest to diagnosis of T2DM was used.

The SCI-DC data extract was linked by the Information Services Division of NHS National Services Scotland to mortality records held by the National Records of Scotland. An independent check of the quality of linkages carried out by the Scottish record linkage team found that there was a false-positive (incorrect links) rate of 3.7% and a false-negative (missed links) rate of 1.9% between two incidence databases in a study of 3,077 subjects (15). Causes of death were aggregated into disease groups: vascular (ICD-9 codes 350–459 and 798; ICD-10 codes I00–I99); respiratory (ICD-9 010–012 and 460–519; ICD-10 J00–J99); cancers of lung, mouth, larynx, pharynx, and esophagus (ICD-9 140–150 and

160–165; ICD-10 C00–C15 and C30–C39); and other malignant neoplasm (ICD-9 151–159 and 166–208; ICD-10 C16–C29 and C40–C97). Patients who died within 2 years of index BMI recording were excluded from the study to limit possible biases attributable to reverse causation. Cause of death was attributed in a hierarchical fashion from both the primary and secondary causes of death. Firstly, if a cancer of the lung, mouth, larynx, pharynx, or esophagus or any other malignant neoplasm was listed as either the primary or secondary cause, this was recorded as the cause of death. Secondly, if no cancer was listed but any vascular code was listed, this was recorded as the cause of death. Thirdly, if no cancer or vascular code was listed but any respiratory code was, this was recorded as the cause of death. Deaths not fitting the above criteria were excluded from the cause-specific mortality analyses but included in all-cause mortality analyses.

Statistical analyses

Previous studies (1) have demonstrated convincingly that all-cause mortality does not increase monotonically with greater BMI but instead follows a U-shaped pattern. Because of this, estimation of a single hazard ratio (HR) across the full range of BMI values is potentially misleading. Recognizing this, and in accordance with the approach by others, we elected to use the category with the largest numbers of individuals (BMI 25–30 kg/m²) as the reference category for all-cause mortality and to model the influence of BMI on cause-specific mortality separately for low and high BMI subsets of the sample (corresponding, respectively, to the lower and upper extremes of the anticipated U-shaped pattern). Associations between BMI and mortality, all-cause and cause-specific, were investigated using Cox proportional hazards regression. The models were restricted to people with BMI values in the range 20 to <50 kg/m² due to small numbers outside this range. For all-cause mortality, patients were grouped into 5 kg/m² BMI categories from 20 to <50 kg/m² and HRs for BMI were estimated relative to the reference group of 25 to <30 kg/m². Estimates were adjusted for the effects of age at BMI determination and for smoking status chronologically closest to the point of BMI determination (current or former smoker vs. never smoker). Models were fitted separately for each sex.

For cause-specific mortality, patients were classified as either low BMI (20 to

<30 kg/m²) or high BMI (30 to <50 kg/m²). This mirrored the approach used in a recent major study (1). For each group, the HR associated with an increase of 5 kg/m² was estimated, adjusted for age and smoking status. Associations between BMI groups and available risk factors were assessed either via a Kruskal-Wallis test (for continuous quantities: total cholesterol/HDL-cholesterol/HbA_{1c}/blood pressure/age) or via the Mantel-Haenszel χ^2 test. The Kruskal-Wallis test was used in preference to ANOVA because the assumption of equal variances in all BMI groups was unsafe in some cases.

RESULTS—The analyses were based on 106,640 individuals for whom an index BMI measurement taken within 1 year after diagnosis of diabetes, and on or before the study end point, was available. Major reasons for exclusion were: death within 2 years of the index BMI measurement being recorded ($N = 11,510$); no index BMI measurement being available within 1 year of diagnosis with diabetes ($N = 94,250$); the index BMI value being outside the permitted range (≥ 20 kg/m² and <50 kg/m²; $N = 4,992$); and smoking status not being available ($N = 1,812$). A full case-flow schedule is given in Supplementary Fig. 1. Overall, 106,640 of 240,648 people (44.3%) with T2DM were eligible for inclusion in the present analysis. The median time in notional months (1 month = 30 days) between the date of diagnosis of diabetes and date of the index BMI measurement was 1.67 (interquartile range 3.90) for men ($n = 58,372$) and 1.8 (interquartile range 4.03) for women ($n = 48,268$). A total of 14.0% of men and 13.1% of women had BMI recorded on the date of diagnosis of diabetes. Characteristics of the 133,929 patients excluded are given in Supplementary Table 1; missing data were the principal reason for exclusion, although where baseline characteristics were available, they were broadly similar with those for people included in the analysis. Supplementary Table 2 gives the age and SIMD for those excluded due to no BMI data being available, available BMI being measured outside 1 year from diagnosis of T2DM, and those who were included; those with BMI outside of 1 year after diagnosis were slightly younger than patients included in analysis, who in turn were markedly younger than people with no BMI data at all. The analyses included 58,372 men (among whom 5,272 deaths were

Table 1—Characteristics of men in the study population by BMI category recorded within 1 year after diagnosis

	20 to <25 kg/m ² (n = 6,586)	25 to <30 kg/m ² (n = 22,057)	30 to <35 kg/m ² (n = 18,962)	35 to <40 kg/m ² (n = 7,427)	40 to <45 kg/m ² (n = 2,506)	45 to <50 kg/m ² (n = 834)	All	P value
Total cholesterol mean (SD)	5.03 (1.30)	5.11 (1.49)	5.13 (1.41)	5.14 (1.53)	5.16 (1.37)	5.11 (1.18)	5.11 (1.44)	<0.001 ^b
HDL _c mean (SD)	1.28 (0.40)	1.18 (0.34)	1.12 (0.31)	1.08 (0.31)	1.07 (0.28)	1.10 (0.31)	1.15 (0.33)	<0.001 ^b
HbA _{1c} (%), mean (SD)	8.26 (2.29)	8.02 (2.06)	7.97 (1.95)	8.04 (1.92)	8.13 (1.89)	8.15 (1.86)	8.04 (2.03)	<0.001 ^b
Systolic BP (mmHg), mean (SD)	137.66 (20.66)	140.05 (19.86)	141.01 (19.38)	142.11 (18.92)	143.79 (18.96)	144.35 (19.40)	140.59 (19.69)	<0.001 ^b
Diastolic BP (mmHg), mean (SD)	78.61 (11.33)	81.08 (11.35)	82.88 (11.41)	84.63 (11.27)	85.89 (11.55)	87.66 (11.22)	82.15 (11.53)	<0.001 ^b
Age (years), mean (SD) ^a	63.2 (12.5)	61.8 (11.5)	58.8 (11.2)	55.0 (11.3)	51.8 (11.1)	50.3 (10.3)	59.5 (11.9)	<0.001 ^b
Smoking status (%)								<0.001 ^c
Current	30.5	25.3	23.5	23.9	22.8	21.6	25.0	
Former	34.8	39.9	41.7	39.0	35.4	30.8	39.5	
Never	34.7	34.8	34.8	37.1	41.8	47.6	35.6	
SIMD ^d (%)								<0.001 ^e
Q1	19.3	18.3	15.4	12.8	11.7	9.0	16.3	
Q2	18.6	19.6	19.2	16.9	16.6	16.0	18.9	
Q3	18.9	19.5	20.4	21.7	19.3	20.4	20.0	
Q4	21.5	21.7	22.7	23.7	24.1	24.6	22.4	
Q5	21.7	20.9	22.2	25.0	28.3	29.9	22.4	
Median year of diagnosis	2003	2003	2003	2003	2004	2003	2003	
Median year of BMI recording	2003	2003	2003	2004	2004	2004	2003	

BP, blood pressure; Q, quintile. ^aAt time of diagnosis with diabetes. ^bValue returned by Kruskal-Wallis test. ^cValue returned by Mantel-Haenszel χ^2 test (alternative hypothesis is linear association between row variable and column variable). ^dData classified by quintiles of SIMD: Q1, least deprived, and Q5, most deprived.

observed) and 48,268 women (4,359 deaths). Mean follow-up (from date of BMI determination to death or 31 December 2007) for men was 4.6 years (SD 3.3 years) and for women was 4.7 years (SD 3.3 years). There were 269,788 person-years of follow-up for men, 5,272 deaths, and 19.5 deaths/1,000 person-years. For women, there were 227,857 person-years of follow-up, 4,359 deaths, and 19.1 deaths/1,000 person-years. The distributions of index BMI measurements by year of recording are shown in Supplementary Fig. 2; 1% of measurements were recorded prior to 1968. A total of 89.6% of all diagnoses of T2DM were made during 1998–2007.

Baseline characteristics (i.e., those recorded closest to diagnosis of diabetes) of the study population by BMI category are described in Table 1 (men) and Table 2 (women). In men, the results were as expected, with decreasing age and HDL-cholesterol and increasing total cholesterol and systolic and diastolic blood pressure as BMI increases (all $P < 0.001$). There was a U-shaped relationship between HbA_{1c} and BMI among men. Smoking prevalence decreased with increasing BMI, and there were higher proportions of men from the more deprived quintiles in higher than lower BMI categories (both $P < 0.001$). For women, the same trends exist for HDL-cholesterol, age, SIMD, diastolic blood pressure, systolic blood pressure, and smoking (all $P < 0.001$). An exception was HbA_{1c}, which was slightly higher among the lower two BMI groups than other BMI groups, although between-group differences in HbA_{1c} were not statistically significant.

Ethnicity was poorly recorded in the dataset: 34.9% of males and 35.0% of females had ethnicity recorded. Of those with recorded ethnicity, 95.1% of males and 95.6% of females were classified as white, consistent with the ethnic distribution of the general population of Scotland.

BMI within a year after diagnosis and mortality

There was a U-shaped relationship between BMI at the time of diagnosis of T2DM and all-cause mortality in both men and women (Fig. 1 and Table 3). In both sexes, there was a higher risk of mortality at BMI 20 to <25 kg/m² relative to BMI 25 to <30 kg/m² (age- and smoking-adjusted HR 1.22 [95% CI 1.13–1.32] in men and 1.32 [1.22–1.44] in women).

Table 2—Characteristics of women in the study population by BMI category recorded within a year after diagnosis

	20 to <25 kg/m ² (n = 5,863)	25 to <30 kg/m ² (n = 14,293)	30 to <35 kg/m ² (n = 13,941)	35 to <40 kg/m ² (n = 8,454)	40 to <45 kg/m ² (n = 4,078)	45 to <50 kg/m ² (n = 1,639)	All	P value
Total cholesterol, mean (SD)	5.46 (1.45)	5.50 (1.46)	5.47 (1.44)	5.41 (1.41)	5.37 (1.19)	5.35 (1.27)	5.45 (1.42)	<0.001 ^b
HDL, mean (SD)	1.44 (0.43)	1.33 (0.38)	1.28 (0.35)	1.24 (0.33)	1.21 (0.31)	1.20 (0.34)	1.30 (0.37)	<0.001 ^b
HbA _{1c} (%), mean (SD)	8.06 (2.23)	7.99 (2.05)	7.93 (1.96)	7.89 (1.88)	7.92 (1.84)	7.92 (1.76)	7.96 (2.00)	0.251 ^b
Systolic BP (mmHg), mean (SD)	141.99 (22.35)	143.41 (21.32)	142.93 (20.52)	142.90 (20.37)	143.16 (19.87)	143.72 (20.20)	143.00 (20.90)	<0.001 ^b
Diastolic BP (mmHg), mean (SD)	78.33 (11.25)	79.99 (11.19)	81.48 (11.19)	83.04 (11.13)	84.42 (11.30)	85.41 (11.32)	81.32 (11.35)	<0.001 ^b
Age (years), mean (SD) ^a	67.7 (11.9)	65.7 (11.5)	62.1 (11.8)	58.4 (12.1)	55.5 (11.7)	52.8 (11.2)	62.3 (12.5)	<0.001 ^b
Smoking status (%)								
Current	26.3	23.3	22.6	22.7	22.6	22.1	23.3	<0.001 ^c
Former	25.7	29.2	30.5	30.0	29.9	28.5	29.3	
Never	48.0	47.5	46.7	47.2	47.5	49.4	47.4	
SIMD ^d (%)								
Q1	18.5	15.6	13.4	11.8	10.4	8.5	13.9	<0.001 ^c
Q2	18.4	17.5	17.5	15.8	15.6	13.8	17.0	
Q3	18.8	19.3	20.6	20.5	19.5	20.9	19.9	
Q4	22.3	24.0	23.6	24.5	25.1	24.6	23.9	
Q5	22.1	23.6	25.0	27.5	29.5	32.3	25.3	
Median year of diagnosis	2003	2003	2003	2003	2003	2003	2003	
Median year of BMI recording	2003	2003	2003	2003	2004	2004	2003	

BP, blood pressure; Q, quintile. ^aAt time of diagnosis with diabetes. ^bValue returned by Kruskal-Wallis test. ^cValue returned by Mantel-Haenszel χ^2 test (alternative hypothesis is linear association between row variable and column variable). ^dData classified by quintiles of SIMD: Q1, least deprived, and Q5, most deprived.

Risk of mortality increased with increasing BMI >35 kg/m², with the risk of mortality 70% higher in men (1.70 [1.24–2.34]) and 81% higher in women (1.81 [1.46–2.24]) with a BMI of 45–50 kg/m² compared BMI of 25 to <30 kg/m². For each 5 kg/m² increase in BMI from 30 to <50 kg/m², the risk of mortality increased by 16% in women (1.16 [1.10–1.22]) and 21% in men (1.21 [1.14–1.29]). These data were analyzed separately for smokers and nonsmokers, and the findings were unchanged (Supplementary Table 3).

Cause-specific mortality

Table 4 shows the HRs for cause-specific mortality by BMI and sex. The U-shaped relationship seen for all-cause mortality persists for vascular and respiratory mortality in both sexes, but was more pronounced in men than women. There is also an increased risk of mortality from non-aerodigestive tract cancers in men as BMI increases >30 kg/m², but not below it. Of particular note was a strikingly lower risk of mortality from respiratory disease for each 5-kg/m² increase in BMI from 20 to <30 kg/m² in both sexes, with an identical increased risk of respiratory mortality in men for each 5-kg/m² increase in BMI from 30 to <50 kg/m² and with broadly similar findings in women. Risk of vascular mortality increased by 23% for each 5-kg/m² increase in BMI from 30 to <50 kg/m² in women (HR 1.23 [95% CI 1.14–1.32]) and 24% in men (1.24 [1.15–1.35]).

To investigate the possible biases attributable to reverse causation (that is, low BMI due to pre-existing disease resulting in increased mortality), sensitivity analyses were conducted excluding no deaths and those within 2 and 5 years after BMI determination. There was little difference seen in the pattern of results when no deaths were excluded compared with deaths within 2 and 5 years of BMI determination (Supplementary Table 4).

To determine whether the survival experience of those excluded from the study was materially different from that of the patients who were included, additional Cox models were fitted including those originally excluded from the analysis. In these models, survival was predicted by age (at diagnosis of diabetes), SIMD quintile, and inclusion status (excluded due to no available BMI, excluded due to no BMI recorded within 1 year post diagnosis with diabetes, or included in the study). Start of follow-up was defined

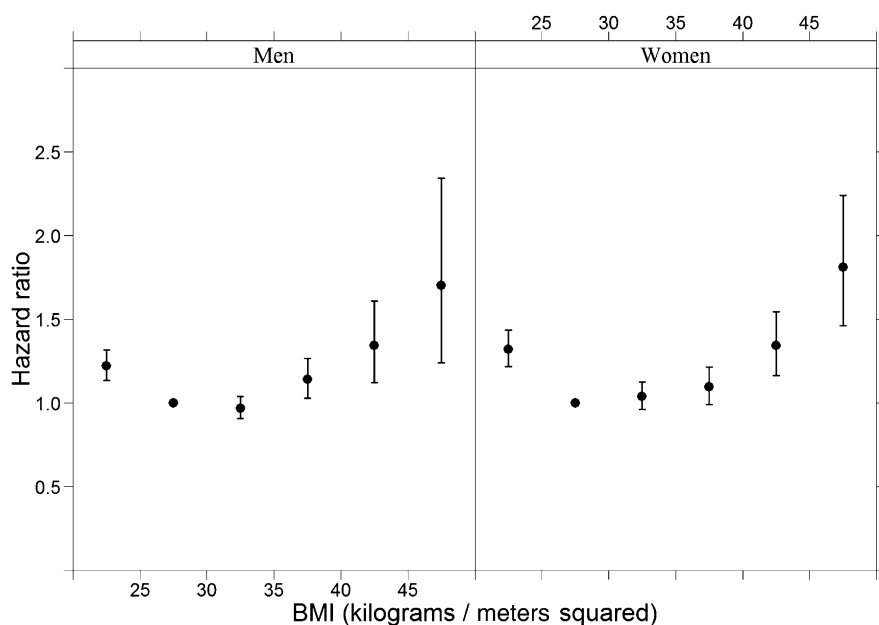


Figure 1—HR estimates for effect of BMI on all-cause mortality. Plotted points are located at the midpoint of the range covered by each BMI band (e.g., the point for band 25 to <30 kg/m² is positioned at 27.5 on the horizontal axis). Estimates are adjusted for age at BMI determination and smoking status. Deaths within 2 years of BMI determination are excluded. Numbers of patients (deaths) are: men, 58,372 (5,272) and women, 48,268 (4,359).

as the date of diagnosis and patients who died within 2 years of being diagnosed with diabetes were excluded. The validity of the proportional hazards assumption for these models was assessed via log (−log[survival]) plots (16,17) (Supplementary Fig. 3A and B). No gross departure from proportionality of hazard was seen. HRs for those excluded due to having no BMI data at all (relative to those included in the study) are 2.06 (95% CI 1.97–2.14) for men and 1.84 (1.76–1.91) for women. Corresponding values for patients excluded due to not having a BMI measurement taken within 1 year of diagnosis with diabetes are 0.76 (0.74–0.79) for men and 0.77 (0.74–0.80) for women. It thus appears that patients who were ineligible for inclusion in the

original analysis due to their having no BMI within 1 year postdiabetes had a better survival experience than those who were included, whereas those with no BMI data at all exhibited poorer survival than those featured in the reported analysis.

Sensitivity analyses were conducted to investigate the potential confounding or mediating effects of HbA_{1c}, SIMD, year of diagnosis, total cholesterol, HDL-cholesterol, and systolic blood pressure. The addition of these variables to the model did not affect the HR estimates for effect of BMI (increase of 5 kg/m²) on mortality from any cause (Supplementary Table 5). As data on these variables were not available for the full cohort, an analysis was performed using only those

individuals with data available for all of the potential confounding/mediating factors listed above; this again showed no attenuation of the effect of BMI on all-cause mortality (results available on request).

CONCLUSIONS—Results from this large population-based T2DM cohort show that individuals with class II obesity or greater (BMI >35 kg/m²) and those of normal weight (BMI 20 to <25 kg/m²), within a year after diagnosis of T2DM have an increased risk of all-cause mortality after ≥2 years compared with people with a BMI in the overweight category (BMI 25 to <30 kg/m²). Examination of the association between BMI within a year after diagnosis of diabetes and cause-specific mortality revealed a U-shaped curve for vascular death in both sexes and for respiratory disease in men. There was also increased mortality from non-aerodigestive tract cancers in men for each 5-kg/m² increase in BMI from 30 to <50 kg/m². The use of BMI within a year of diagnosis allowed the association to be examined with much lower likelihood of the confounding effects that specific treatment, diabetes duration, and glycemic control have on both body mass and mortality. The large cohort also allowed individuals who died within the first 2 years of follow up to be excluded to limit the effects of reverse causality.

The association between BMI and mortality has gained much attention recently, with three large prospective studies of the general population (1–3). These three studies showed broadly similar results, finding the lowest mortality at BMI 22.5 to <25 kg/m², which clearly contrasts with our finding of the lowest risk among people with T2DM being perhaps midway between 25 and 35 kg/m². The prospective studies collaboration (PSC) (1) also examined cause-specific mortality, and we performed our analysis to allow comparison with these results. Reflecting the fact that it is a meta-analysis of studies of the general population, the PSC had a mean age at recruitment of 46 years, though with a mean follow-up period of 11 years, the mean age of death was 67; 61% of the study population were male. However, although the PSC examined mortality for each 5-kg/m² rise in BMI from 15 to <25 kg/m² and 25 to <50 kg/m², we used categories of 20 to <30 kg/m² and 30 to <50 kg/m². In other words, the U-shaped association of BMI with mortality seems to be right-shifted in patients with T2DM.

Table 3—HR estimates for effect of BMI on all-cause mortality

BMI (kg/m ²)	Men [HR (95% CI)]	Women [HR (95% CI)]
20 to <25	1.22 (1.13–1.32)	1.32 (1.22–1.44)
25 to <30 [referent]	1.00	1.00
30 to <35	0.97 (0.91–1.04)	1.04 (0.96–1.12)
35 to <40	1.14 (1.03–1.27)	1.10 (0.99–1.21)
40 to <45	1.34 (1.12–1.61)	1.34 (1.17–1.55)
45 to <50	1.70 (1.24–2.34)	1.81 (1.46–2.24)

Estimates are adjusted for age at BMI determination and smoking status (never vs. current/former). Deaths within 2 years of BMI determination are excluded. Numbers of patients (deaths) are: men, 58,372 (5,272) and women, 48,268 (4,359).

Table 4—HR estimates for effect of BMI (increase of 5 kg/m² from 20 to <30 kg/m² or from 30 to <50 kg/m² according to stratum) on mortality from specific causes, split by sex

Cause of death	Men			
	20 to <30 kg/m ² (n = 28,643)		30 to <50 kg/m ² (n = 29,729)	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
All	3,291	0.82 (0.76–0.88)	1,981	1.21 (1.14–1.29)
Vascular	1,667	0.89 (0.80–0.99)	1,086	1.24 (1.15–1.35)
Respiratory	264	0.45 (0.35–0.58)	95	1.38 (1.05–1.81)
Cancer (lung, etc.)	356	0.77 (0.61–0.96)	208	1.08 (0.89–1.32)
Cancer (other)	738	1.02 (0.87–1.20)	448	1.14 (0.99–1.30)
Cause of death	Women			
	20 to <30 kg/m ² (n = 20,156)		30 to <50 kg/m ² (n = 28,112)	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
All	2,419	0.77 (0.71–0.84)	1,940	1.16 (1.10–1.22)
Vascular	1,333	0.80 (0.71–0.89)	1,036	1.23 (1.14–1.32)
Respiratory	204	0.60 (0.45–0.78)	141	1.27 (1.04–1.54)
Cancer (lung, etc.)	185	0.71 (0.53–0.94)	137	1.03 (0.85–1.26)
Cancer (other)	484	0.91 (0.76–1.09)	463	1.01 (0.90–1.13)

Estimates are adjusted for age at BMI recording and for smoking status (never vs. current/former). Deaths within 2 years of BMI determination are excluded.

The estimates of relative mortality are remarkably similar to that of the PSC for all-cause mortality, aerodigestive tract cancers, other cancers, and respiratory disease, although the PSC data are not stratified by sex. For example, the HR for all-cause mortality in the PSC population was 0.79 (95% CI 0.77–0.82) per 5-kg/m² increase in BMI (adjusted for age, sex, and smoking status) from 15 to <25 kg/m² (1); in our population with T2DM, the HR in men was 0.82 (0.76–0.88) and women 0.77 (0.71–0.84) per 5-kg/m² increase in BMI from 20 to <30 kg/m². Therefore, our results from a population-based diabetes cohort show a very similar pattern to those found in large general-population studies, but with the lowest mortality category ~5 kg/m² higher among people with T2DM than the general population.

T2DM is in an obesity-related disease, with this study population having a mean BMI at the time of diagnosis of 31.3 kg/m² (SD 5.7 kg/m²) (18). People who have a lower body mass at the time of diagnosis may have a different, potentially more aggressive, pathophysiology from those who develop it when obese: an increased sensitivity to visceral fat accumulation, a stronger genetic tendency to insulin resistance, or early pancreatic islet failure, all factors potentially giving a different disease phenotype associated with higher mortality. This so called “obesity paradox” has been reported in chronic diseases such as chronic heart failure and

coronary artery disease (19–22), with a lower BMI associated with a more severe disease phenotype.

The baseline characteristics of the population in this study show expected associations with increasing BMI except HbA_{1c}, with a trend toward higher HbA_{1c} in leaner individuals in both sexes. The reasons behind this are not known; it may be that leaner individuals are thought less at risk for T2DM, leading to a delay in diagnosis and consequently more advanced disease at diagnosis or a more aggressive phenotype. Such explanations might explain an increased risk of mortality seen in the BMI 20–25 kg/m² category. Other explanations for increased mortality in the lower BMI group include residual confounding factors such as intensity of smoking and other adverse lifestyle factors or a higher prevalence of comorbid conditions at lower BMI. This finding of an increased risk of mortality in people who have T2DM diagnosed at a BMI <25 kg/m² is in keeping with recent findings from a smaller study by Carnethon et al. (11).

Our observation of a right-shifted U-shaped association of BMI with mortality in T2DM patients is interesting. This could partly be explained by secular trends in BMI distribution: in the general population of Scotland the prevalence of obesity increased from 16.9% in 1995 to 22.3% in 2003 with rising median BMI over time (23). There has also been an increase in life expectancy within that time, coupled with improvements in

cardiovascular disease and diabetes management (24). However, in the work by Pischon et al. (3) with data from 1992–2000, the nadir of mortality risk was 25.3 kg/m² for men and 24.3 kg/m² for women, values that appear still to be much lower than results presented in this study for people with type 2 diabetes. Thus a right shift may be genuine and is in keeping with the higher average BMI in patients diagnosed with T2DM (18).

The major strength of this work was the availability of data on a large, contemporary diabetes population with available data on other cardiovascular disease risk factors. Although missing BMI data within 12 months of diagnosis excluded a large proportion of individuals, we have no reason to believe that the group with data available was unrepresentative. We performed sensitivity analyses including patients with BMI data recorded outside of 12 months after diagnosis or no BMI recorded; patients with no BMI recorded within 1 year of diagnosis had a better survival experience, whereas those with no BMI data exhibited poorer survival than those featured in the main analysis. The reasons for these finding remains conjectural but does not negate the relationship seen between BMI and mortality outcomes.

Nevertheless, we had statistical power to examine the associations between BMI and mortality in far greater detail than had been done previously, including by sex and cause of death. Unfortunately, ethnicity was poorly recorded in this cohort. However, Scotland has a predominantly white European population, and the findings of this study are therefore limited to this ethnic group. Also, the use of a single BMI measurement after diagnosis of T2DM may not fully reflect the risk of lifetime exposure to excess weight (25). There are factors that may be associated with BMI and mortality, as mediators or confounders of risk, such as alcohol, physical activity, and diabetes medications; however, we did not have these data available for analysis in this study. We have used SIMD as a proxy of individual level of socioeconomic position, as the individual units of summarization are relatively small (<1,000 individuals) and therefore likely to be grossly homogeneous; data on individual-level socioeconomic position were not available. The data used in this study span a large period of time, and data pre-2000 were collected retrospectively; however, the majority of the data were from post-2000, and further statistical adjustment for year of

diagnosis of diabetes did not alter the results or conclusions.

In summary, this study has shown a U-shaped relationship between BMI within a year after diagnosis of diabetes and subsequent mortality, with BMI of 25 to $<30 \text{ kg/m}^2$ associated with the lowest mortality risk ≥ 2 years after diagnosis of diabetes. Consequently, the lowest mortality group in diabetes patients had an $\sim 5 \text{ kg/m}^2$ higher BMI than that observed in a large general-population study, in keeping with the average BMI of diabetes patients being considerably higher than average BMI for the population. Our results, seen around the time of diagnosis of diabetes, also suggest that the mechanisms for obesity-related mortality risk in diabetes may not be explained by dysglycemia alone. Reducing or at least stabilizing body mass in obese patients with T2DM may potentially lead to a reduction in mortality risk beyond the benefits on glycemic control and should be considered a clinical priority. Further research is needed to investigate the mechanisms of obesity-related mortality risk, potential mechanisms for increased mortality at lower BMI, and also the effect of weight loss interventions on morbidity and mortality in people with T2DM with differing levels of baseline BMI.

Acknowledgments—This work was supported by the Wellcome Trust through a Scottish Health Informatics Programme Grant (WT086113). Scottish Health Informatics Programme is a collaboration among the Universities of Aberdeen, Dundee, Edinburgh, Glasgow, and St. Andrews and the Information Services Division of NHS Scotland. Funding for diabetes register linkage was provided by the Scottish Government, and the authors acknowledge the financial support of NHS Research Scotland through the Scottish Diabetes Research Network.

No potential conflicts of interest relevant to this article were reported.

J.L. conceived and designed the study, wrote the first draft, and contributed to article revision. J.J.W. performed the statistical analyses and contributed to article revision. G.L., R.L., J.M., A.M., and S.P. contributed to article revision. S.W. and N.S. conceived and designed the study and contributed to article revision. S.W. and J.W. 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.

These data are available for analysis by members of the Scottish Diabetes Research Network epidemiology group thanks to the hard work of numerous NHS staff who enter the data and people and organizations (the SCI-DC

Steering Group, the Scottish Diabetes Group, Scottish Diabetes Survey Monitoring Group, and the managed clinical network managers and staff in each Health Board) involved in setting up, maintaining, and overseeing SCI-DC.

References

- 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
- Berrington de Gonzalez A, Hartge P, Cerhan JR, et al.; Berrington de GA. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211–2219
- Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105–2120
- Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with type 2 diabetes in the U.K. *Diabet Med* 2006;23:516–521
- Zoppini G, Verlato G, Leuzinger C, et al. Body mass index and the risk of mortality in type II diabetic patients from Verona. *Int J Obes Relat Metab Disord* 2003;27:281–285
- 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
- Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. *BMJ* 1989;299:1127–1131
- Knuiman MW, Welborn TA, Whittall DE. An analysis of excess mortality rates for persons with non-insulin-dependent diabetes mellitus in Western Australia using the Cox proportional hazards regression model. *Am J Epidemiol* 1992;135:638–648
- Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics) I: Causes and death rates. *Diabetologia* 1990;33:538–541
- Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Am J Epidemiol* 1991;133:1220–1230
- 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
- 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
- Scottish Diabetes Survey Monitoring Group. Scottish Diabetes Survey 2007. Available from www.diabetesinscotland.org.uk. Accessed 25 Feb 2012
- Scottish Government Health Department. Scottish Index of Multiple Deprivation. Available from www.scotland.gov.uk/Topics/Statistics/SIMD. Accessed 6 Feb 2012
- Scottish Public Health Observatory. ISD Linked Database. Available from www.scotpho.org.uk/publications/overview-of-key-data-sources/scottish-national-data-schemes/isd-linked-database. Accessed 31 Jan 2012
- Allison PD. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC, SAS Publishing, 1995
- Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis — choosing a model and assessing its adequacy and fit. *Br J Cancer* 2003;89:605–611
- Logue J, Walker JJ, Colhoun HM, et al.; Scottish Diabetes Research Network Epidemiology Group. Do men develop type 2 diabetes at lower body mass indices than women? *Diabetologia* 2011;54:3003–3006
- Munro R, Capell H. Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. *Ann Rheum Dis* 1997;56:326–329
- Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;156:13–22
- Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666–678
- Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009;250:166–172
- Hotchkiss JW, Leyland AH. The relationship between body size and mortality in the linked Scottish Health Surveys: cross-sectional surveys with follow-up. *Int J Obes* 2011;35:838–851
- Leon DA. Trends in European life expectancy: a salutary view. *Int J Epidemiol* 2011;40:271–277
- Abdullah A, Wolfe R, Stoelwinder JU, et al. The number of years lived with obesity and the risk of all-cause and cause-specific mortality. *Int J Epidemiol* 2011;40:985–996