Relationship of Obesity to Adverse Events Among Patients With Mean 10-Year History of Type 2 Diabetes Mellitus: Results of the ACCORD Study

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Background—Recent evidence from cohort studies and meta-analyses suggests that the obesity paradox phenomenon may exist in patients with diabetes mellitus. The goal of this study was to assess the association between adverse events and obesity by using 2 different measures of obesity, body mass index (BMI; kg/m^2) and waist circumference, in patients with a mean 10-year history of type 2 diabetes mellitus.

Methods and Results—We used data from the ACCORD (the Action to Control Cardiovascular Risk in Diabetes) study to evaluate the relationship between obesity and adverse events in patients with a mean 10-year history of type 2 diabetes mellitus. The primary outcome of this study was all-cause mortality. Secondary outcomes were cardiac death, nonfatal myocardial infarction, and stroke. Patients who were class III obese with BMI ≥40 had the highest risk of all-cause mortality, followed by patients with class II obesity, whereas overweight patients had the lowest risk. We found significant correlations between BMI and waist circumference (r=0.802). We observed that the relationships between waist circumference and primary and second end points were much like the relationships between BMI and primary and second end points (J-shaped relationship for all-cause mortality, V-shaped relationship for cardiac death, U-shaped relationship for nonfatal myocardial infarction, and reverse linear relationship for noncardiac death).

Conclusions—No evidence of the obesity paradox was observed in patients with a 10-year history of diabetes mellitus. Class III obese patients showed the highest risk of adverse events (all-cause mortality, cardiac death, nonfatal myocardial infarction, and noncardiac death). BMI and waist circumference showed similar relationships with adverse events.

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Key Words: all-cause death • body mass index • diabetes mellitus • obesity paradox • waist circumference

T
he prevalence of obesity has almost doubled over the past 3 decades and has been become a health problem worldwide.[1,2] Although obesity is associated with an increased risk of coronary atherosclerotic heart disease and related cardiovascular risk factors, such as hypertension and diabetes mellitus (DM), multiple clinical trials have demonstrated that obesity offers a striking protective effect over "normal" body mass index (BMI; kg/m^2), a phenomenon known as the *obesity paradox*.[3–5] This protective role of

obesity has been demonstrated in different populations, including patients with coronary artery disease, heart failure, and atrial fibrillation.[6–8] Recent evidence from cohort research and meta-analyses suggests that the obesity paradox may also exist in patients with DM.[9,10] In those studies, patients who were a normal weight at the time of diagnosis of DM had higher all-cause mortality than those patients who were overweight or obese.[9] However, whether the protective role of obesity in type 2 DM (T2DM) decreases with the progress of DM is still in dispute. So et al found a V-shaped relationship of BMI with mortality in Chinese populations with a mean 5-year duration of DM.[11] Kokkinos observed an inverse linear relationship of BMI with mortality in black and white populations with unspecified durations of DM.[10] Cardiovascular disease (CVD) is the leading cause of death and the single biggest driver of healthcare costs in patients with T2DM. However, it usually takes ≥10 years after diagnosis for patients with DM to develop CVD. Prior studies have focused mainly on newly diagnosed T2DM patients and those with a short history of T2DM. The relationships

Clinical Perspective

What Is New?

- We studied the relationship between 2 measures of obesity (body mass index and waist circumference) and adverse events in patients with a mean 10-year history of type 2 diabetes mellitus.

What Are the Clinical Implications?

- No evidence of the obesity paradox was observed in patients with a 10-year history of diabetes mellitus.
- Class III obese patients with body mass index ≥40 had the highest risk of adverse events (all-cause mortality, cardiac death, nonfatal myocardial infarction, and noncardiac death), followed by patients with class II obesity. Overweight patients had the lowest risk.
- Body mass index and waist circumference showed similar relationships with adverse events.

between obesity and mortality in these populations have been described previously.[9,12] Little is known about the relationship between obesity and adverse events in T2DM patients with a long history of DM. Furthermore, previous studies have included relatively small sample sizes and small proportions of patients with extreme obesity (BMI ≥40), which makes their conclusions less convincing.[3,5,9,12] Recent studies have focused on abdominal obesity, as evaluated by waist circumference.[13,14] However, no relevant study has investigated the relationship among obesity, waist circumference, and adverse clinical outcomes. In the current study, we sought to evaluate the relationship between obesity (defined by both BMI and waist circumference) and adverse events in this population with a mean 10-year history of T2DM.

Method

The national database data used for this study, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of the agreement with the Biological Specimen and Data Repository Information Coordinating Center (BioLINCC). Ethics approval and consent to participate were not applicable.

Data Collection and Study Population

The rationale and design of the ACCORD (the Action to Control Cardiovascular Risk in Diabetes) trial have been described previously and the results published.[15–17] Briefly, ACCORD was a multicenter randomized controlled trial performed to determine whether intensive control of blood glucose, blood pressure, and lipids could reduce the incidence of CVD in T2DM patients at high risk of CVD. The trial recruited 10 251 volunteers with T2DM whose mean age was 62 years. At the time of recruitment, participants had T2DM for a median of 10 years. They had a mean glycated hemoglobin (HbA1c) level of 8.3%. Some also had a history of previous CVD or CVD risk factors (dyslipidemia, hypertension, current status as a smoker, or obesity). The participants were recruited from 77 clinical centers across the United States and Canada. Surprisingly, intensive control of blood glucose, blood pressure, and lipids was found to have a neutral effect on death and nonfatal cardiovascular events but increased cardiac death.[18]

Exposure Variable

This study is based on the ACCORD trial derived from BioLINCC. We excluded 6 patients for whom no BMI data were available. We further excluded 3 patients in the *underweight* category because of the small proportion in this category (0.03%). BMI is defined as their weight in kilograms divided by the square of their height in meters. Patients were classified according to BMI standards: *normal*, 18.5 to <25; *overweight*, 25 to <30; *class I obese*, 30 to <35; *class II obese*, 35 to <40; and *class III obese*, BMI ≥40. Waist circumference was determined according to the NHANES (the National Health and Nutrition Examination Survey) III protocol during normal minimal respiration by placing a measuring tape around the waist just above the uppermost lateral border of the iliac crest.[13,19] The primary outcome of the present study was all-cause mortality. Secondary outcomes were cardiac death, nonfatal myocardial infarction (MI), and stroke, which have been defined previously.[15,17]

Statistical Analysis

Baseline characteristics of patients across the categories were summarized as frequencies and percentages for categorical variables and as means and standard deviations or interquartile range for continuous variables, depending on whether data distribution was normal (assessed by normal Q-Q plots). Categorical variables were compared using χ^2 analysis, and continuous variables were compared by ANOVA test or Mann–Whitney U test, according to distribution type. Cox proportional hazards regression models that included statistically significant covariates and clinically meaningful confounders were performed to investigate the relationship between BMI and clinical end points. The adjusted event hazard associated with each BMI stratum was compared with the class III obese group (BMI ≥40). Survival curves from Cox regression models, inclusive of the 5 BMI groups defined earlier, with statistically significant covariates and clinically meaningful confounders as co-covariates, were performed

Table 1. Baseline Demographic, Clinical, and Laboratory Examination Characteristics

| | BMI Category (kg/m²) | | | | | |
	Normal Weight, <25	Overweight, 25 to <30	Class I Obese, 30 to <35	Class II Obese, 35 to <40	Class III Obese, ≥40	P Value
n	860	2962	3368	2069	985	
BMI, kg/m²	23.4±1.36	27.8±1.37	32.4±1.43	37.2±1.43	42.3±1.61	0.000
Age, y	64.0±7.53	63.9±6.95	62.9±6.51	61.6±6.00	60.9±5.78	0.000
Sex, %						0.000
Male	555 (64.5)	2024 (68.3)	2156 (64.0)	1139 (55.1)	421 (42.7)	
Female	306 (35.5)	938 (31.7)	1212 (36.0)	930 (44.9)	564 (57.3)	
Race						0.000
White	355 (41.2)	1698 (57.3)	2216 (65.8)	1428 (69.0)	692 (70.3)	
Nonwhite	506 (58.8)	1264 (32.8)	1152 (34.2)	641 (31.0)	293 (37.6)	
Median duration of DM, y	11.8±7.8	11.6±8.0	10.2±7.30	10.4±7.17	10.4±7.59	0.000
Hypertension	592 (68.8)	2178 (73.5)	2543 (75.5)	1618 (78.2)	790 (80.2)	0.000
Hyperlipidemia	556 (64.7)	2085 (70.4)	2423 (71.9)	1409 (68.1)	687 (69.7)	0.000
Previous cardiovascular events	282 (32.8)	1099 (37.1)	1219 (36.2)	694 (33.5)	311 (31.6)	0.000
Current smoker	182 (21.2)	468 (15.8)	430 (12.8)	244 (11.8)	102 (10.4)	0.000
Previous heart failure	35 (4.10)	117 (4.00)	133 (3.90)	136 (6.60)	71 (7.20)	0.000
Proteinuria	146 (17.0)	524 (17.7)	651 (19.3)	469 (22.7)	243 (24.7)	0.000
Depression	113 (13.1)	563 (19.0)	783 (23.2)	614 (29.7)	348 (35.3)	0.000
Waist circumference, cm	86.8±7.23	97.8±7.89	107.9±8.51	117.1±9.48	125.5±10.0	0.000
HR, beats/min	72.0±11.8	71.5±11.6	73.3±11.8	73.6±11.6	75.1±11.8	0.000
SBP, mm Hg	136±18.2	137±16.8	136±17.0	136.4±17.1	136±17.3	0.523
DBP, mm Hg	72.7±10.7	73.6±10.5	75.8±10.6	75.9±10.5	77.3±10.8	0.000
Glycated hemoglobin, %	8.29±1.06	8.29±1.03	8.29±1.03	8.31±1.03	8.33±1.07	0.290
GFR, mL/min	93.3±37.7	90.7±27.9	90.6±24.2	91.7±26.4	90.1±27.1	0.043
FPG, mg/dL	174.7±66.3	172.8±54.9	175.8±55.3	177.4±54.7	177.±54.7	0.061
Cholesterol, mg/dL						
Total	184.3±42.6	180.7±41.8	183.6±42.4	185.0±40.4	186.0±41.9	0.001
LDL	108.1±35.1	104.3±33.3	104.8±34.1	104.8±33.3	106.3±33.9	0.021
HDL	46.6±14.6	41.9±11.4	41.0±11.2	41.2±11.0	41.8±11.1	0.000
Urinary albumin, mg/dL	10.8±36.0	8.70±27.1	10.0±36.1	12.2±45.3	11.3±36.6	0.015
Medications						
Insulin	57 (6.6)	295 (10.0)	367 (10.9	267 (12.9)	154 (15.6)	0.000
Metformin	534 (62)	1862 (62.9)	2211 (65.7)	1324 (64.0)	622 (63.1)	0.112
Sulfonylurea	493 (57.3)	1648 (55.6)	1806 (53.6)	1068 (51.6)	458 (46.5)	0.000
Thiazolidinedione	137 (6.1)	566 (25.1)	742 (22.0)	534 (25.8)	277 (28.1)	0.001
β-Blocker	200 (23.4)	839 (28.3)	1030 (33.5)	696 (33.7)	312 (31.7)	0.000
ACEI	399 (46.7)	1642 (55.5)	1834 (54.7)	1159 (56.1)	530 (53.9)	0.000
Statin	508 (59.6)	1920 (65.0)	2172 (64.8)	1302 (63.1)	595 (60.5)	0.005
Aspirin	405 (47.5)	1594 (54.0)	1907 (57.0)	1135 (55.0)	534 (54.4)	0.000

Data are shown as mean±SD or n (%) except as noted. ACEI indicates angiotensin-converting enzyme inhibitor; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; SBP, systolic blood pressure.
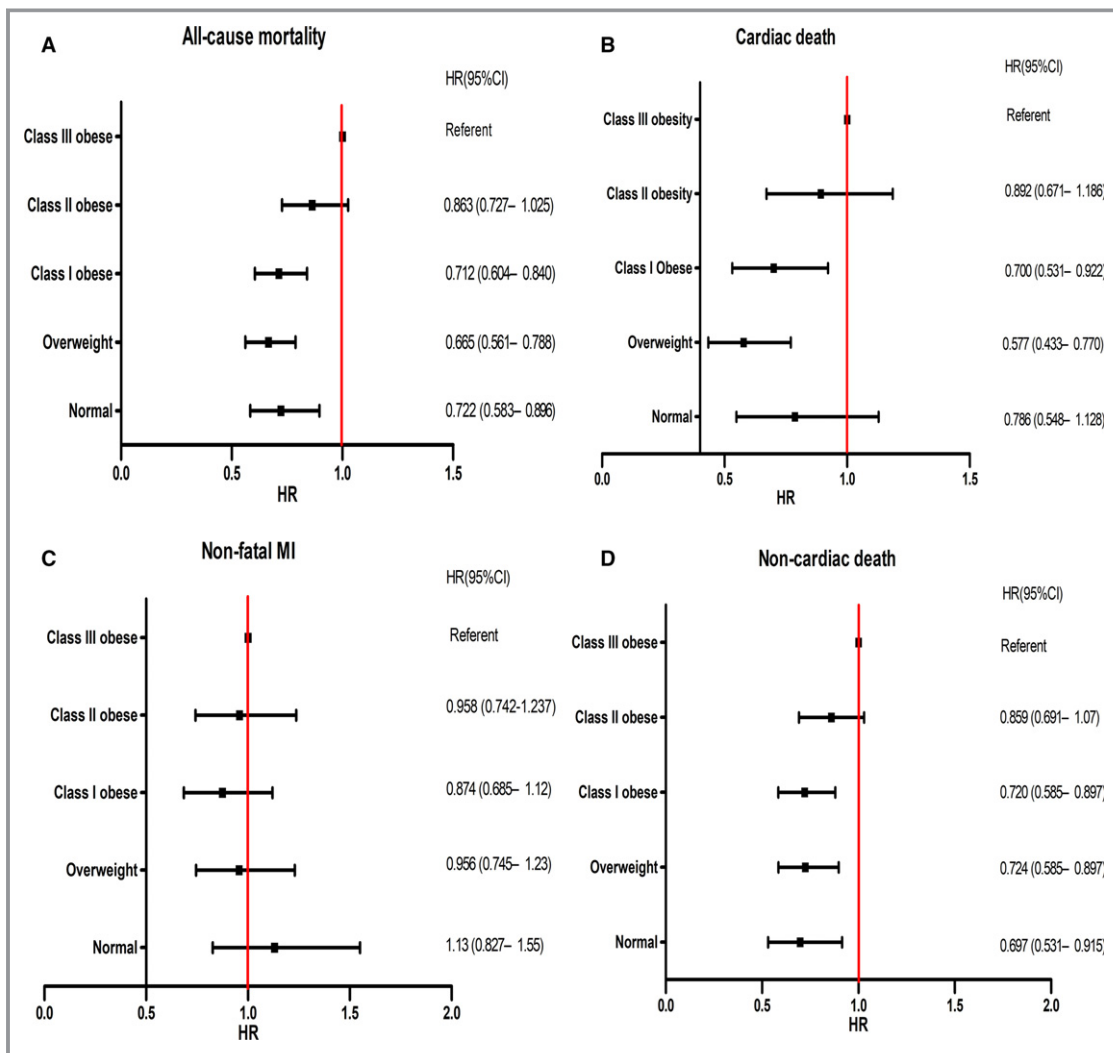
Table 2. Crude Primary and Secondary End Points Among BMI Categories

|	BMI Category (kg/m²)					
	Normal Weight, <25	Overweight, 25 to <30	Class I Obese, 30 to <35	Class II Obese, 35 to <40	Class III Obese, ≥40	*P* Value
All-cause mortality	169 (19.6)	567 (19.1)	612 (18.2)	409 (19.8)	197 (19.1)	0.533
Cardiac death	59 (6.9)	171 (5.8)	215 (6.4)	152 (7.3)	71 (7.2)	0.195
Nonfatal MI	83 (9.6)	282 (9.5)	290 (8.6)	191 (9.2)	88 (9.1)	0.739
Noncardiac death	110 (12.8)	396 (13.4)	397 (11.8)	257 (12.4)	126 (12.8)	0.445

Data are shown as n (%). BMI indicates body mass index; MI, myocardial infarction.

using class III obese patients as references. In the multivariable model, we adjusted sex, age, race, hypertension, smoking, hyperlipidemia, previous cardiovascular events, previous heart failure, proteinuria, depression, heart rate, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, glycated hemoglobin, and glomerular filtration rate, according to previous studies.[11,20–22] A cubic spline smoothing

Figure 1. Primary and secondary end points by body mass index category. **A**, All-cause mortality. **B**, Cardiac death. **C**, Nonfatal MI. **D**, Noncardiac death. All models were adjusted for sex, age, race, hypertension, smoking, hyperlipidemia, previous cardiovascular events, previous heart failure, proteinuria, depression, heart rate, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein, high-density lipoprotein, glycated hemoglobin, and glomerular filtration rate. CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction.
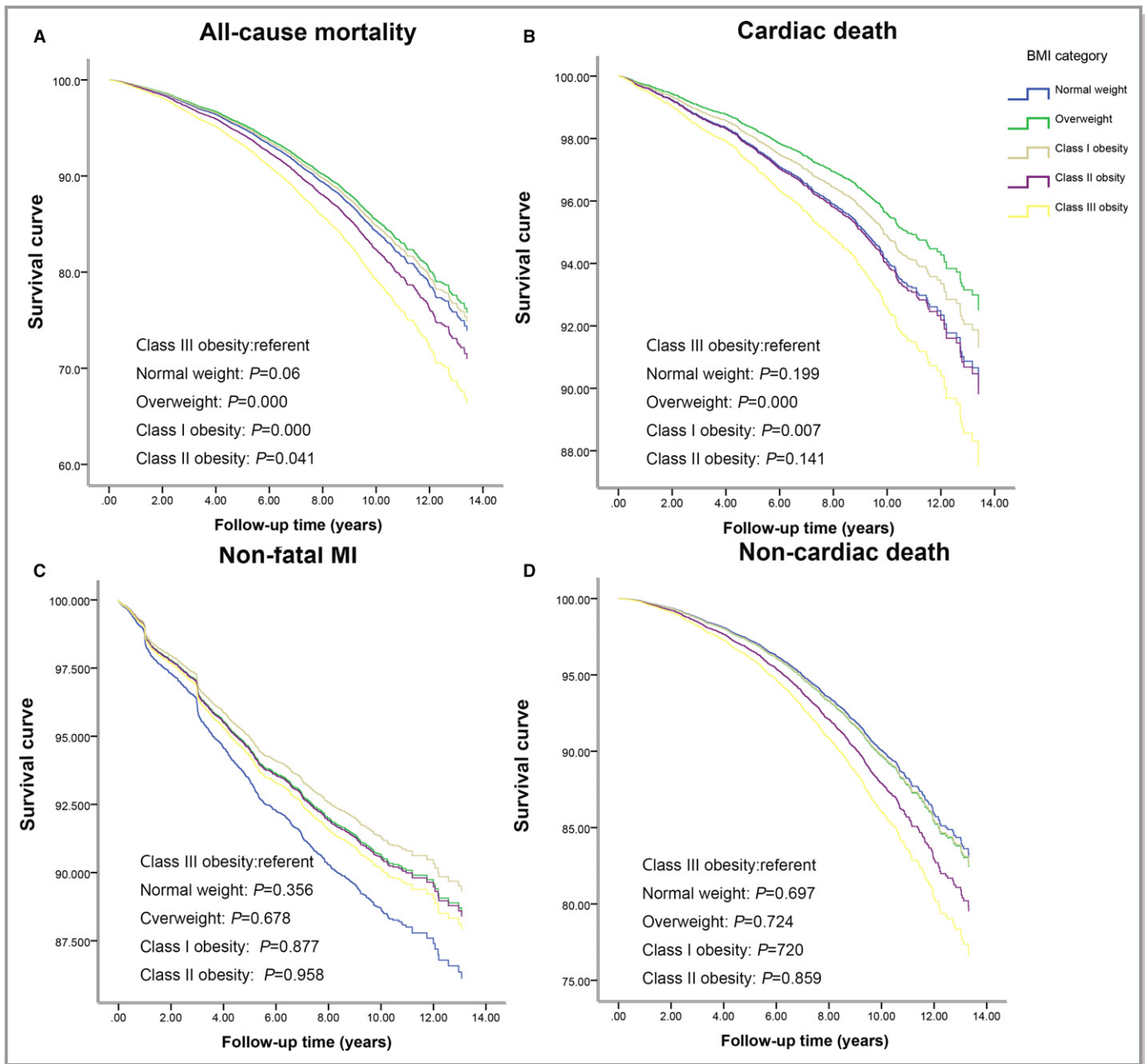
Figure 2. Survival curves for primary and secondary end points for 5 predefined body mass index categories after adjusting multivariate rates. **A**, All-cause mortality. **B**, Cardiac death. **C**, Nonfatal MI. **D**, Noncardiac death. All models were adjusted for cofounders in Figure 1. MI indicates myocardial infarction.

technique was used to study the shape of the relationship of BMI and waist circumference with the logarithm of the relative risk of adverse events adjusted for the above-mentioned confounding factors. The correlation between BMI and waist circumference was determined using the Pearson correlation coefficient (*r*). All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant. All analyses were performed using IBM-SPSS (v22; IBM Corp), Empower (X&Y Solutions), and R (R Foundation for Statistical Computing).

Results

Baseline Characteristics

The proportions of included participants with T2DM by BMI category were as follows: 8.39% normal weight, 28.9% overweight, 32.9% class I obese, 20.2% class II obese, and 9.61% class III obese. The mean age was 64.0±7.53 years, and the majority (61.4%) of the patients were male. Class III obese participants with DM were >3 years younger than their
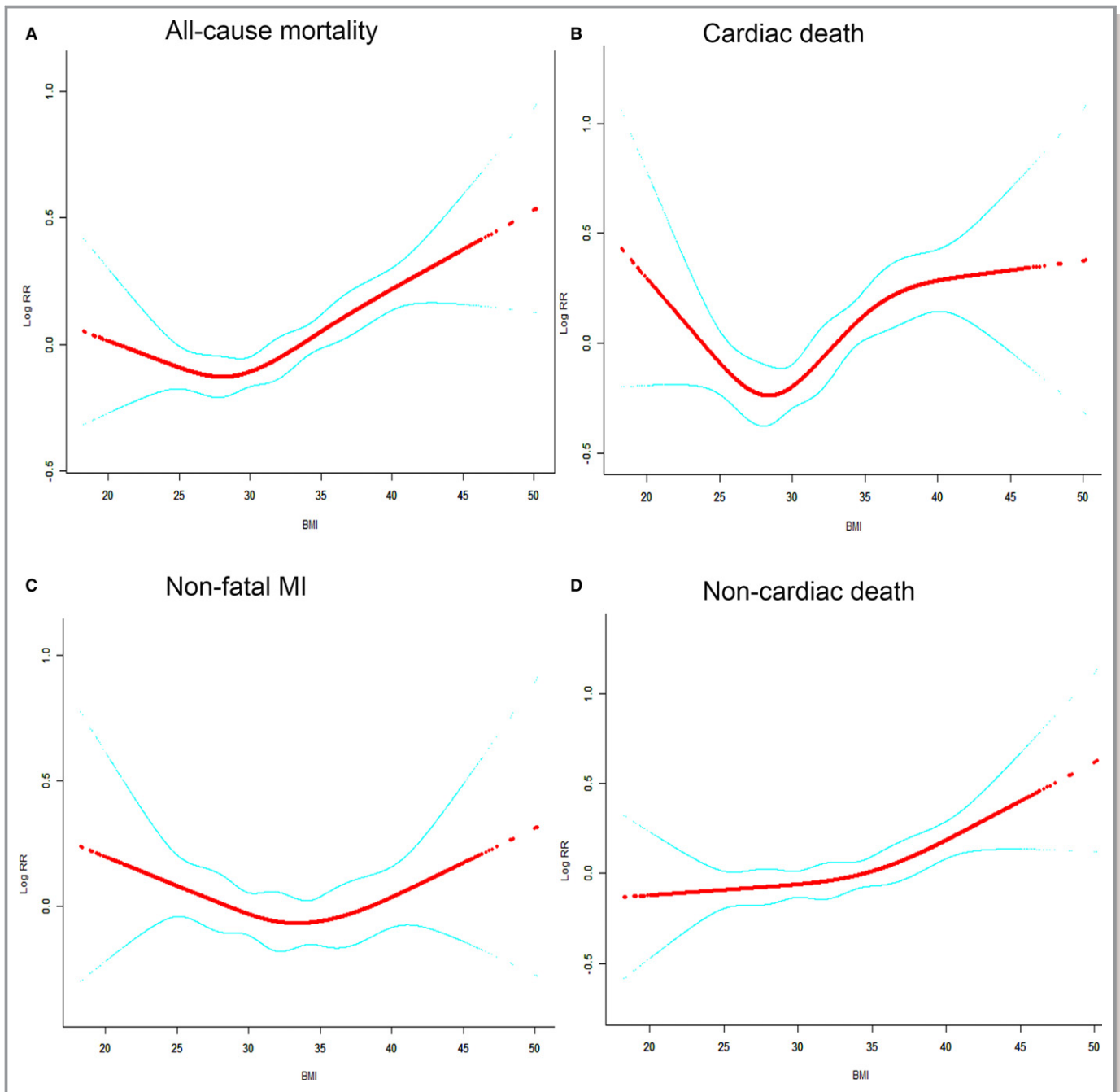
Figure 3. Smooth spline curves of BMI for the estimation of risk of primary and second end points after adjusting multivariate rates. **A**, All-cause mortality. **B**, Cardiac death. **C**, Nonfatal MI. **D**, Noncardiac death. Red line denotes fitted curves, and blue line represents 95% confidence intervals for the association between BMI and adverse events. All models were adjusted for cofounders in Figure 1. BMI indicates body mass index; MI, myocardial infarction.

normal-weight counterparts. Baseline demographic, clinical, laboratory examination, and medication information is shown in Table 1 according to BMI groups. Obese patients were younger and more likely to have cardiovascular risk factors, specifically hypertension, hyperlipidemia, and proteinuria, than were normal-weight patients. Class III obese participants with DM were more likely to be women and to develop depression. Smoking and previous cardiovascular events decreased, whereas other traditional cardiac risk factors, duration of DM, and rate of depression increased across increasing categories of obesity. Obese patients were more likely to accept evidence-based therapies, including aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and thiazolidinedione than were normal-weight patients.
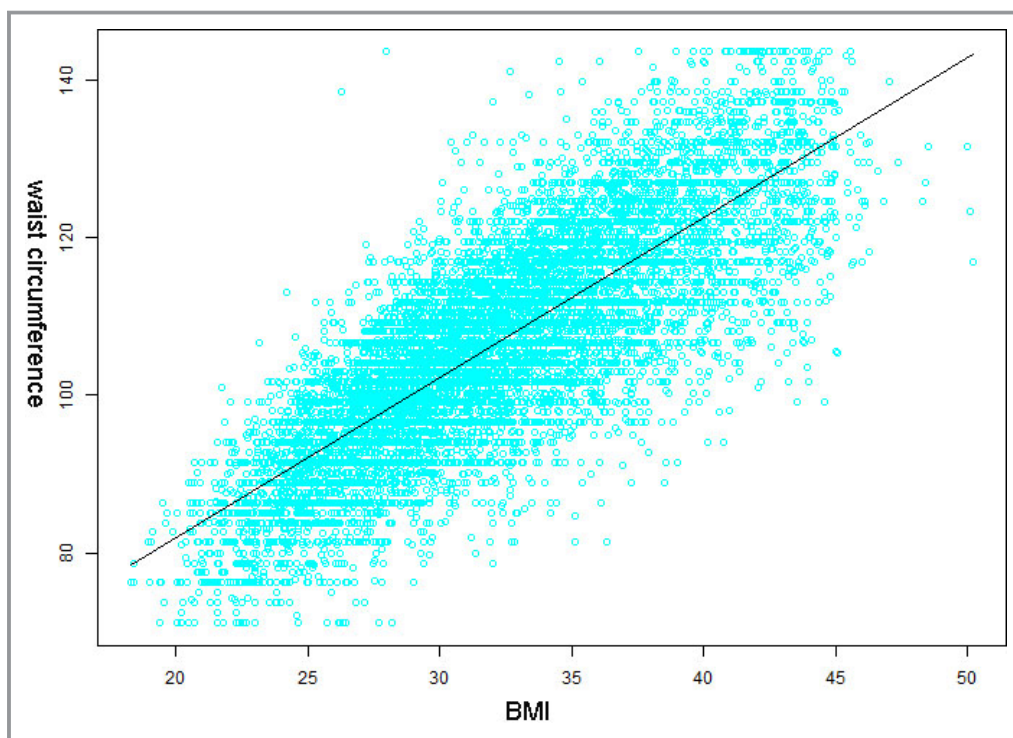
Figure 4. Correlation and agreement between body mass index (BMI) and waist circumference.

Crude Events Rates

During a mean follow-up of 9.43±2.37 years, 1950 patients died (669 patients from cardiac death), 936 patients (9.1%) survived nonfatal MI, and 516 patients developed stroke (5.0%). Crude clinical outcomes among BMI categories are shown in Table 2. The rates of all adverse events across all categories were similar.

Multivariate Adjusted Analyses

After adjusting statistically significant covariates and clinically meaningful confounders, patients who were class III obese with BMI ≥40 had the highest risk of all-cause mortality, followed by patients with class II obesity, whereas overweight patients had the lowest risk (Figure 1A). The adjusted hazard ratio ranged from 0.665 (95% confidence interval, 0.561–0.788) to 0.863 (95% confidence interval, 0.727–1.025) compared with the reference group. The same pattern was also observed for cardiac death. The highest cardiac death rate was also in the class III obese group, followed by that in the patients with class II obesity, whereas the lowest cardiac death rate was in the overweight patients (Figure 1B). No significant differences were noted between groups with respect to the incidence of nonfatal MI (Figure 1C). The highest noncardiac death rate was also in the class III obese group, followed by the patients with class II obesity, whereas the lowest

noncardiac death rate was among normal-weight patients (Figure 1D). Figure 2 shows statistically significant covariates and clinically meaningful confounders adjusted survival curves for all-cause mortality, cardiac death, nonfatal cardiac events, and noncardiac death based on the 5 predefined categories of BMI.

BMI as a Continuous Variable

Overweight patients with lower risk of multivariate-adjusted rates across the entire group followed a J-shaped pattern in terms of all-cause mortality, with the highest rates observed in class III obese patients and the lowest in overweight patients (Figure 3A). A V-shaped relationship was observed between BMI and cardiac death, where event rate decreased sharply with increasing BMI between 20 and 27, and then began to increase sharply at BMI >27 (Figure 3B). BMI was related to nonfatal MI in a U-shaped manner after adjusting for confounding factors, where the nadir of the risk curve was at BMI 33 (Figure 3C). The risk of noncardiac death was found to increase with BMI (Figure 3D).

Waist Circumference as a Continuous Variable

We found significant correlations between BMI and waist circumference (r=0.802; Figure 4). When we used waist circumference as a continuous variable to study the
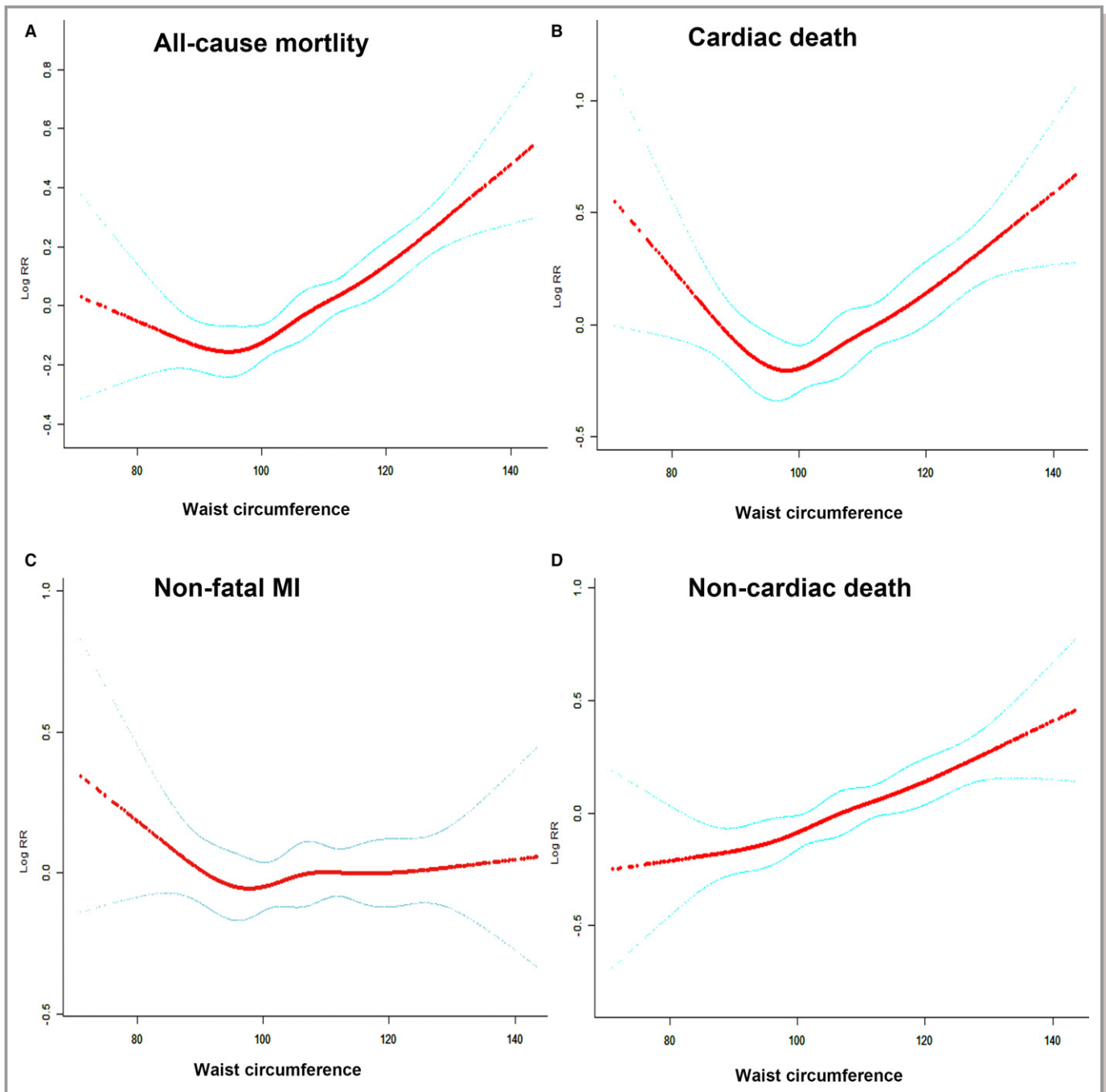
Figure 5. Smooth spline curves of waist circumference for the estimation of risk of primary and second end points after adjusting the confounding factors. **A**, All-cause mortality. **B**, Cardiac death. **C**, Nonfatal MI. **D**, Noncardiac death. Red line denotes fitted curves, and blue line represents 95% confidence intervals for the association between waist circumference and adverse events. All models were adjusted for cofounders in Figure 1. MI indicates myocardial infarction.

continuous relationship between waist circumference and primary and secondary end outcomes after adjusting for multivariate rates, we observed relationships similar to those between BMI and primary and secondary end points (J-shaped relationship for all-cause mortality, V-shaped relationship for cardiac death, U-shaped relationship for nonfatal MI, and reverse linear relationship for noncardiac death; Figure 5).

Discussion

This study was performed using the data from a large randomized controlled trial with a median follow-up of 9.4 years. We studied the recent controversial issue of the obesity paradox in the context of all-cause mortality, cardiac death, nonfatal MI, and noncardiac death in T2DM patients.

Our results, benefiting as they do from our use of a large randomized controlled trial with a long duration of follow-up and a relatively large proportion of obese patients, reasonably dispel any notion of an obesity paradox for T2DM patients.

Although the reasons for an obesity paradox are not clear, the characteristics of included patients could be involved. Zamorta et al[23] compared 2527 heart failure patients with and without DM. The obesity paradox was present in heart failure patients without DM but not in those with DM, as if DM had removed this phenomenon from patients with heart failure. Other baseline characteristics may have had significant interactions with BMI and so affected Zamorta and colleagues' conclusions. Overweight and obese patients tend to be younger, and younger patients tend to have better prognoses. Overweight and obese patients usually also have more comorbidities, which lead to more aggressive treatment of cardiovascular risk factors, increasing the likelihood of improving prognosis.

Abi Khalil et al[24] categorized 5005 T2DM patients with acute heart failure in groups with BMI <20 (2%), 20 to 24.9 (20.8%), 25 to 29.9 (36.6%), 30 to 34.9 (23.3%), and ≥35 (17.6%), with 12 months of follow-up. The results showed that BMI was inversely correlated with mortality. Furthermore, in this study we included relatively few participants with class II or III obesity (BMI ≥35). Thus, this result is not very informative regarding any relationship between extreme obesity and adverse events. Furthermore, Das et al[25] assessed the impact of extreme obesity (class III obesity) on the outcomes of patients with ST-segment–elevation MI. Patients with extreme obesity suffered higher mortality than their counterparts, a finding that is consistent with our results. Some cohort studies[6,20] found a U-shaped relation between BMI and all-cause mortality. The nadirs of these curves were around a BMI of 30 to 35. If these studies include more class I obese patients (the nadir of the curve) and relatively few class II or III obesity patients in future studies, a reverse relationship or the obesity paradox might appear.

Both underweight status and extreme obesity might increase the incidence of mortality.[6,26] Patients who are underweight may have severe undiagnosed diseases.[23,27] Conversely, extremely obese patients usually have an increased risk of coronary atherosclerotic heart disease and related cardiovascular risk factors, such as hypertension and DM.

Obesity was not determined solely using BMI but also by waist circumference, which provides information on body fat distribution. Most of these overweight or obese patients were abdominally obese. A recent study found that the similarly significant associations between BMI and cardiovascular risk factors, such as hypertension, hyperlipidemia, and DM, are also true of waist circumference.[13] A study performed by Flegal and Graubard found that waist circumference and BMI

predicted virtually the same number of all-cause deaths.[28] Our research found similar results compared with previous studies.

Limitations

Our analyses should be viewed in the context of some limitations. BMI and waist circumference were calculated at admission without reevaluation during the follow-up period. However, the change in weight was small in overweight or obese patients.[29] We did not have enough patients who were extremely lean (BMI ≤18.5) to draw conclusions between BMI and adverse events in these participants.

Conclusion

Data from the ACCORD study revealed no evidence of the obesity paradox in patients with a 10-year history of DM. Class III patients have the highest risk of adverse events (all-cause mortality, cardiac death, nonfatal MI, and noncardiac death). BMI and waist circumference had a similar relationship to adverse events.

Acknowledgments

Author Contributions

Hu and Xing designed the study and provided methodological expertise. Huang and Pei drafted the article. Chen and Peng drafted the tables and figures.

Disclosures

None.

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