ORIGINAL ARTICLE

Risks for Cardiovascular and Cardiac Deaths in Nonobese Patients With Diabetes and Coronary Heart Disease

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Abstract

Objective: To assess whether obese diabetic patients with coronary heart disease (CHD) have a lower risk for cardiovascular or cardiac mortalities than do nonobese diabetic patients with CHD.

Patients and Methods: We conducted a prospective cohort study using data from the National Health and Nutrition Examination Survey 1999-2010 and followed up the study participants from the survey participation date until December 31, 2011. For primary analyses, we built Cox proportional hazard models restricted to diabetic patients with CHD; unadjusted and adjusted hazard rates of cardiovascular mortality were compared between obese and nonobese participants.

Results: A total of 3,056 diabetic participants (504 with and 2,552 without CHD) and 22,556 nondiabetic participants (953 with and 21,603 without CHD) aged 20 to 79 years without malignant disease were included. Follow-up was completed in 99.8% of study participants. Hazard ratio (HR) for cardiovascular mortality for diabetic participants with CHD was significantly lower among the obese than among the nonobese (adjusted HR, 0.38; 95% CI, 0.18-0.82; P=.01); these findings were not observed in diabetic participants without CHD. Among nondiabetic participants, cumulative event rates for cardiovascular deaths were not significantly different between the obese and the nonobese, regardless of CHD status. Similar results for cardiac mortality were observed in both diabetic and nondiabetic participants.

Conclusion: Obesity in diabetic patients with CHD was associated with lower cardiovascular and cardiac mortality risks compared with absence of obesity. That is, nonobese patients having diabetes and CHD may have an increased risk for serious cardiovascular events.

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Obesity, an important risk factor for diabetes and cardiovascular diseases, has been increasing in epidemic proportions worldwide.[1,2] In addition, a recent study has suggested that obesity may be associated with increased risk of cancer.[3] However, the obesity paradox, association between obesity and reduced mortality or cardiovascular events compared with that in absence of obesity, has been reported among patients with several comorbidities, such as coronary heart disease (CHD).[4-7] In addition, some studies have suggested that the obesity paradox might be present after diabetes has developed[8-10]; however, others have reported otherwise.[11,12] The conflicting results for the obesity paradox in diabetes may be attributed to patient selection bias and incomplete adjustment.[13,14] Moreover, the results for the obesity paradox in diabetes may be different between patients with and without CHD.[4,5]

In this study, using nationally representative data, we assessed whether obese diabetic patients with CHD have a lower risk of cardiovascular or cardiac mortalities compared with nonobese diabetic patients with CHD. In addition, to assess the coronary risk among diabetic populations with CHD, we investigated cardiac mortalities in obese and nonobese populations. Similar analyses were conducted in diabetic populations without CHD, nondiabetic populations with CHD, and nondiabetic populations without CHD.

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PATIENTS AND METHODS

Data Source and Study Population

This was a prospective cohort study using data from the US National Health and Nutrition Examination Survey (NHANES).[15] Written informed consent was obtained from all participants. The National Center for Health Statistics Research Ethics Review Board approved the NHANES protocols.[16] The NHANES was conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. It uses a stratified, multistage probability sampling design, which enabled representation of the US civilian noninstitutionalized population.[15] In this study, data were collected at home and mobile examination centers (MECs). Blood specimens were collected during an MEC examination.

Among the population participating in the NHANES during the period 1999 to 2010, the unweighted response rate of household interviews was 80.6% and that of MEC examination was 77.1%.[17] We focused on participants aged 20 to 79 years, which resulted in a sample number of 29,725. We excluded those with missing information on body mass index (BMI; n=1,849) and those with BMI of less than 15 kg/m^2 (n=11) because these participants may have other comorbidities. In addition, we excluded those with a history or comorbidities of cancer (n=2,115) and those with diabetes at age less than 20 years (n=138) to avoid the possible effects of genetic or autoimmune diseases. We prospectively followed up the study participants from the date of survey participation for interviews until December 31, 2011.

Definition of Diabetes, Obesity, and CHD

We defined diabetes using 1 of the following 3 criteria: previous diagnosis of diabetes, intake of antidiabetic medications or insulin, or glycated hemoglobin (HbA1c) level of 6.5% or more.[18] Participants who did not satisfy any of these 3 criteria were defined as without diabetes. We extracted information on BMI, calculated as weight (kg) divided by height (m) squared, from the MEC measurements in the 1999-2010 NHANES. Among the study participants, *obesity* was defined as a BMI of 30 kg/m^2 or more. *Coronary heart disease* was defined as a previous diagnosis of CHD, myocardial infarction, or angina pectoris.

Outcome Measures

The main outcome measures were cardiovascular and cardiac mortalities. In addition, we assessed noncardiovascular and all-cause mortalities. We used the abovementioned mortality follow-up data provided in the Public-use Linked Mortality Files.[19] To identify causes of deaths occurring in participants in or after 1999, the NHANES used the *International Classification of Diseases, Tenth Revision* codes.[20] The specific codes used were I00 to I09, I11, I13, and I20 to I51 for causes of death from diseases of the heart (cardiac death) and I60 to I69 for causes of death from cerebrovascular diseases. *Cardiovascular death* was defined as death from cardiac and cerebrovascular diseases. *Noncardiovascular death* was defined as any death due to noncardiovascular causes.

Other Measurements

We extracted data on potential confounders, including age, sex, race and ethnicity, educational attainment, smoking status, hypertension, hyperlipidemia, and HbA1c level. Race and ethnicity were classified into 4 categories: non-Hispanic white, non-Hispanic black, Mexican American, and others including other Hispanics, Asian, and multiracial participants. We classified educational attainment as more than high school, high school graduation or General Education Development certificate, or less than high school. *Hypertension* was defined as either a previous diagnosis of hypertension or intake of antihypertensive medications. *Dyslipidemia* was defined as a previous diagnosis of hyperlipidemia or intake of lipid-lowering medications. The HbA1c level was measured upon MEC examination in this survey.

Statistical Analyses

Demographic data were presented as numbers with proportions (%) or means with SDs. Both diabetic and nondiabetic participants were divided according to the presence or absence of CHD. Study participants with obesity were compared with those without obesity using *t* test for continuous variables and chi-square test for categorical variables. For primary analyses of cardiovascular and cardiac mortality outcomes, we used Cox proportional hazard models to analyze unadjusted and adjusted hazard ratios (HRs) in diabetic participants with obesity, compared with those without obesity. Noncardiovascular and all-cause mortality outcomes were also similarly assessed. Kaplan-Meier survival curves were constructed for cardiovascular and cardiac mortality outcomes in diabetic participants with and without obesity. In the multivariable model 1, we included age, sex, race and ethnicity, educational attainment, and smoking status for adjustment. In the multivariable model 2, dyslipidemia and hypertension were added to the factors in model 1 for adjustment; if a participant had diabetes, glycemic control (HbA1c level of <7.0% or ≥7.0%) was added to model 2. To exclude the potential effect of "Others" on race and ethnicity, including the Asian population who were more likely to develop diabetes at a lower BMI, we conducted additional analyses limited to non-Hispanic white, non-Hispanic black, and Mexican American participants. Furthermore, we performed sensitivity analyses to assess the association between obesity and cardiovascular mortality based on 3 classifications of BMI, namely, normal weight (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), and obese (BMI, ≥30 kg/m^2). We performed similar analyses on nondiabetic participants with and without CHD.

All statistical analyses were conducted using Stata software (version 11.1, Stata Corp), accounting for the complex survey design. We used an appropriate weight for each analysis, based on the variables selected. These weights accounted for unequal probabilities of selection and nonresponses to make unbiased national estimates. *P* values of less than .05 were considered statistically significant for all tests.

RESULTS

A total of 25,612 participants were included in the study population. The characteristics of the participants with and without diabetes are presented in Table 1. The study included 3,056 diabetic participants (504 with CHD and 2,552 without CHD) and 22,556 nondiabetic participants (953 with CHD and 21,603 participants without CHD). The weighted prevalence of obesity was significantly higher in nondiabetic participants with CHD than in those without CHD (39.1% vs 30.2%; *P*<.001), whereas it did not differ significantly between diabetic participants with and without CHD (65.3% vs 62.6%; *P*=.41). Obese diabetic participants were significantly younger than nonobese diabetic participants. The proportion of females among diabetic participants without CHD was significantly higher in obese participants than in nonobese participants, but it was not significantly different between obese and nonobese diabetic participants with CHD. The proportion of non-Hispanic whites was significantly higher in obese diabetic participants with and without CHD, whereas that of others, including other Hispanics, Asian, and multiracial participants, was significantly higher in nonobese diabetic participants with and without CHD. The HbA1c levels did not differ significantly between obese and nonobese diabetic participants, independent of CHD prevalence.

Outcomes in Diabetic Participants With and Without CHD

Kaplan-Meier survival curves and event rates for cardiovascular and cardiac deaths of diabetic participants are shown in Figure 1A and B, respectively. Mean ± SD follow-up periods in diabetic participants were 5.5±3.2 years in those with CHD and 5.9±3.2 years in those without CHD. All participants with CHD and 99.8% of participants without CHD completed follow-up. The weighted event rates for cardiovascular death in obese and nonobese diabetic participants with CHD were 7.6 (4.4-12.3) and 23.5 (15.8-33.7) per 1000 person-year, respectively, whereas those in obese and nonobese diabetic participants without CHD were 4.2 (2.9-5.9) and 5.2 (3.8-6.8) per 1000 person-year, respectively (Table 2). Similarly, the cumulative event rate for cardiac death was the highest in nonobese diabetic participants with CHD.

Among diabetic participants with CHD, the unadjusted HR (95% CI) for cardiovascular death was 0.31 (0.14-0.72) in obese participants compared with nonobese participants (*P*=.007). Using multivariable Cox proportional hazard models, we found that cardiovascular deaths in diabetic participants with CHD were significantly lower in obese than in nonobese participants (model 1: HR, 0.41;

TABLE 1. Characteristics of the Study Participants Based on the Presence or Absence of Diabetes and CHD[a,b]

	DM						Non-DM					
	CHD (−)			CHD (+)			CHD (−)			CHD (+)		
Characteristics	Obese (−)	Obese (+)	*P* value	Obese (−)	Obese (+)	*P* value	Obese (−)	Obese (+)	*P* value	Obese (−)	Obese (+)	*P* value
Unweighted participants	1,058	1,494		196	308		14,673	6,930		581	372	
Age (y)	57.3±13.1	53.7±11.7	<.001	67.0±9.2	61.1±9.1	<.001	41.5±11.4	43.0±11.4	<.001	60.4±11.1	57.3±11.1	.003
Female sex	42.5%	54.8%	<.001	40.0%	39.2%	.94	50.2%	54.7%	<.001	34.9%	39.8%	.28
Race/ethnicity												
Non-Hispanic white	47.0	60.1	<.001	58.1	69.4	.02	70.2	66.6	<.001	79.2	78.7	.84
Non-Hispanic black	17.5	19.1	.37	15.0	18.2	.03	9.6	15.1	<.001	6.8	11.1	.004
Mexican American	11.5	10.2	.23	9.1	4.8	.39	8.3	9.4	<.001	4.7	3.7	.37
Others[c]	24.0	10.6	<.001	17.8	7.6	.003	11.9	8.9	<.001	9.3	6.5	.30
Education attainment												
<High school	34.9	26.0	<.001	45.4	37.5	.14	17.4	19.0	.04	26.7	25.7	.75
High school or GED	22.4	27.3	.02	25.5	27.1	.77	24.1	27.1	<.001	25.0	31.1	.14
>High school	42.7	46.7	.13	29.1	35.4	.17	58.4	53.9	<.001	48.3	43.2	.28
Current smoking	23.3	19.1	.05	21.0	16.1	.27	26.9	20.9	<.001	27.5	24.3	.29
Waist circumference (cm)	96.0±9.1	118.9±12.5	<.001	98.1±9.5	120.6±11.9	<.001	88.4±8.0	112.0±9.9	<.001	94.7±8.8	113.8±10.1	<.001
Body mass index (kg/m^2)[d]	26.3±2.7	37.4±6.1	<.001	26.1±2.9	37.2±5.8	<.001	24.7±2.5	35.4±4.4	<.001	25.6±2.7	34.7±4.4	<.001
Dyslipidemia	57.2	57.1	.82	66.0	75.7	.07	32.3	37.9	<.001	66.6	64.5	.61
Hypertension	47.5	64.0	<.001	75.1	78.0	.50	16.2	32.1	<.001	57.2	68.1	.01
HbA1c[e]	7.6 (2.2)	7.4 (1.6)	.15	7.2 (1.7)	7.3 (1.3)	.79	5.2 (0.3)	5.4 (0.3)	<.001	5.5 (0.3)	5.6 (0.3)	.001

[a]CHD = coronary heart disease; DM = diabetes mellitus; GED = General Educational Development; HbA1c = glycated hemoglobin.

[b]Data are represented as number of participants, percent, or mean ± SD. An appropriate weight was used for each analysis, except for the number of participants.

[c]The category includes other Hispanics and other races, including multiracial participants.

[d]Body mass index was calculated as the weight in kilograms divided by the square of height in meters.

[e]HbA1c: 7.6% = 60 mmol/mol; 7.4% = 57 mmol/mol; 7.2% = 55 mmol/mol; 7.3% = 56 mmol/mol; 5.2% = 33 mmol/mol; 5.4% = 36 mmol/mol; 5.5% = 37 mmol/mol; 5.6% = 38 mmol/mol.

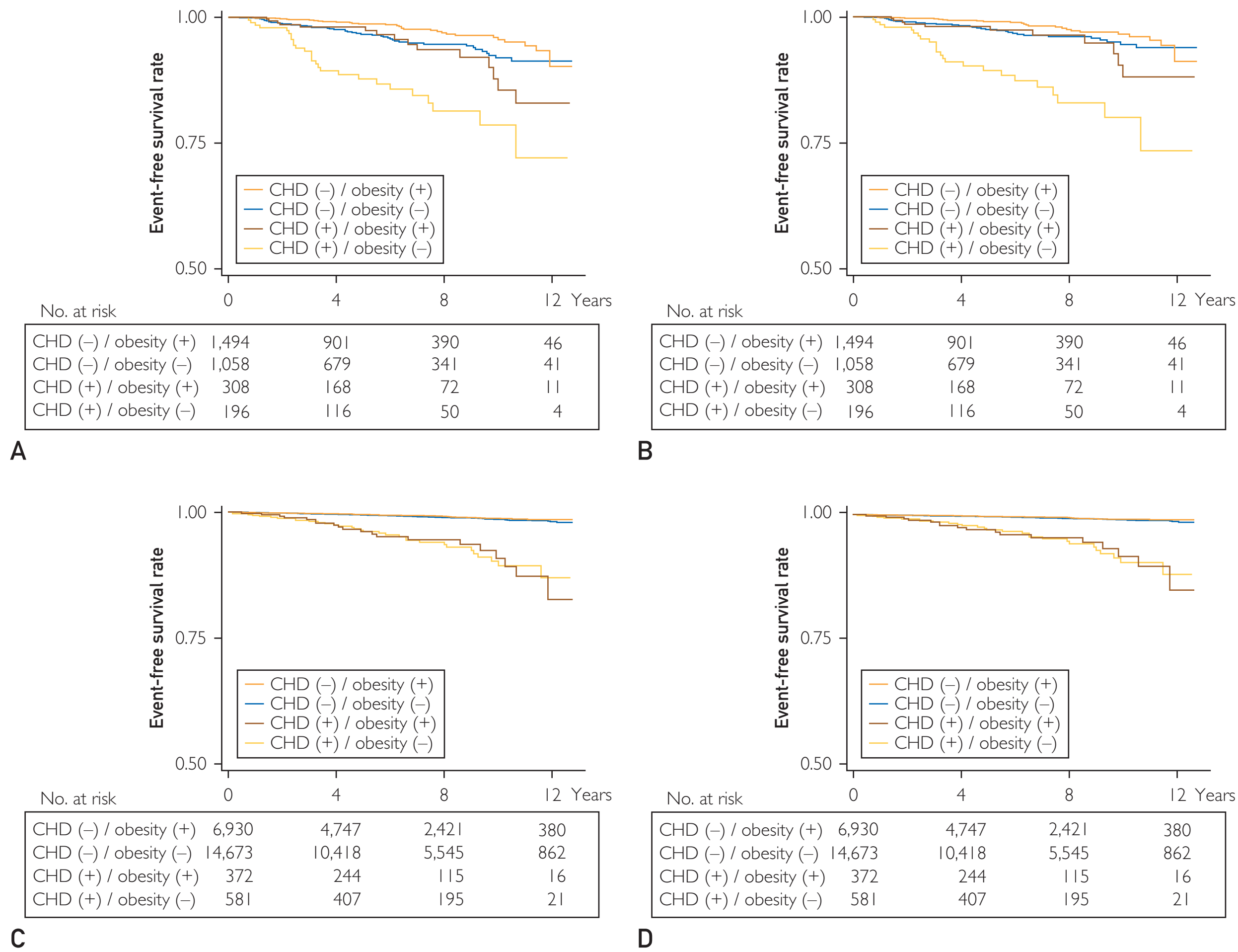

FIGURE 1. Rates of freedom from cardiovascular and cardiac deaths in participants with and without diabetes. Graphs for cardiovascular (A) and cardiac (B) deaths in diabetic participants and those for cardiovascular (C) and cardiac (D) deaths in nondiabetic participants. CHD = coronary heart disease; DM = diabetes mellitus.

95% CI, 0.18-0.92; *P*=.03; model 2: HR, 0.38; 95% CI, 0.18-0.82; *P*=.01). Similarly, compared with nonobese diabetic participants with CHD, the unadjusted HR for cardiac death was 0.26 (95% CI, 0.10-0.64) in obese diabetic participants with CHD (*P*=.004). Using the multivariable Cox proportional hazard models, we found that cardiac deaths in diabetic participants with CHD were also significantly lower in obese than in nonobese participants (model 1: HR, 0.35; 95% CI, 0.14-0.85; *P*=.02; model 2: HR, 0.35; 95% CI, 0.15-0.81; *P*=.01).

However, multivariable Cox proportional hazard analysis among diabetic participants without CHD showed that cardiovascular mortality was not significantly lower in obese participants compared with nonobese participants (model 1: HR, 1.09; 95% CI, 0.55-2.15; *P*=.78; model 2: HR, 0.92; 95% CI, 0.44-1.88; *P*=.81). In addition, cardiac mortality in diabetic participants without CHD was not significantly lower in obese participants compared with that in nonobese participants (model 1: HR, 1.39; 95% CI, 0.63-3.08 *P*=.40; model 2: HR, 1.20; 95% CI, 0.48-3.01; *P*=.68). These results did not change when we limited the analysis to non-Hispanic white, non-Hispanic black, and Mexican American participants (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

TABLE 2. Risks for Cardiovascular and Cardiac Mortalities in Diabetic and Nondiabetic Participants With and Without Obesity[a,b]

	Previous CHD (−)			Previous CHD (+)		
Characteristics	Obese (−)	Obese (+)	*P* value	Obese (−)	Obese (+)	*P* value
DM						
Cardiovascular mortality						
No. of events/total participants	46/1,058	32/1,494		27/196	15/308	
Event rate (per 1000 person-year)	5.2	4.2		23.5	7.6	
Unadjusted HR (95% CI)	1.00 [ref]	0.85 (0.43-1.66)	.63	1.00 [ref]	0.31 (0.14-0.72)	.007
Model 1: Adjusted HR (95% CI)[c]	1.00 [ref]	1.09 (0.55-2.15)	.78	1.00 [ref]	0.41 (0.18-0.92)	.03
Model 2: Adjusted HR (95% CI)[d]	1.00 [ref]	0.92 (0.44-1.88)	.81	1.00 [ref]	0.38 (0.18-0.82)	.01
Cardiac mortality						
No. of events/total participants	33/1,058	26/1,494		24/196	11/308	
Event rate (per 1000 person-year)	3.2	3.4		20.7	5.6	
Unadjusted HR (95% CI)	1.00 [ref]	1.12 (0.51-2.44)	.76	1.00 [ref]	0.26 (0.10-0.64)	.004
Model 1: Adjusted HR (95% CI)	1.00 [ref]	1.39 (0.63-3.08)	.40	1.00 [ref]	0.35 (0.14-0.85)	.02
Model 2: Adjusted HR (95% CI)	1.00 [ref]	1.20 (0.48-3.01)	.68	1.00 [ref]	0.35 (0.15-0.81)	.01
Non-DM						
Cardiovascular mortality						
No. of events/total participants	134/14,673	51/6,930		32/581	20/372	
Event rate (per 1000 person-year)	0.8	0.9		6.8	6.9	
Unadjusted HR (95% CI)	1.00 [ref]	1.19 (0.79-1.82)	.38	1.00 [ref]	1.03 (0.49-2.14)	.93
Model 1: Adjusted HR (95% CI)	1.00 [ref]	1.21 (0.78-1.87)	.37	1.00 [ref]	1.34 (0.62-2.85)	.44
Model 2: Adjusted HR (95% CI)	1.00 [ref]	1.26 (0.72-2.20)	.39	1.00 [ref]	1.38 (0.65-2.95)	.39
Cardiac mortality						
No. of events/total participants	96/14,673	36/6,930		27/581	17/372	
Event rate (per 1000 person-year)	0.6	0.7		6.0	6.1	
Unadjusted HR (95% CI)	1.00 [ref]	1.35 (0.83-2.18)	.21	1.00 [ref]	1.03 (0.45-2.33)	.94
Model 1: Adjusted HR (95% CI)	1.00 [ref]	1.33 (0.81-2.19)	.25	1.00 [ref]	1.34 (0.59-3.03)	.46
Model 2: Adjusted HR (95% CI)	1.00 [ref]	1.30 (0.72-2.35)	.36	1.00 [ref]	1.38 (0.58-3.25)	.45

[a]CHD = coronary heart disease; DM = diabetes mellitus; HR = hazard ratio; ref = reference.

[b]Data are presented as number or HR (95% CI). An appropriate weight was used for each analysis, except for the number of events and total number.

[c]Multivariable model 1 was made by adjusting for age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (less than high school, high school graduation or General Education Development certificate, and more than high school), and current smoking status.

[d]Multivariable model 2 was made by adjusting for age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (less than high school, high school graduation or General Education Development certificate, and more than high school), current smoking status, dyslipidemia, hypertension, and glycated hemoglobin.

Noncardiovascular and all-cause mortalities in diabetic participants are presented in Supplemental Table 2, available online at http://www.mayoclinicproceedings.org. Noncardiovascular mortality did not differ significantly between obese and nonobese diabetic participants, regardless of the presence or absence of CHD. All-cause mortality in diabetic participants without CHD was nonsignificantly higher in obese participants compared with that in nonobese participants (model 1: HR, 1.15; 95% CI, 0.82-1.60; *P*=.39; model 2: HR, 1.15; 95% CI, 0.78-1.68; *P*=.46), whereas that in diabetic participants with CHD was nonsignificantly lower in obese participants compared with that in nonobese participants (model 1: HR, 0.75; 95% CI, 0.47-1.21; *P*=.24; model 2: HR, 0.78; 95% CI, 0.42=1.46; *P*=.44).

Outcomes in Nondiabetic Participants With and Without CHD

Kaplan-Meier survival curves and event rates for cardiovascular and cardiac deaths in nondiabetic participants are shown in Figure 1C and D, respectively. Mean ± SD follow-up periods in nondiabetic participants were 6.5±2.9 years in those with CHD and 6.7±2.7 years in those without CHD. A total of 99.9% participants with CHD and 99.8% participants without CHD completed follow-up. Among nondiabetic participants, the cumulative event rates for cardiovascular and cardiac deaths were not significantly different

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between obese and nonobese participants, independent of the presence or absence of CHD (Table 2). Noncardiovascular and all-cause mortalities in nondiabetic participants without CHD were higher in obese participants compared with those in nonobese participants, whereas these in nondiabetic participants with CHD were not significantly different between obese and nonobese participants (Supplemental Table 2).

Sensitivity Analysis

Kaplan-Meier survival curves and event rates for cardiovascular and cardiac deaths of normal, overweight, and obese diabetic participants are shown in Figure 2 and Table 3. The cumulative event rates for cardiovascular and cardiac outcomes in diabetic participants were the highest in the normal BMI group. Among diabetic participants with CHD, the obese group had significantly lower unadjusted HR for cardiovascular death compared with the normal BMI group (unadjusted HR, 0.28; 95% CI, 0.10-0.78; *P*=.01). Using multivariable Cox proportional hazard model, we found that cardiovascular mortality was significantly lower in the obese group compared with the normal BMI group (model 1: HR, 0.35; 95% CI, 0.13-0.93; *P*=.03; model 2: HR, 0.33; 95% CI, 0.13-0.80; *P*=.01). Cardiac mortality in diabetic participants with CHD was also significantly lower in the obese group than in the normal BMI group (model 1: HR, 0.26; 95% CI, 0.09-0.73; *P*=.01; model 2: HR, 0.28; 95% CI, 0.11-0.69; *P*=.006). However, cardiovascular and cardiac mortalities were not significantly different between the obese and normal BMI groups in diabetic

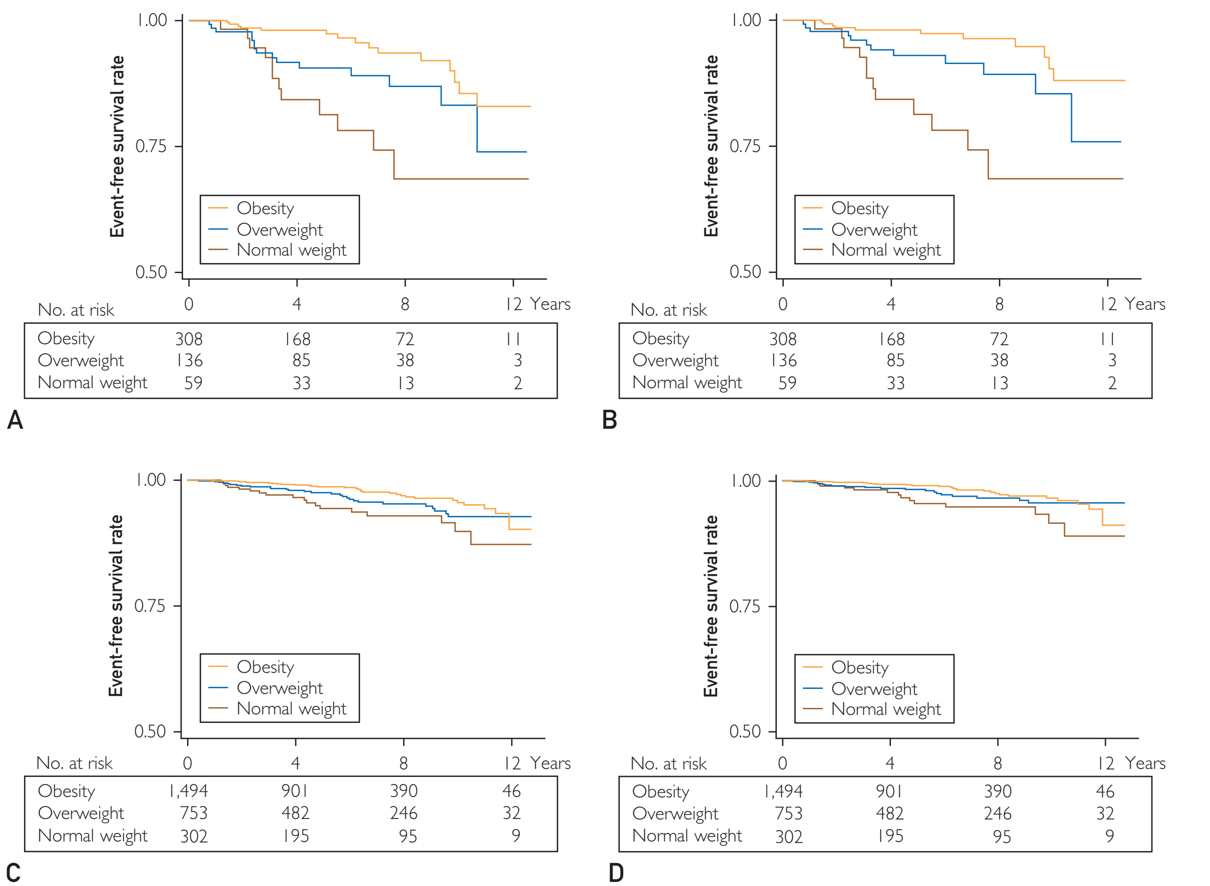

FIGURE 2. Rates of freedom from cardiovascular and cardiac deaths in normal-weight, overweight, and obese diabetic participants. Graphs for cardiovascular (A) and cardiac (B) deaths in diabetic participants with CHD and those for cardiovascular (C) and cardiac (D) deaths in diabetic participants without CHD. CHD = coronary heart disease; DM = diabetes mellitus.

TABLE 3. Risks for Cardiovascular and Cardiac Mortalities in Diabetic and Nondiabetic Participants Based on Normal Weight, Overweight, and Obese[a,b]

Characteristics	Previous CHD (−)			Previous CHD (+)		
	Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
DM						
Cardiovascular mortality						
No. of events/total participants	18/302	28/753	32/1,494	12/59	15/136	15/308
Event rate (per 1000 person-year)	6.7	4.6	4.2	26.9	22.1	7.6
Unadjusted HR (95% CI)	1.00 [ref]	0.67 (0.28-1.63)	0.64 (0.28-1.48)	1.00 [ref]	0.83 (0.28-2.46)	0.28 (0.10-0.78)
Model 1: Adjusted HR (95% CI)[c]	1.00 [ref]	0.63 (0.24-1.62)	0.67 (0.27-1.64)	1.00 [ref]	0.77 (0.22-2.68)	0.35 (0.13-0.93)
Model 2: Adjusted HR (95% CI)[d]	1.00 [ref]	0.49 (0.14-1.68)	0.37 (0.13-1.04)	1.00 [ref]	1.34 (0.27-6.64)	0.33 (0.13-0.80)
Cardiac mortality						
No. of events/total participants	14/302	19/753	26/1,494	12/59	12/136	11/308
Event rate (per 1000 person-year)	4.4	2.7	3.4	26.9	18.2	5.6
Unadjusted HR (95% CI)	1.00 [ref]	0.61 (0.22-1.65)	0.81 (0.31-2.07)	1.00 [ref]	0.68 (0.23-1.98)	0.20 (0.74-0.57)
Model 1: Adjusted HR (95% CI)	1.00 [ref]	0.61 (0.22-1.71)	0.83 (0.31-2.20)	1.00 [ref]	0.53 (0.16-1.77)	0.26 (0.09-0.73)
Model 2: Adjusted HR (95% CI)	1.00 [ref]	0.51 (0.13-1.89)	0.60 (0.21-1.71)	1.00 [ref]	1.00 (0.18-5.59)	0.28 (0.11-0.69)
Non-DM						
Cardiovascular mortality						
No. of events/total participants	57/6,675	71/7,627	51/6,930	16/223	14/344	20/372
Event rate (per 1000 person-year)	0.7	0.8	0.9	10.3	5.0	7.0
Unadjusted HR (95% CI)	1.00 [ref]	1.02 (0.63-1.65)	1.25 (0.77-2.02)	1.00 [ref]	0.47 (0.19-1.15)	0.68 (0.31-1.48)
Model 1: Adjusted HR (95% CI)	1.00 [ref]	0.74 (0.46-1.19)	1.16 (0.71-1.90)	1.00 [ref]	0.63 (0.25-1.58)	0.88 (0.38-2.04)
Model 2: Adjusted HR (95% CI)	1.00 [ref]	0.92 (0.49-1.73)	1.35 (0.66-2.77)	1.00 [ref]	0.74 (0.29-1.84)	0.97 (0.37-2.52)
Cardiac mortality						
No. of events/total participants	44/6,675	47/7,627	36/6,930	13/223	13/344	17/372
Event rate (per 1000 person-year)	0.5	0.5	0.7	8.3	4.8	6.1
Unadjusted HR (95% CI)	1.00 [ref]	0.97 (0.54-1.75)	1.39 (0.82-2.35)	1.00 [ref]	0.56 (0.21-1.52)	0.73 (0.30-1.77)
Model 1: Adjusted HR (95% CI)	1.00 [ref]	0.71 (0.41-1.23)	1.31 (0.77-2.21)	1.00 [ref]	0.76 (0.27-2.16)	0.94 (0.39-2.28)
Model 2: Adjusted HR (95% CI)	1.00 [ref]	0.70 (0.33-1.46)	1.21 (0.59-2.46)	1.00 [ref]	1.02 (0.37-2.78)	1.08 (0.37-3.17)

[a]CHD = coronary heart disease; DM = diabetes mellitus; HR = hazard ratio.

[b]Data are presented as number or HR (95% CI). An appropriate weight was used for each analysis, except for the number of events and total number.

[c]Multivariable model 1 was made by adjusting for age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (less than high school, high school graduation or General Education Development certificate, and more than high school), and current smoking status.

[d]Multivariable model 2 was made by adjusting for age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), educational attainment (less than high school, high school graduation or General Education Development certificate, and more than high school), current smoking status, dyslipidemia, hypertension, and glycated hemoglobin.

Normal weight, overweight, and obese were defined as body mass index of 18.5 to 25 kg/m^2, 25 to 30 kg/m^2, and ≥30 kg/m^2, respectively.

participants without CHD and among nondiabetic participants, regardless of the presence or absence of CHD (Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In the present study using data that were representative of the national population, obesity in diabetic patients with CHD was found to be associated with a significantly lower risk for cardiovascular and cardiac mortalities compared with the absence of obesity. In addition, a similar association was found for all-cause mortality in diabetic patients with CHD. Noncardiovascular mortality did not differ significantly between obese and nonobese diabetic patients with CHD, which indicated that competing risk might not be an explanation for decreased cardiovascular and cardiac mortalities. Diabetes is a risk factor for cardiovascular disease,[21] and cardiovascular disease, particularly CHD, is one of the major causes of death in diabetic patients.[22,23] Therefore, assessing the risk for subsequent cardiovascular and cardiac deaths in both obese and nonobese diabetic patients who have already developed CHD is of great importance. Meanwhile, these mortalities did not differ significantly between obese and nonobese diabetic populations without CHD. In the short-term follow-up, cardiovascular and cardiac mortalities were not significantly different between obese and nonobese nondiabetic populations.

Obesity is a well-established risk factor for diabetes.[24,25] In addition, it has been associated with an increased risk of CHD and cardiovascular mortality in many observational studies; in an analysis of pooled data from 97 prospective cohort studies that included 1.8 million individuals, both being overweight and obese was associated with a significantly increased risk of CHD.[26] However, some studies have suggested that once CHD develops, a protective effect of obesity may begin.[4,5] Moreover, recent studies have reported that this protective effect of obesity may exist even after type 2 diabetes has developed.[8,27] Regardless, this obesity paradox in patients with diabetes is still controversial.[11-14] Studies that investigate nationally representative data of diabetic patients with and without complications may be appropriate to assess the various effects of obesity on cardiovascular events. Considering the results of previous studies,[4,5] it is highly important to assess the association between obesity and cardiovascular mortality based on the presence or absence of CHD. Some studies that reported against the obesity paradox in diabetes included no or few patients with a history of cardiovascular events.[11,12]

To our knowledge, this is the first prospective cohort study using nationally representative data to investigate these underlying limitations by gathering large-scale data and revealing that obesity in diabetic patients with CHD is associated with lower cardiovascular and cardiac mortality risks compared with that in absence of obesity. Our results suggest that the obesity paradox may be found only in diabetic patients with CHD. Conversely, the risk for cardiovascular and cardiac deaths may be extremely high in diabetic patients with coexisting CHD, despite the obesity risk being absent. A recent retrospective study on diabetic patients with cardiovascular events reported that normal-weight individuals had 30% higher mortality risk than obese individuals.[27] However, this study has also shown that normal-weight diabetic patients without cardiovascular events had increased mortality risk. Another recent study has shown that diabetic patients with acute myocardial infarction did not experience a survival benefit from an elevated BMI.[28] These results were not consistent with our results. A reason for the different results may be the different study population and methods of adjustment. Particularly, one study used age as the categorical variable (<60 or ≥60 years) for adjustment, and neither study considered the presence of other relevant conditions, such as cancer.[27,28] Variables such as age and malignant disease are strongly associated with body weight and survival rate and may have confounded their results.

Although pathophysiological mechanisms are still unclear,[7,14,29] the obesity paradox may not reflect the protective effect of obesity; however, it may reflect conditions in nonobese individuals that may predispose them to CHD risks. Individuals with normal weight who acquire a chronic disease for which obesity is a risk factor may have unknown and more severe risk factors for cardiovascular events and death. Given this hypothesis, the patients with diabetes and CHD, despite being nonobese, may be at increased risk for serious cardiovascular events. Further studies are needed to investigate the underlying reasons for these findings.

This study has several limitations. First, this was a short-term follow-up study and a relatively small number of events might influence the results; the outcomes and prognosis of the obese population need to be followed for several decades in more large-scale studies. Second, the time of CHD diagnosis could not be considered. The influence of obesity may not have been investigated on diabetic patients who have just suffered acute coronary syndrome. However, although the selection bias is a serious problem for assessment of the obesity paradox, the present study included a nationally representative population with or without CHD in the United States. Third, this study had inherent limitations associated with an observational design, including possible residual confounding effects from unmeasured covariates.

CONCLUSION

This study showed that in a diabetic population with CHD, nonobese individuals had higher risks for cardiovascular and cardiac mortalities compared with obese individuals.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **CHD** = coronary heart disease; **HbA1c** = glycated hemoglobin; **HR** = hazard ratio; **MEC** = mobile examination center; **NHANES** = National Health and Nutrition Examination Survey

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