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The Obesity Paradox in Type 2 Diabetes Mellitus: Relationship of Body Mass Index to Prognosis

A Cohort Study

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Background: Whether obesity is associated with a better prognosis in patients with type 2 diabetes mellitus is controversial.

Objective: To investigate the association between body weight and prognosis in a large cohort of patients with type 2 diabetes followed for a prolonged period.

Design: Prospective cohort.

Setting: National Health Service, England.

Patients: Patients with diabetes.

Measurements: The relationship between body mass index (BMI) and prognosis in patients with type 2 diabetes without known cardiovascular disease at baseline was investigated. Information on all-cause mortality and cardiovascular morbidity (such as the acute coronary syndrome, cerebrovascular accidents, and heart failure) was collected. Cox regression survival analysis, corrected for potential modifiers, including cardiovascular risk factors and comorbid conditions (such as cancer, chronic kidney disease, and lung disease), was done.

Results: 10 568 patients were followed for a median of 10.6 years (interquartile range, 7.8 to 13.4). Median age was 63 years (interquartile range, 55 to 71), and 54% of patients were men. Overweight or obese patients (BMI >25 kg/m^2) had a higher rate of cardiac events (such as the acute coronary syndrome and heart failure) than those of normal weight (BMI, 18.5 to 24.9 kg/m^2). However, being overweight (BMI, 25 to 29.9 kg/m^2) was associated with a lower mortality risk, whereas obese patients (BMI >30 kg/m^2) had a mortality risk similar to that of normal-weight persons. Patients with low body weight had the worst prognosis.

Limitation: Data about cause of death were not available.

Conclusion: In this cohort, patients with type 2 diabetes who were overweight or obese were more likely to be hospitalized for cardiovascular reasons. Being overweight was associated with a lower mortality risk, but being obese was not.

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Type 2 diabetes mellitus and obesity are common, growing, and related problems (1). Obesity, which promotes insulin resistance, may account for 80% of the population-attributable risk for type 2 diabetes (2). According to estimates from the World Health Organization, in 2005 a total of 1.6 billion adults worldwide were overweight and at least 400 million were obese—numbers that are expected to reach 2.3 billion and 700 million, respectively, by 2015 (3). If these predictions come true, then the prevalence of type 2 diabetes is also likely to increase (4).

The association between obesity and increased risk for cardiovascular disease (CVD) is well-established in the general population (5, 6). However, once CVD occurs, paradoxically, obesity seems to confer a survival advantage. There is growing evidence that overweight patients with CVD survive longer than their normal-weight counterparts, an effect called the "obesity paradox" (7).

Although obesity accounts for much of the risk for type 2 diabetes, a similar obesity paradox might exist after type 2 diabetes has developed. However, results conflict, with studies reporting both positive and negative associations between higher body mass index (BMI) or other weight indices and CVD (8–22) (Table 1). Population selection, inadequate study power, and incomplete adjustment for age and comorbid conditions may account for inconsistent results.

We investigated the relationship among obesity, CVD, and mortality in a large cohort of persons with type 2 diabetes followed prospectively since 1995 by a single clinical service.

See also:

Summary for Patients I-26

METHODS

Study Population

Patients with a known diagnosis of type 2 diabetes that attended the outpatient clinic service for diabetes in Kingston upon Hull, which serves a population of approximately 600 000 persons, were enrolled in a registry between 1995 and 2005. Data were collected by medical and nursing staff and entered into a specifically designed electronic database (Angoss [Westman Medical Software]). More than 99% of patients had no known history of CVD (ischemic heart disease, cerebrovascular disease, heart failure [HF], or peripheral vascular disease). Data on age, duration of diabetes, smok-

ing history, height, weight, and blood pressure were collected at the initial visit. Information on comorbid conditions (cancer, chronic obstructive pulmonary disease [COPD], and chronic kidney disease [CKD]) was collected at baseline (Table 2). The cohort was followed for clinical events until December 2011. The study was approved by a research ethics committee. Research ethical approval was granted by National Research Ethics Service (reference number 13/SW/0168).

Outcomes

The primary outcome of the analysis was all-cause mortality. A national register informed the hospital of the death of any patient under the hospital's care regardless of whether the patient left the region; information on cause of death was not given. Secondary outcomes were hospitalizations for cardiovascular events, including the acute coronary syndrome (ACS), cerebrovascular accident (CVA), or HF. Information on hospitalizations, coded using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), and mortality was collected through the Patient Information Service of the Hull and East Yorkshire Hospitals National Health Service Trust, the sole hospital provider of emergency medical services in the region. Hospitalizations occurring when the patient was not a resident in the region would be missed, but the rates of emigration of the adult population in this area are low.

Statistical Analysis

Results are presented as medians and interquartile ranges (IQRs) for continuous variables. The primary analysis of interest was the relationship between BMI, expressed in clinical categories according to the World Health Organization (25), and either cardiovascular morbidity or all-cause mortality. The interaction between age (tertiles) and BMI categories was also explored. Tertiles rather than quartiles of age were chosen to maintain the size and statistical power of subgroups while a clear separation between younger and older patients was maintained.

Kruskal–Wallis tests for nonparametric data and chi-square tests were used to compare continuous and dichotomous covariates between BMI groups, respectively. Proportional hazard assumption was tested with Schoenfeld residuals.

Kaplan–Meier survival curves were constructed, and log-rank chi-square testing was used to assess the time to cardiovascular event (ACS, CVA, or HF) and all-cause mortality. If a patient had more than 1 admission for a given cause, only the time to first admission was analyzed.

We constructed a multivariable Cox regression model for all-cause mortality, adjusting for age, sex, duration of diabetes, smoking history, systolic blood pressure, COPD, cancer, CKD, and previous CVD. To assess the interaction among age, BMI, and outcomes, a Cox regression analysis was done by dividing the population in age tertiles and BMI categories.

Patients with COPD, cancer, or CKD may have had an increased mortality risk. Therefore, we assessed the effect of excluding these patients. Patients who died in the first 2 years of follow-up, who might have had a preexisting serious disease leading to weight loss, were excluded in the sensitivity analysis. We also assessed the shape of the association between BMI and survival at different lengths of follow-up (2, 5, or 10 years). The interaction between age (as a continuous variable) and BMI categories was also investigated using a logistic regression analysis (26, 27). We repeated the analysis using body surface area instead of BMI.

A 2-tailed *P* value less than 0.05 was considered statistically significant. All analyses were done using SPSS, version 19.0 (SPSS). Kaplan–Meier curves and logistic regression analysis were produced using Stata, version 11.0 (StataCorp).

Role of the Funding Source

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EDITORS' NOTES

Context

Obesity confers a survival advantage in patients with established cardiovascular disease (CVD). It remains unclear whether obesity provides a similar benefit for type 2 diabetes mellitus.

Contribution

This longitudinal study involved patients with type 2 diabetes without baseline CVD. Investigators collected information on CVD events and all-cause mortality during a median of 10.6 years of follow-up.

Caution

Information was not available on patient fitness levels, medication use, or cause of death.

Implication

Overweight and obese patients had an increased risk for CVD events. A survival advantage was found in overweight but not obese patients.

RESULTS

The cohort included 10 568 patients (54% men; median age, 63 years [IQR, 55 to 71]) who were followed for a median of 10.6 years (IQR, 7.8 to 13.4). The median baseline BMI was 29.0 kg/m^2 (IQR, 26.0 to 32.0). There were many differences among the BMI categories for the characteristics considered (Table 2).

Nine hundred twelve patients were admitted for ACS (9%), 760 for CVA (7%), and 598 for HF (6%); 3728 (35%) patients died. Overweight or obese patients (BMI >25 kg/m^2) had a higher rate of cardiac events (ACS

Table 1. Previous Studies Investigating the Relationship Between BMI and Survival Outcomes in Patients With Type 2 Diabetes Mellitus

Study, Year (Reference)	Follow-up Start Year	Study Type	Population or Location	Underweight Excluded	Participants, *n*	Women, %
Pettitt et al, 1982 (8)	1965	Prospective	Pima Indians	No	499	NR
Balkau et al, 1993 (9)	1968	Prospective	France	No	1003	0
Ford and DeStefano, 1991 (10)	1971	Prospective	United States	No	602	63
Ross et al, 1997 (11)	1972	Prospective	United States	No	373	NR
Rosengren et al, 1989 (12)	1974	Prospective	Swedish	No	232	0
Morrish et al, 1990 (13)	1975	Prospective	British	No	246	48
Chaturvedi and Fuller, 1995 (14)	1975	Prospective, multicenter	Europeans, East Asians, and Native Americans	No	2960	52
Tobias et al, 2014 (23)	1976	Prospective	United States	Yes	11 427	73
Carnethon et al, 2012 (15)	1979§	Patient-data meta-analysis	United States	Yes	2625	30
Sasaki et al, 1989 (16)	1979	Prospective	Japanese	Unclear	1939	NR
Zoppini et al, 2003 (17)	1986	Retrospective	Italy	Unclear	3398	NR
Mulnier et al, 2006 (18)	1992	Case–control	United Kingdom	No	28 725	47
McAuley et al, 2007 (19)	1995	Prospective	United States	Yes	831	0
Khalangot et al, 2009 (20)‖	1997	Prospective, multicenter	Ukraine	No	89 443	66
Logue et al, 2013 (21)	2001	Retrospective	United Kingdom	No	106 640	45
McEwen et al, 2007 (22)	2004	Prospective	United States	No	8733	53

BMI = body mass index; NR = not reported; PY = person-year.
* Values are years except where noted.
† Values are kg/m^2 except where noted.
‡ Measures the methodologic quality of the study; the highest score is 21. See reference 24.
§ Pooled analysis of different observational studies, with the oldest (Framingham) starting in 1979.
‖ Only type 1 diabetes mellitus.

and HF) than normal-weight persons (BMI, 18.5 to 24.9 kg/m^2). The risk for CVA was greater only in obese patients (BMI, 30 to 34.9 kg/m^2) (**Figures 1** and **2** and **Table 2**).

Obesity was associated with a higher rate of ACS in the youngest tertile of patients (aged <57 years), with a similar trend in the middle tertile (aged 57 to 67 years) but not among the oldest tertile. The risk for CVA was higher in obese patients only in the middle tertile. The risk for HF was higher in obese patients in all age tertiles (**Appendix Figure 1**, available at www.annals.org).

Although the risk for cardiovascular events was higher in patients who were overweight or obese, mortality risk was not. Uncorrected Kaplan–Meier estimates suggested a survival advantage for higher BMI categories (log-rank chi-square, 105; $P < 0.001$) (**Figure 1**). Furthermore, the Cox regression analysis, accounting for covariates (see Methods), showed that being overweight was associated with a reduced mortality risk, whereas obesity was not associated with an increased mortality risk, using normal BMI as the reference group (**Figure 2** and **Appendix Table**, available at www.annals.org).

Logistic regression analysis suggested that the lower mortality risk conferred by being overweight or obese seemed to develop around age 60 years (**Appendix Figure 2**, available at www.annals.org).

Neither excluding patients who died in the first 2 years of follow-up nor repeating the analyses using body surface area instead of BMI affected the results. Different lengths of follow-up (2, 5, or 10 years) gave similar results in terms of mortality, suggesting that the relationship between outcome and BMI was not due to occult malignant disease. The results were not affected by excluding patients with cancer, CKD, or COPD, separately or combined, at baseline (**Appendix Figure 3**, available at www.annals.org).

DISCUSSION

Being overweight or obese was associated with a higher risk for nonfatal cardiovascular events but not mortality during long-term follow-up in this cohort of patients with type 2 diabetes. Those whose weight was below the normal range had a high mortality risk. The BMI associated with the best survival rate was shifted from the conventional normal-weight (18.5 to 24.9 kg/m^2) (28) to the overweight (25 to 29.9 kg/m^2) BMI category. Many more patients died than were admitted for a cardiovascular event; therefore, our findings on mor-

Table 1–Continued

Age, *y*	Follow-up*	Outcome	BMI With Best Outcome†	Author Conclusions	Detsky Score‡
15–74	11	All-cause mortality	35–40	Mortality risk greatest in BMI >40 kg/m^2 but not between 30 and 40 kg/m^2	5
49	16	All-cause mortality	<28	BMI >28 kg/m^2 associated with higher mortality risk	9
NR	10	All-cause mortality	None	BMI not associated with mortality risk	10
40–79	14	All-cause mortality	21–27	U-shaped curve	10
55 (SD, 2)	7	All-cause mortality	<23; >26	BMI not related to coronary events or mortality risk	11
47	12	All-cause mortality	None	BMI not associated with mortality risk	10
47	13	All-cause mortality	<26	Obesity associated with greater mortality risk in Europeans	11
61	16	All-cause mortality, cardiovascular mortality, and mortality from other causes	22.5–25.0	Obesity associated with increased mortality risk	18
60	10 000 PYs	All-cause mortality and cardiovascular mortality	>25	BMI >25 kg/m^2 associated with lower mortality risk	18
NR	9	All-cause mortality	NR	Lower BMI associated with higher mortality risk	10
NR	10	All-cause mortality	BMI fourth quartile >65 y	Age <65 y and obesity associated with higher mortality risk; age >65 y and obesity associated with lower mortality risk	8
67	7	All-cause mortality	25–29	U-shaped curve	10
61	11	All-cause mortality	>25	Normal weight associated with higher mortality risk	12
62	3	All-cause mortality	25–30	U-shaped curve	12
56	5	All-cause and cardiovascular mortality	25–30	U-shaped curve	12
61	4	All-cause mortality	>26	Normal weight associated with higher mortality risk	14

tality are more robust than those for nonfatal cardiovascular events. The rate of hospital admission seems low compared with that for mortality, reflecting the restricted number of primary diagnoses on which we focused.

Sixteen studies have been published investigating the relationship between obesity (mostly defined by BMI) and mortality in type 2 diabetes (Table 1). The results are inconsistent and contradictory. Nine studies reported an increase in mortality in obese patients with type 2 diabetes, with a U-shaped relationship (increased risk at lower and higher BMIs) (9, 11, 14, 17, 18, 20, 21, 23). In contrast, 4 studies showed that being overweight or obese was associated with better overall survival rates (15, 16, 19, 22). Four studies showed no association between BMI and mortality (8, 10, 12, 13).

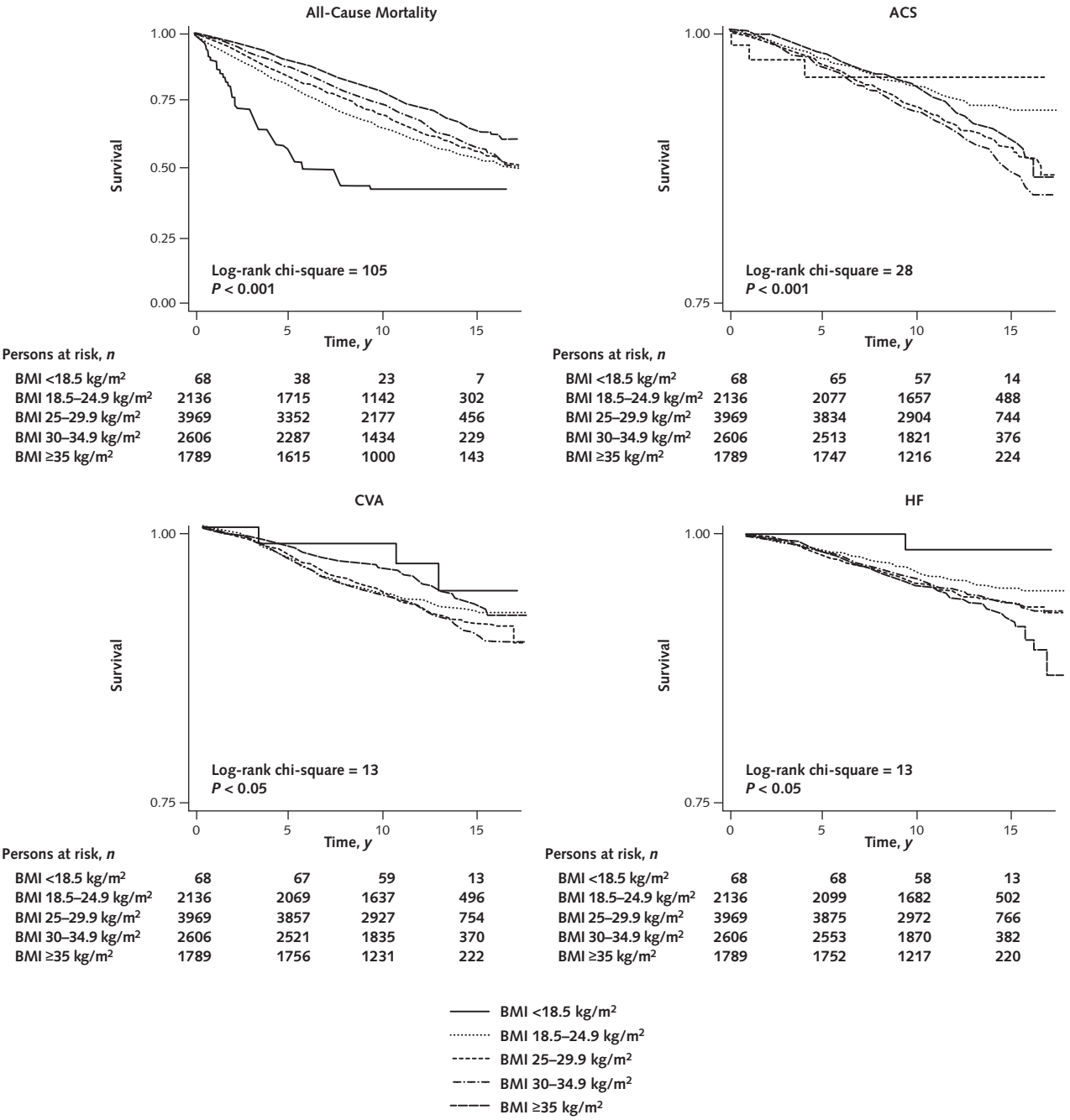
An observational study should be prospective; have a substantial number of patients and events; have

Table 2. Baseline Characteristics

Variable	Total Population	BMI					*P* Value
		<18.5 kg/m^2	18.5–24.9 kg/m^2	25–29.9 kg/m^2	30–34.9 kg/m^2	≥35 kg/m^2	
Total, *n*	10 568	68	2136	3969	2606	1789	<0.001
Median age (IQR), *y*	63 (19)	63 (19)	66 (12)	65 (8)	62 (8)	59 (9)	<0.001
Men, %	54	46	53	62	55	37	<0.001
Median diabetes duration (IQR), *y*	1.0 (6.0)	2.0 (3.7)	3.0 (5.0)	1.5 (3.0)	1.0 (2.0)	1.0 (1.5)	<0.001
Median follow-up (IQR), *y*	11.0 (6.0)	6.0 (4.7)	10.5 (3.7)	10.9 (2.9)	10.8 (2.6)	10.7 (2.3)	<0.001
Median height (IQR), *m*	1.66 (0.10)	1.66 (0.10)	1.67 (0.10)	1.68 (0.10)	1.68 (0.10)	1.67 (0.10)	<0.001
Median weight (IQR), *kg*	81.0 (23.0)	48.0 (5.0)	64.0 (6.0)	77.0 (7.0)	90.0 (7.5)	101.0 (22.0)	<0.001
Median BMI (IQR), *kg/m^2*	29.0 (7.0)	17.6 (0.4)	23.1 (1.2)	27.5 (1.4)	32.0 (1.2)	38.0 (2.4)	<0.001
Smokers, %	16	34	19	15	15	15	<0.001
Median SBP (IQR), *mm Hg*	140 (29)	130 (16)	140 (17)	140 (15)	144 (15)	145 (14)	<0.001
Comorbid conditions, %							
CKD	17	12	17	20	17	14	<0.050
COPD	7	13	6	7	8	9	<0.001
Cancer	15	12	13	16	15	14	<0.001
Previous CVD	1.0	0.0	0.7	1.1	1.2	1.3	NS

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; IQR = interquartile range; NS = not significant; SBP = systolic blood pressure.

Figure 1. Unadjusted Kaplan–Meier estimates of cardiovascular events and all-cause mortality.



Persons at risk, *n*

BMI <18.5 kg/m²	68	38	23	7
BMI 18.5–24.9 kg/m²	2136	1715	1142	302
BMI 25–29.9 kg/m²	3969	3352	2177	456
BMI 30–34.9 kg/m²	2606	2287	1434	229
BMI ≥35 kg/m²	1789	1615	1000	143

Persons at risk, *n*

BMI <18.5 kg/m²	68	65	57	14
BMI 18.5–24.9 kg/m²	2136	2077	1657	488
BMI 25–29.9 kg/m²	3969	3834	2904	744
BMI 30–34.9 kg/m²	2606	2513	1821	376
BMI ≥35 kg/m²	1789	1747	1216	224

Persons at risk, *n*

BMI <18.5 kg/m²	68	67	59	13
BMI 18.5–24.9 kg/m²	2136	2069	1637	496
BMI 25–29.9 kg/m²	3969	3857	2927	754
BMI 30–34.9 kg/m²	2606	2521	1835	370
BMI ≥35 kg/m²	1789	1756	1231	222

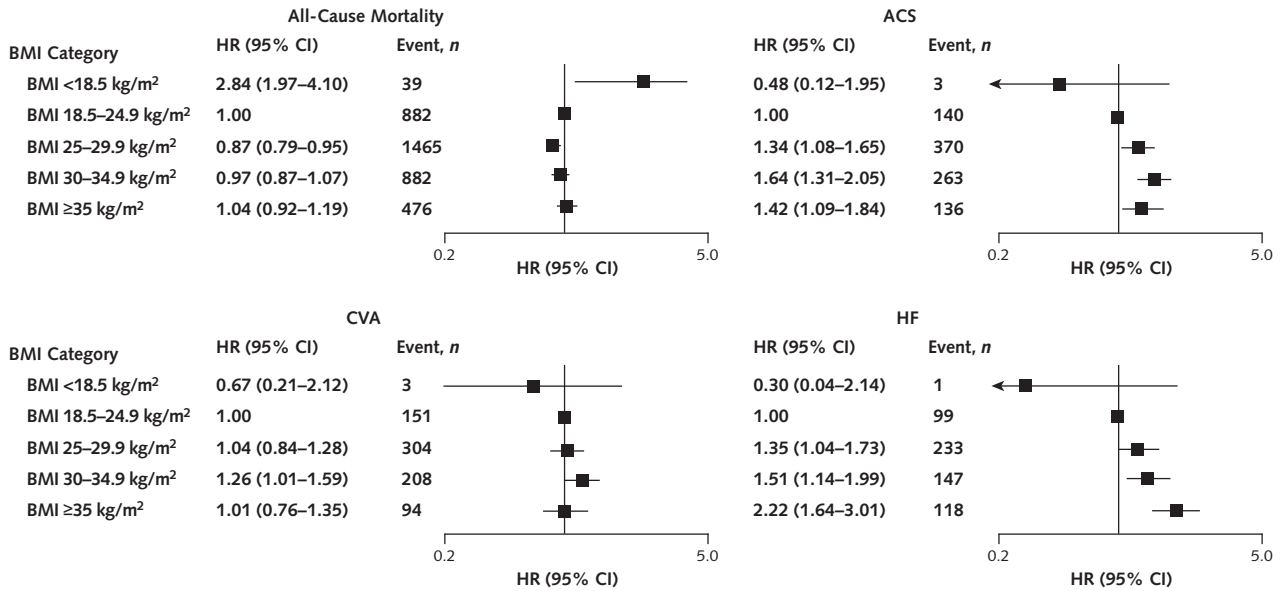
Persons at risk, *n*

BMI <18.5 kg/m²	68	68	58	13
BMI 18.5–24.9 kg/m²	2136	2099	1682	502
BMI 25–29.9 kg/m²	3969	3875	2972	766
BMI 30–34.9 kg/m²	2606	2553	1870	382
BMI ≥35 kg/m²	1789	1752	1217	220

Patients were followed for a median of 10.6 y (interquartile range, 7.8–13.4). Admissions for ACS occurred in 912 patients (9%), CVA in 760 patients (7%), and HF in 598 patients (6%); 3728 patients (35%) died. ACS = acute coronary syndrome; BMI = body mass index; CVA = cerebrovascular accident; HF = heart failure.

long-term follow-up; include relevant confounding factors, such as comorbid conditions; not include patients who are underweight in the normal-weight group; use primary data (collected by the investigator for the purpose of the study); and use consistent data definitions, which might be best achieved in a single center (29, 30). None of the previous studies fulfill all of these criteria, which may explain their conflicting results. In particular, 6 studies had inadequate statistical power, with fewer than 1000 patients enrolled (2, 10–13, 19); 7 did not have long-term follow-up (<10 years) (12, 15, 16, 18, 20–22); 2 were retrospective; 1 was a case–control study (17, 18, 21); and only 2 clearly separated underweight and normal-weight categories (15, 23).

Figure 2. Cox regression analysis, according to BMI categories, for cardiovascular events and all-cause mortality.



Adjusted for age, sex, duration of diabetes, systolic blood pressure, smoking, and comorbid conditions (such as cancer, chronic obstructive pulmonary disease, and chronic renal failure). The reference group is the normal BMI category (18.5–24.9 kg/m^2). Squares represent HRs, and bars represent 95% CIs. The *y*-axis corresponds to an HR of 1. ACS = acute coronary syndrome; BMI = body mass index; CVA = cerebrovascular accident; HF = heart failure; HR = hazard ratio.

The results are discordant, even among the 4 methodologically strongest reports. Carnethon and colleagues (15) reported an analysis of data from 2625 patients with type 2 diabetes from 2 separate studies. They suggested that those with a BMI greater than 25 kg/m^2 had a higher mortality risk than normal-weight patients. Comorbid conditions were not taken in account. McEwen and colleagues (22) investigated 8733 patients in a multicenter study of patients with type 2 diabetes followed for 4 years. They found a higher mortality risk among normal-weight persons than among overweight or obese persons, but they did not adjust for comorbid conditions and underweight patients were classified as "normal." When follow-up was extended to 8 years, the results were not confirmed (31). In a large diabetes registry with a median follow-up of 4.7 years, there was a U-shaped relationship between BMI and death, with the lowest mortality risk found in the range of 25 to 29.9 kg/m^2 (21). Tobias and colleagues (23) reported an analysis of 11 427 women without CVD or cancer and with incident type 2 diabetes from the Nurses' Health Study and the Health Professionals Follow-up Study. Those with type 2 diabetes who were overweight or obese at diagnosis had a mortality risk similar to those of normal weight.

Our study had considerable strengths. The study sample was large; follow-up was long; and adjustment was made for other key characteristics, such as smoking and systolic blood pressure. We also considered comorbid conditions, such as cancer, CKD, and lung disease. In addition, all data were collected in a single center with direct access to the patients' records, limiting the risk for heterogeneity in measurement collection and ensuring consistent data definitions.

Our study suggests that type 2 diabetes induced by the metabolic stress of obesity may fundamentally differ from that which develops in the absence of obesity (32, 33). Obese patients with type 2 diabetes might not have diabetes if they lost weight (34). Those with greater genetic susceptibility to type 2 diabetes may be more likely to develop it at a lower BMI "stress" and might also be at greater risk for complications or other diseases and consequently have a poor prognosis (15, 35). If this is true, then even if an obese patient with type 2 diabetes has a better prognosis than a normal-weight patient with diabetes, prognosis might still be improved by losing weight.

Whether weight loss can reduce mortality risk is still unclear. Randomized, controlled trials of weight loss should be done to determine whether it improves prognosis. The Look-AHEAD (Action for Health in Diabetes) trial tried to address this topic by assessing an intense lifestyle change designed to reduce weight in patients with type 2 diabetes. Despite decreasing blood pressure and slowing deterioration of renal function, a reduction in cardiovascular events and mortality was not achieved. However, the intervention had little effect on weight (36, 37). The failure of the intervention to improve outcome may reflect the inability to reduce weight substantially rather than failure of weight loss to provide benefit. Several other studies have suggested that lifestyle interventions may improve prognosis in

patients with type 2 diabetes (38). Attention is switching from weight to the general fitness of patients; obesity may be an inexact surrogate for the participant's level of fitness (39). In a general population, exercise capacity on a treadmill predicts cardiovascular events better than BMI; in men with type 2 diabetes, those who were overweight or mildly obese but physically fit were less likely to have cardiovascular events than men of normal weight who were unfit (40, 41).

Another approach would be to analyze large databases that include patients with and without type 2 diabetes to determine whether the excess associated risk differs according to BMI. If type 2 diabetes provoked by obesity is associated with a more benign prognosis, then the prognosis of persons with high BMI should be similar, regardless of whether they have type 2 diabetes, but markedly worse for those with type 2 diabetes and lower BMI. A recent report of 2035 patients with type 2 diabetes followed for 9 years supports this hypothesis, showing that mortality risk was similar among obese patients with and without type 2 diabetes; however, normal-weight patients with type 2 diabetes had a higher risk (42).

There are several other possible explanations for the obesity paradox. Patients with type 2 diabetes and a low BMI might have higher tobacco and alcohol consumption, contributing both to the development of diabetes at a lower BMI and conferring an adverse prognosis (43, 44). We adjusted for smoking but not pack-years, and overweight patients had a significant mortality benefit only if they did not smoke (**Appendix Figure 4**, available at www.annals.org). We did not have data on alcohol consumption.

Another possible explanation is that obese patients may be more likely to be checked for diabetes, leading to an earlier diagnosis. The median age of those in the highest category of BMI was substantially younger than those in the normal-weight category, as others also reported (23). Being overweight might provide a metabolic reserve in older patients, protecting against frailty, malnutrition, and osteoporosis (45, 46). Age-related sarcopenia may be as important a medical problem as obesity, if not more so (47, 48).

We used BMI as a measure of adiposity, but waist circumference and waist–hip ratio may better explain the relationship between obesity and health (49). However, BMI is still conventionally accepted as a measure of obesity (50). Body surface area might be more strongly related to prognosis, especially in patients with HF, than weight or BMI (51), but substituting BMI with body surface area in our analysis did not change the results.

Some previous studies reported data on incident cases of diabetes. Our results were obtained from prevalent cases with different durations of disease, which is a limitation of this study because development and treatment of type 2 diabetes may influence body weight. The results could also represent a higher mortality risk among patients with lower BMI who were already ill for reasons unrelated to diabetes. However, the long-term follow-up and adjustment for key comorbid conditions that might account for weight loss limited this potential bias. Exclusion of deaths in the first 2 years and patients with a history of cancer, CKD, or COPD did not change the results (**Appendix Figure 3**). Another limitation is the lack of information about the medications taken, cholesterol level, and ethnicity. These could have helped in interpreting our results.

Another limitation of this study is the lack of data about fitness, which has been shown to be a better predictor of survival than BMI (40, 41).

The cause of death was not available. We do not know whether the excess mortality seen with lower BMI was due to cardiovascular or noncardiovascular deaths.

For patients with type 2 diabetes, being overweight or obese is associated with a higher risk for nonfatal cardiovascular events but not mortality. The BMI associated with the best survival was shifted from the conventional normal-weight (18.5 to 24.9 kg/m^2) to the overweight (25 to 29.9 kg/m^2) BMI category. The obesity paradox is open to several interpretations that should be addressed by further research rather than promoting preconceptions about the ideal BMI. These results should not discourage patients from adopting a healthy lifestyle.

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Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Costanzo (e-mail, pierluigicostanzo83@gmail.com). *Data set:* Not available.

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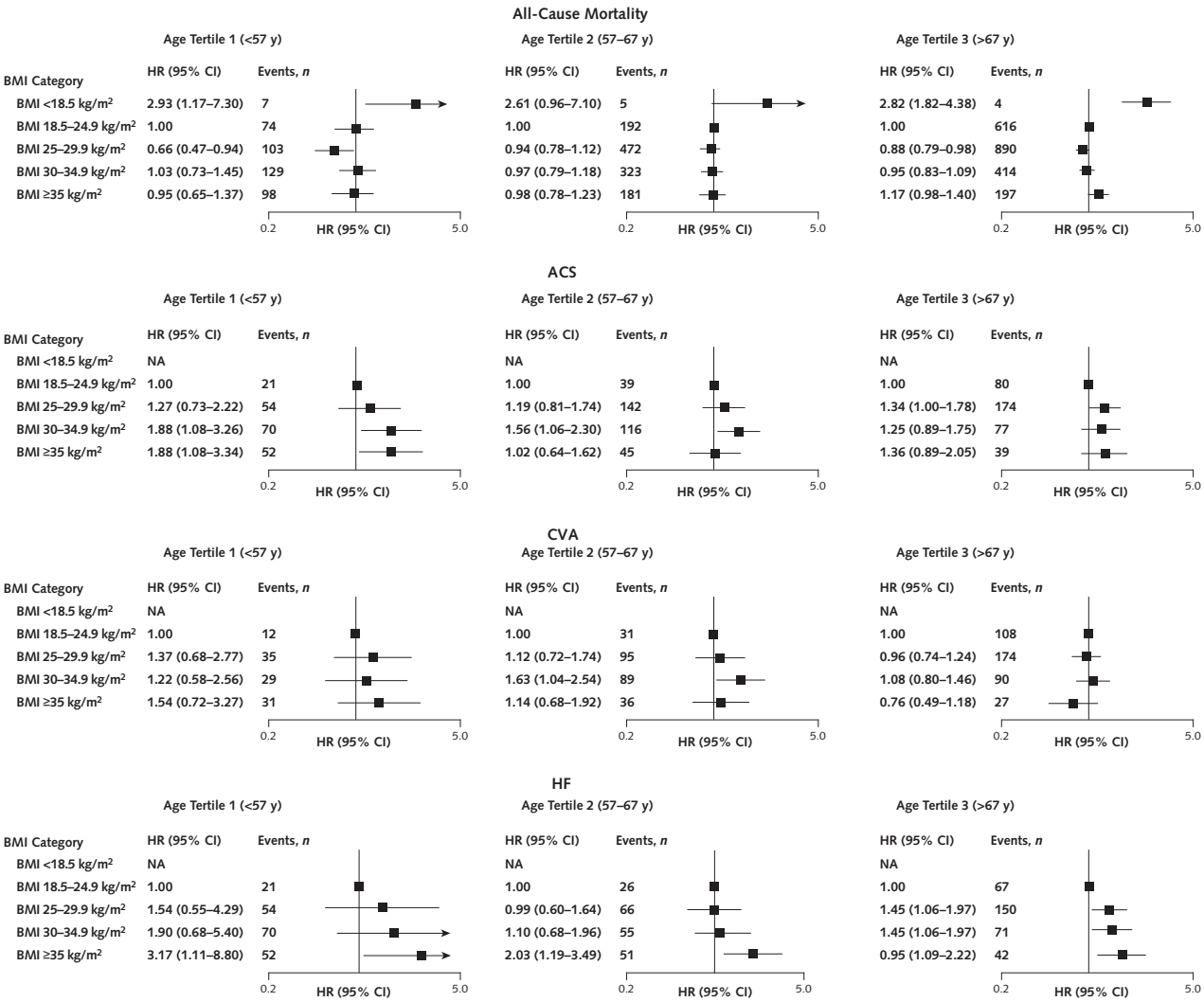
Appendix Figure 1. Cox regression analysis, according to age tertiles and BMI categories, for cardiovascular events and all-cause mortality.



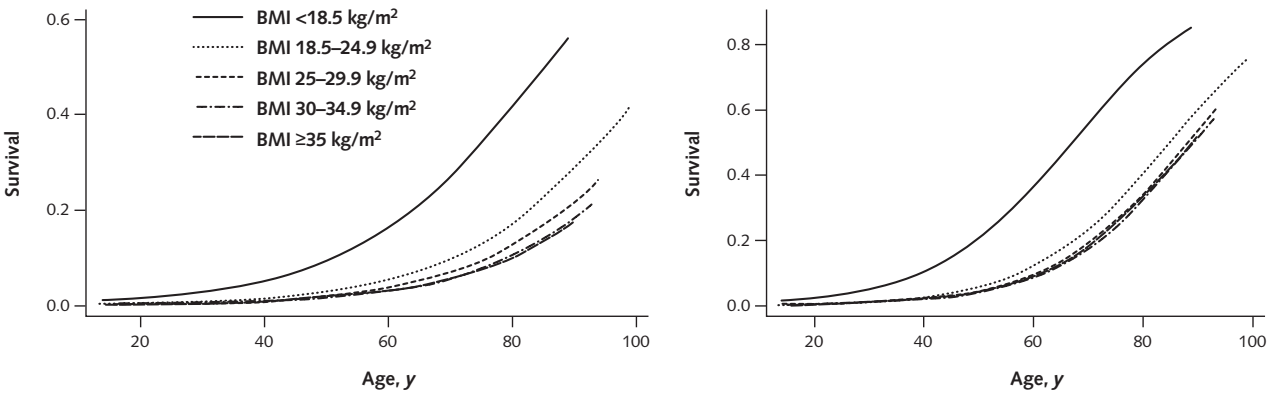
Adjusted for age, sex, diabetes duration, systolic blood pressure, smoking, and comorbid conditions (such as cancer, chronic obstructive pulmonary disease, and chronic renal failure). There were 3522 patients in each tertile. The reference is the normal-weight BMI category (18.5–24.9 kg/m^2). Squares represent HRs, and bars represent 95% CIs. The *y*-axis corresponds to an HR of 1. ACS = acute coronary syndrome; BMI = body mass index; CVA = cerebrovascular accident; HF = heart failure; HR = hazard ratio; NA = not applicable.

Appendix Table. Multivariate Cox Regression Analysis for Cardiovascular Events and All-Cause Mortality*

Variable	HR (95% CI)	*P* Value
All-cause mortality		
BMI <18.5 kg/m^2	2.84 (1.97–4.10)	<0.001
BMI of 18.5–24.9 kg/m^2	1 (reference)	–
BMI of 25–29.9 kg/m^2	0.87 (0.79–0.95)	<0.01
BMI of 30–34.9 kg/m^2	0.97 (0.87–1.07)	0.5
BMI ≥35 kg/m^2	1.04 (0.92–1.19)	0.4
Age	1.08 (1.07–1.08)	<0.001
Men	1.17 (1.10–1.27)	<0.001
Diabetes duration	1.01 (1.00–1.02)	<0.001
Smoker	1.45 (1.32–1.61)	<0.001
SBP	1.01 (1.00–1.01)	<0.08
CKD	1.26 (1.39–1.74)	<0.001
COPD	1.44 (1.32–1.64)	<0.001
Cancer	1.7 (1.57–1.83)	<0.001
CVD	2 (1.46–2.74)	<0.001
ACS		
BMI <18.5 kg/m^2	0.48 (0.12–1.95)	0.3
BMI of 18.5–24.9 kg/m^2	1 (reference)	–
BMI of 25–29.9 kg/m^2	1.34 (1.08–1.65)	<0.01
BMI of 30–34.9 kg/m^2	1.64 (1.31–2.05)	<0.001
BMI ≥35 kg/m^2	1.42 (1.09–1.84)	<0.05
Age	1.02 (1.02–1.03)	<0.001
Men	1.09 (0.95–1.26)	0.22
Diabetes duration	0.99 (0.98–1.00)	0.2
Smoker	1.45 (1.21–1.73)	<0.001
SBP	1.01 (1.00–1.01)	0.2
CKD	0.68 (0.17–2.74)	0.6
COPD	2.02 (1.66–2.47)	<0.001
Cancer	0.96 (0.79–1.16)	0.5
CVD	1.02 (0.45–2.7)	0.9
CVA		
BMI <18.5 kg/m^2	0.67 (0.21–2.1)	0.5
BMI of 18.5–24.9 kg/m^2	1 (reference)	–
BMI of 25–29.9 kg/m^2	1.04 (0.84–1.28)	0.7
BMI of 30–34.9 kg/m^2	1.26 (1.01–1.59)	<0.05
BMI ≥35 kg/m^2	1.01 (0.76–1.35)	0.9
Age	1.04 (1.03–1.05)	<0.001
Men	0.99 (0.84–1.16)	0.9
Diabetes duration	1 (0.99–1.01)	0.9
Smoker	1.24 (1.00–1.53)	0.05
SBP	1.01 (1.00–1.01)	0.001
CKD	0.41 (0.58–2.92)	0.7
COPD	1.58 (1.25–2.00)	<0.001
Cancer	0.86 (0.69–1.06)	0.5
CVD	0.58 (0.18–1.80)	0.3
HF		
BMI <18.5 kg/m^2	0.3 (0.04–2.14)	0.2
BMI of 18.5–24.9 kg/m^2	1 (reference)	–
BMI of 25–29.9 kg/m^2	1.35 (1.04–1.73)	<0.05
BMI of 30–34.9 kg/m^2	1.51 (1.14–1.99)	<0.01
BMI ≥35 kg/m^2	2.22 (1.64–3.01)	<0.001
Age	1.05 (1.04–1.06)	<0.001
Men	1.21 (1.01–1.45)	0.03
Diabetes duration	0.99 (0.98–1.01)	0.5
Smoker	1.32 (1.05–1.67)	<0.05
SBP	1 (1.00–1.01)	0.7
CKD	0.45 (0.06–3.22)	<0.001
COPD	3.17 (2.56–3.91)	<0.001
Cancer	0.97 (0.77–1.21)	0.8
CVD	0.64 (0.20–2.02)	0.4

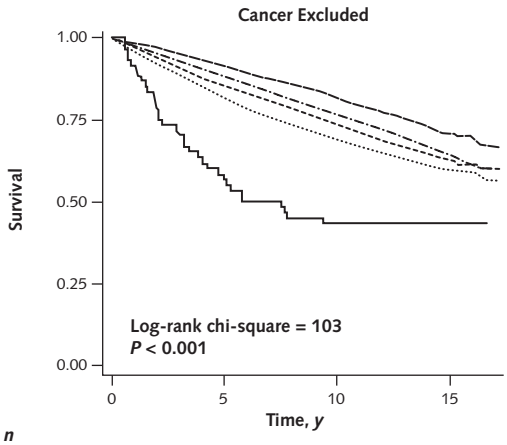
ACS = acute coronary syndrome; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; SBP = systolic blood pressure.
* BMI of 18.5–24.9 kg/m^2 is the reference group.

Appendix Figure 2. Logistic regression analysis for the interaction between age (as a continuous variable) and BMI quartiles.



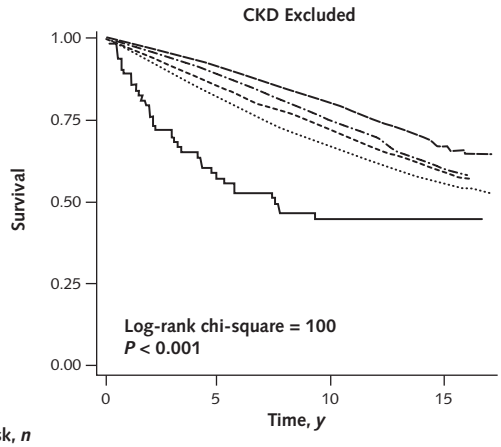
On the *y*-axis, the probability of all-cause mortality is shown against age (*x*-axis) by BMI quartiles ($P < 0.001$) at 2-y (*left*) and 5-y (*right*) follow-up. BMI = body mass index.

Appendix Figure 3. Unadjusted Kaplan–Meier for time to all-cause mortality, excluding patients with cancer, CKD, COPD, or all of these disorders.



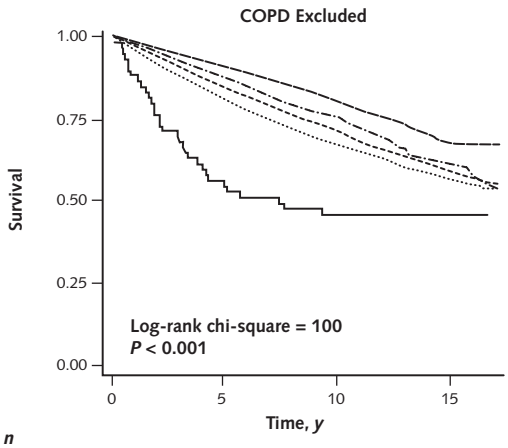
Persons at risk, *n*

BMI <18.5 kg/m²	60	34	21	7
BMI 18.5–24.9 kg/m²	1858	1517	1039	285
BMI 25–29.9 kg/m²	3325	2843	1891	407
BMI 30–34.9 kg/m²	2213	1963	1257	206
BMI ≥35 kg/m²	1546	1407	888	126



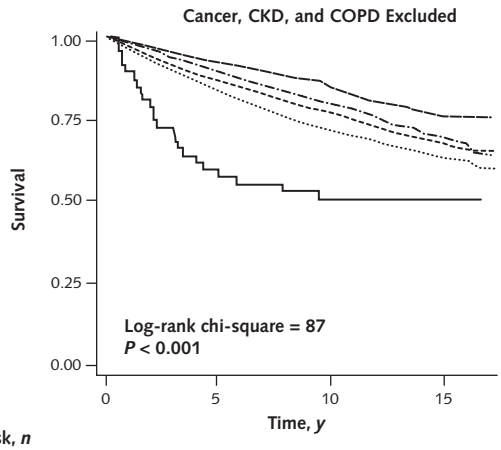
Persons at risk, *n*

BMI <18.5 kg/m²	60	34	22	7
BMI 18.5–24.9 kg/m²	1782	1460	968	265
BMI 25–29.9 kg/m²	3175	2713	1747	334
BMI 30–34.9 kg/m²	2170	1938	1204	176
BMI ≥35 kg/m²	1545	1420	863	116



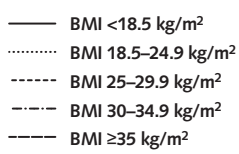
Persons at risk, *n*

BMI <18.5 kg/m²	59	32	21	7
BMI 18.5–24.9 kg/m²	2006	1622	1095	299
BMI 25–29.9 kg/m²	3703	3132	2059	432
BMI 30–34.9 kg/m²	2392	2102	1334	215
BMI ≥35 kg/m²	1624	1471	925	129



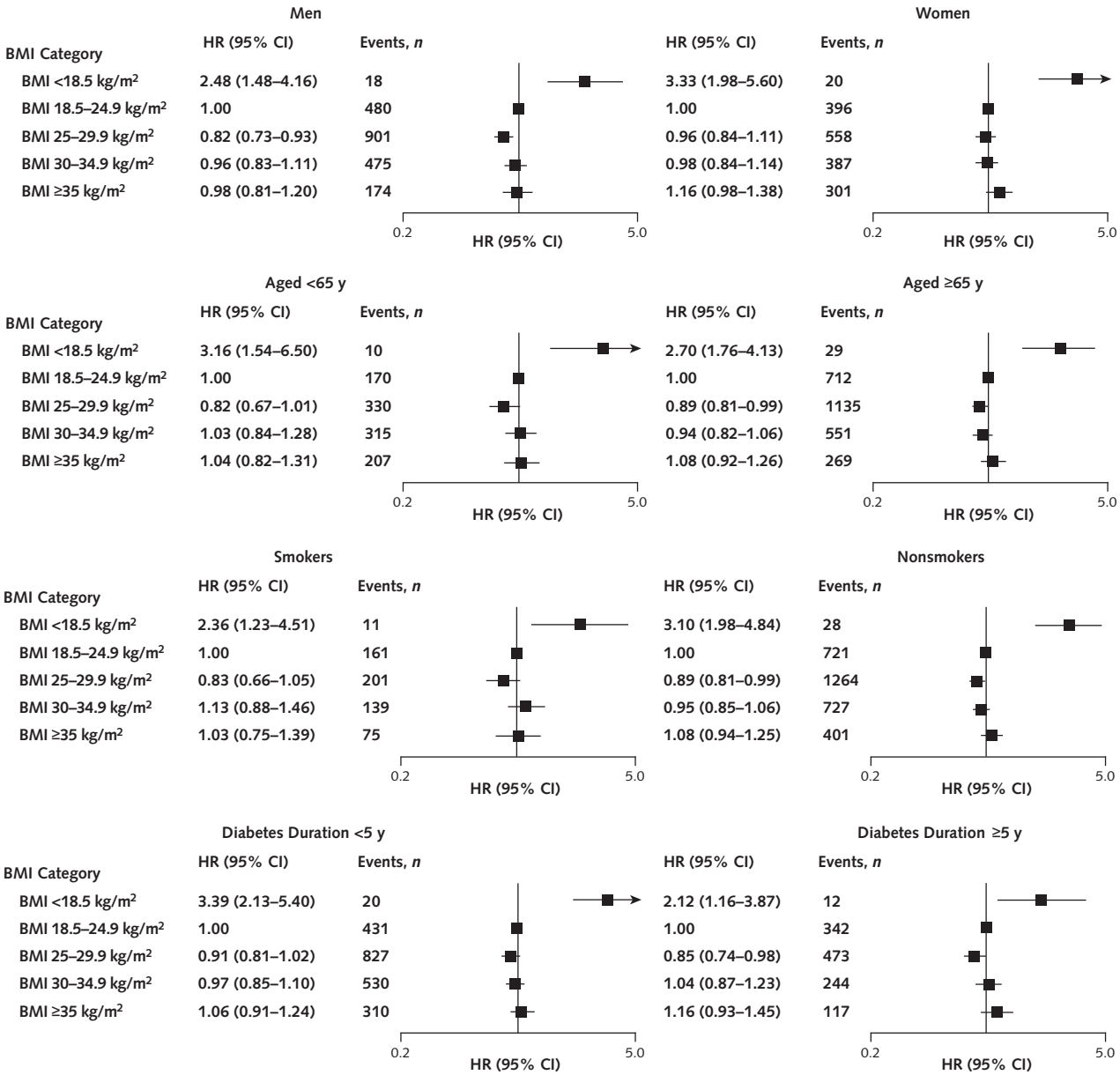
Persons at risk, *n*

BMI <18.5 kg/m²	45	26	19	7
BMI 18.5–24.9 kg/m²	1478	1243	864	252
BMI 25–29.9 kg/m²	2548	2216	1476	290
BMI 30–34.9 kg/m²	1735	1568	998	147
BMI ≥35 kg/m²	1234	1152	722	95



Cumulative survival is shown on the *y*-axis. BMI = body mass index; CKD = chronic kidney disease; COPD = chronic pulmonary obstructive disease.

Appendix Figure 4. Cox regression analysis for all-cause mortality, by BMI quartiles in prespecified groups (men vs. women, age <65 y vs. ≥65 y, smokers vs. nonsmokers, and diabetes duration <5 y vs. ≥5 y).



Squares represent HRs, and bars represent 95% CIs. The *y*-axis corresponds to an HR of 1. BMI = body mass index; HR = hazard ratio.