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BMI and Mortality: The Diabetes-Obesity Paradox Examined in a Large US Cohort

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Background/Objectives: BMI is a major risk factor for diabetes incidence, but a controversial predictor of mortality among those with diabetes.

Subjects/Methods: We conducted a mortality follow-up (2002–2019) of participants aged 40–79 with young-onset (diagnosed < age 30, n = 1335), older-onset (diagnosed ≥ 30, n = 15,194), and without (n = 62,295) diabetes at cohort entry. Cox analysis with age as the time scale assessing mortality according to BMI after adjusting for multiple potential confounding factors was used.

Results: Mean baseline age and diabetes duration at cohort entry were 50.1 and 29.4 years and 55.3 and 7.7 years among those with young- and older-onset diabetes, respectively. During an average of 12.3 years of follow-up, 47% of the young-onset, 40% of the older-onset diabetes, and 22.6% of those without diabetes at cohort entry died. In multivariable adjusted analyses, compared to a BMI of 18.5-<25 kg/m^2, HRs (95% CIs) were 4.10 (1.65–10.18), 0.69 (0.54–0.88), 0.81 (0.63–1.05), 0.64 (0.48–0.86) and 0.64 (0.54–0.77) for BMI categories <18.5, 25-<30 30-<35, 35-<40, 40+ kg/m^2 in those with young-onset diabetes. Corresponding HRs (95% CIs) were 2.02 (1.54–2.67), 0.74 (0.68–0.80), 0.74 (0.68–0.80), 0.83 (0.75–0.91) and 1.09 (0.99–1.19) in those with older-onset diabetes, and 1.50 (1.36–1.67), 0.76 (0.73–0.79), 0.73 (0.70–0.77), 0.83 (0.78–0.89) and 1.03 (0.95–1.10) in those without diabetes. Results were generally similar in analyses stratified by smoking status, gender, race and among those on insulin therapy.

Conclusion: Among this low socioeconomic status population with diabetes, overweight and obesity tend to be inversely associated with mortality. Risk factors for complications of diabetes other than BMI may be more clinically relevant when treating patients with diabetes.

Keywords: diabetes, BMI, obesity, obesity paradox

A higher BMI, especially in younger age groups, has been associated with higher lifetime risk of diabetes.[1] BMI is a controversial predictor of mortality, however, with protective relationships often observed among those with pre-existing chronic illnesses or populations with shorter than average lifespans.[2] Though BMI is one of the strongest predictors of diabetes, its relationship with mortality among those with diabetes is often observed to be protective at higher levels of overweight and obesity.[3] This "obesity paradox", observed both for diabetes[4,5] and other chronic diseases such as cardiovascular disease,[6–8] renal disease,[9] and cancer,[10] often engenders strong emotional reactions, criticisms, and a plethora of alternative explanations as to why this may be just an artifact of statistical or epidemiologic methodology. It has been attributed to reverse causation, collider bias (bias that results in spurious, and at times, paradoxical, associations due to inappropriate adjustment for a post-exposure variable), other forms of selection bias, and residual confounding for known and unknown factors.[11–13] Despite the consistent finding of a U-, inverted J-, or inverse relationship between BMI and mortality, particularly in the setting of chronic disease, the burden of the proof falls on the investigator observing such findings to defend why their results are contrary to "what is known", or conventional medical and public health knowledge that a BMI above the "normal" range as being harmful.

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The thrifty gene hypothesis, which proposes that certain populations that are now highly prone to obesity and type 2 diabetes have genes that historically helped them to preferentially store fat as a survival mechanism from famines, a protection that is no longer needed, has been roundly debunked,[14–17] even by its originator. Yet it seems not unreasonable to suggest that in a wasting disease such as diabetes, higher adiposity or a higher BMI would be protective. Furthermore, insulin, a therapeutic agent in the management of diabetes, particularly in Type 1 diabetes, is associated with weight gain due to its anabolic properties and its caloric preservation by preventing urinary glucose loss, but also associated with weight loss as people further advance in the pathological natural history of Type 2 diabetes.[18,19] Specifically, those with end organ complications of the disease are more likely to be prescribed insulin therapy. In adults with Type 1 diabetes, for whom insulin therapy is an absolute requirement and who generally represent those with longer diabetes duration and greater prevalence and severity of complications when considering the broader adult diabetes population, U-shaped and inverted J-shaped associations are observed even after accounting for wasting complications of the disease.[20,21] However, these findings are sometimes dismissed as being due to residual confounding in Type 1 diabetes, or a more pernicious form of the disease in those with Type 2 diabetes who are lean at or prior to diagnosis.

The thrifty gene hypothesis, though rarely mentioned these days and attributed to racist origins,[17,22] posits that survival pressures in times of famine, plague, or severe wasting illnesses favored those with the relative ability to store fat such that among populations with relatively limited lifespans, the more corpulent were more likely to survive, mate and reproduce.[23,24] While these thrifty genes have not been found[15,16] and corpulence may no longer selectively favor mating and reproduction, and arguably may never have,[15] increased body weight may still favor survival among those with more limited lifespans.

Given the above unsettled hypotheses, we evaluated the relationship between BMI and mortality in a large population of low-income African Americans and White Americans with diabetes living in the southeast United States, a population shown to have mortality rates higher than that of the general population.[25] Since people diagnosed with diabetes in youth or young adulthood, whether Type 1 or Type 2 diabetes, are hypothesized to have a more pernicious form of diabetes, we stratified analysis by young- (diagnosed before the age of 30) vs older-onset diabetes. Additionally, since our data and others have shown that BMI accounts for less of the burden of diabetes in African Americans than in White Americans, ie a lower attributable fraction of diabetes due to BMI, and occurs at lower levels of BMI, we also stratified analysis by race among African Americans and White Americans. To determine whether any obesity paradox existed, we also investigated the relationship of BMI with mortality among those without diabetes drawn from the same source population.

Materials/Subjects and Methods

The Southern Community Cohort Study (SCCS) is a population-based prospective study designed to investigate causes of health disparities among African Americans and Whites in the incidence of and mortality from cancer and other chronic diseases. Details of the rationale, study design, and methods have been previously described.[26] Briefly, between 2002 and 2009, over 85,000 participants aged 40 to 79 were recruited from community health centers (85%) and their surrounding communities (15%) from twelve states in the southeastern United States. Community health centers, ie federally qualified health centers, are government-funded health care facilities offering basic health care and preventive services to the medically underserved. The states included were Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia. All study procedures were approved by the Institutional Review Boards of Vanderbilt University and Meharry Medical College. Our study complies with the Declaration of Helsinki.

After providing informed consent, participants enrolled at community health centers completed a 40–60 minute in-person interview, which collected data on medical history, lifestyle, and socioeconomic factors that had been previously validated in a pilot study.[26–28] Those enrolled from general population sampling self-completed the same questionnaire. A participant who answered "yes" to the question "Has a doctor ever told you that you have diabetes or high blood sugar?" was asked questions about age at diabetes diagnosis and medications prescribed to treat the disease. Women were specifically asked not to include gestational diabetes in their reporting. For the current analysis, we excluded participants missing information on diabetes status or age at first diabetes diagnosis. Participants diagnosed with diabetes at or after the age of 30 (N = 15,707) formed our older-onset diabetes cohort and subjects diagnosed positive for diabetes before the

age of 30 formed our young-onset diabetes cohort (N = 1378). Classification as Type 1, Type 2 or mixed diabetes was not ascertained, but nearly all of those with Type 1 diabetes would be in the young-onset (age < 30) group and nearly all those with later onset would have had Type 2 diabetes.

Body mass index (BMI) was based on participant's self-reported height and weight. BMI was calculated as weight in kilograms divided by the square of the height in meters. BMI was categorized into the following six categories: underweight (BMI < 18.5 kg/m^2), normal weight (18.5-<25 kg/m^2), overweight (25-<30 kg/m^2), obese class I (30-<35 kg/m^2), obese class II (35-<40 kg/m^2), and obese class III (BMI ≥ 30 kg/m^2). Height and weight were measured for approximately 25% of SCCS participants, with a high (96%) correlation between the self-reported and measured BMI values.[29]

Mortality status was determined from linkages of the SCCS population with the National Death Index (NDI) database, with mortality censored on December 31, 2019. General linear models were used to test for differences in continuous variables and chi-square tests for categorical data. Race was self-reported based on pre-specified categories. Due to sample size limitations in other racial/ethnic groups, race-specific analyses of effect modification by race were conducted exclusively among African Americans and White Americans. Cox proportional hazards modeling, using age as the time scale, was used to determine multivariable adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for all-cause mortality first among subjects with early onset and late onset diabetes, and then for those without diabetes at cohort entry. The models were computed overall and separately for African American and White participants. For those with diabetes, multivariable adjusted modelling controlled for sex, race, duration of diabetes, BMI, type of anti-hyperglycemic therapy, and baseline histories of ischemic heart disease, stroke/transient ischemic attack, hypertension, high cholesterol, treatment for high cholesterol, and smoking (never/current/former), education, income and the presence of insurance. Race-specific multivariable adjusted modelling controlled for sex, duration of diabetes, anti-hyperglycemic therapy, high cholesterol and treatment for high cholesterol, and smoking (never/current/former), education, income and the presence of insurance. We also carried out sensitivity analyses to examine whether being on insulin therapy, having a history of smoking, or comorbidities/cardiovascular complications might have confounded our observations of the relationship between BMI and mortality among our population. The sensitivity analysis excluded 3585 participants with diabetes who had missing data on insulin therapy. The criterion for statistical significance was a two-tailed P-value of <0.10 for multiplicative interaction and <0.05 otherwise. Statistical analyses were conducted using SAS version 9.4 (Cary, North Carolina).

Results

Characteristics of the Southern Community Cohort Study by diabetes status and age of diabetes onset at study baseline are presented in Table 1. At study baseline, respectively, 0.5% among both those with young- and older-onset diabetes were underweight, 13.9% and 10.0% were of normal weight, 25.6% and 23.4%, were overweight, 23.3% and 26.6% were obese class 1, 16.9% and 19.0% were obese class 2, and 19.8% and 20.5% were obese class 3. The percentages in the upper BMI categories were consistently higher among those with than those without diabetes. People with young-onset diabetes were younger at study baseline, of longer diabetes duration, and had a slightly lower BMI at study baseline though the distribution of participants in the six BMI categories was fairly similar. When compared to the older-onset diabetes group, they were nearly twice as likely to be on insulin therapy but less likely to have hypercholesterolemia or hypertension. There was a greater prevalence of a history of coronary heart disease and stroke/transient ischemic attack among the young-onset diabetes population. Prevalence of each of these illnesses was higher (often by 2-fold or more) among those with than those without diabetes. Socioeconomic characteristics were fairly similar between the two diabetes groups, and somewhat lower compared with those without diabetes.

During an average of 12.3 years of follow-up, there were 6770 deaths among those with diabetes (47.1% of those with young-onset diabetes and 40.4% of those with older-onset diabetes had died). The multivariable adjusted associations of BMI with mortality in those with young- and older-onset diabetes are presented in Table 2. Among those with young-onset diabetes, underweight status was associated with a 4-fold increase in mortality and overweight, and class I, II and III obesity with an approximately 20% to 40% reduction in mortality risk compared having a BMI in the normal weight range, with mortality following a hockey stick pattern. Among those with older-onset diabetes, those who were

Table 1 Baseline Characteristics of the Southern Community Cohort Study Participants by Diabetes Status

	Young-Onset	Older-Onset	p-value	No Diabetes
	n = 1335	n = 15,194		N = 62,295
Baseline age (mean, sd)	50.0 ± 7.9	55.2 ± 8.8	<0.0001	51.5 ± 8.6
Diabetes duration (yrs)	29.3 ± 11.5	7.7 ± 7.2	<0.0001	
Sex, female (%)	70.1	64.4	<0.0001	57.7
Race			0.08†	
White (%)	25.2	27.9		31.0
Black (%)	70.0	67.9		65.1
Other race (%)	4.8	4.2		3.8
Mean BMI (kg/m^2)	33.3 ± 8.3	34.0 ± 8.0	0.001	29.3 ± 7.1
BMI category				
<18.5 (%)	0.45	0.51	<0.0001†	1.5
18.5–24.9 (%)	13.9	10.1		28.2
25–29.9 (%)	25.8	23.4		31.6
30–34.9 (%)	23.3	26.6		20.5
35–39.9 (%)	16.9	19.0		10.1
≥40 (%)	19.8	20.5		8.2
Insulin use* (%)	66.0	34.0	<0.0001	
Hypercholesterolemia			<0.0001†	
No (%)	49.1	44.3		72.4
Treated (%)	33.6	40.2		13.7
Not treated (%)	17.3	15.5		14.0
Hypertension (%)	71.3	79.6	<0.0001	48.0
Hx of CHD (%)	17.9	13.4	<0.0001	5.2
Hx of TIA/stroke (%)	15.1	11.0	<0.0001	5.3
Hx of smoking (%)	56.8	59.4	0.06	65.5
<high school graduate (%)	9.5	11.4	0.04	7.0
Household income <$15,000/year (%)	66.2	60.2	<0.0001	53.6
Health insurance (%)	65.2	68.1	0.03	58.4

Notes: †Test for global differences. *An additional 3585 participants had missing data on insulin use.

underweight had a nearly doubled mortality risk compared with those of normal weight. Risk was decreased among the overweight and obese class I, then tended to rise thereafter, consistent with an inverted J-shaped pattern.

While underweight status was a strong risk factor for both young- and older-onset diabetes, other risk factors associated with mortality tended to differ between those with younger- compared to older-onset diabetes. Included

Table 2 Multivariable Adjusted Association of BMI Category with Mortality in Younger- and Older-Onset Diabetes

	Young-Onset	Older-Onset	No Diabetes
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
BMI category, kg/m^2			
<18.5	4.10 (1.65–10.18)	2.02 (1.54–2.67)	1.50 (1.36–1.67)
18.5–24.9	Ref	Ref	Ref
25–29.9	0.69 (0.54–0.88)	0.74 (0.68–0.80)	0.76 (0.73–0.79)
30–34.9	0.81 (0.63–1.05)	0.74 (0.68–0.80)	0.73 (0.70–0.77)
35–39.9	0.64 (0.48–0.86)	0.83 (0.75–0.91)	0.83 (0.78–0.89)
≥40	0.87 (0.65–1.15)	1.09 (0.99–1.19)	1.03 (0.95–1.10)
Sex, female	0.64 (0.54–0.77)	0.63 (0.60–0.67)	0.61 (0.59–0.63)
Race			
White	Ref	Ref	Ref
African American	0.96 (0.79–1.16)	0.96 (0.90–1.01)	0.95 (0.91–0.98)
Other race	0.90 (0.60–1.37)	0.97 (0.85–1.10)	0.87 (0.79–0.96)
Diabetes duration	0.94 (0.93–0.95)	1.00 (1.00–1.00)	-
Hypercholesterolemia			
No	Ref	Ref	Ref
Treated	1.04 (0.87–1.25)	0.78 (0.74–0.83)	0.67 (0.64–0.70)
Not treated	1.01 (0.80–1.27)	0.93 (0.86–1.00)	0.78 (0.74–0.82)
Hypertension	1.28 (1.05–1.56)	1.03 (0.96–1.11)	1.19 (1.15–1.24)
Hx of CHD	1.43 (1.18–1.74)	1.35 (1.26–1.44)	1.39 (1.31–1.47)
Hx of TIA/stroke	1.18 (0.96–1.45)	1.28 (1.19–1.38)	1.25 (1.18–1.33)
Hx of smoking	1.39 (1.17–1.65)	1.55 (1.47–1.64)	1.86 (1.78–1.94)
<high school graduate	1.12 (0.87–1.44)	0.79 (0.74–0.85)	0.82 (0.78–0.86)
Household income <$15,000/year	1.44 (1.20–1.73)	1.47 (1.39–1.56)	1.73 (1.67–1.80)
Health insurance	1.07 (0.90–1.28)	0.72 (0.68–0.77)	0.78 (0.75–0.81)

Notes: Unadjusted HRs (95% CI) for young-onset diabetes were 1.87 (0.76–4.58), 0.72 (0.56–0.92), 0.77 (0.60–0.98), 0.64 (0.49–0.85), and 0.84 (0.65–1.08), respectively for underweight, overweight, obesity class 1, obesity class 2, and obesity class 3 compared to normal weight. Unadjusted HRs (95% CI) for older-onset diabetes were 2.20 (1.67–2.89), 0.69 (0.63–0.75), 0.66 (0.61–0.72), 0.70 (0.64–0.77), and 0.87 (0.79–0.95), respectively for underweight, overweight, obesity class 1, obesity class 2, and obesity class 3 compared to normal weight. Unadjusted HRs (95% CI) for no diabetes were 1.59 (1.44–1.77), 0.67 (0.64–0.70), 0.59 (0.57–0.62), 0.62 (0.59–0.66), and 0.74 (0.69–0.79), respectively for underweight, overweight, obesity class 1, obesity class 2, and obesity class 3 compared to normal weight.

were a lack of a protective effect of hyperlipidemia, treated or untreated, among younger-onset diabetes cases, an increased risk associated with hypertension in those with younger-onset diabetes, and a lack of a protective effect of having insurance coverage with mortality among those with younger-onset diabetes.

Race stratified analyses are presented in Table 3. Due to the very limited numbers in the underweight category, this category was merged with the normal weight category. Compared to those with a BMI <25kg/m^2, being in a higher BMI category was associated with a reduced risk of mortality among both Black and White Americans, though some associations did not reach statistical significance. Among those with young-onset diabetes, the mortality risk reduction associated with a higher BMI category was similar among both races, and effect modification by race was not observed (interaction p-value = 0.24). By contrast, for those with older-onset diabetes, effect modification by race was observed (interaction p-value = 0.0001) and being in the overweight category or any one of the obese categories compared to having a BMI <25kg/m^2 appeared to be more protective for Black Americans. Class 3 obesity was associated with an increased risk of mortality among White Americans with older-onset diabetes.

When stratified by sex, the results were essentially similar. An inverse relationship was observed between BMI and mortality among both sexes in both those with young- and older-onset diabetes, with the exception of class 3 obesity among those with older-onset diabetes. Sex-stratified results are presented in Table 4.

To determine whether the protective relationships of overweight and obesity observed were specific to our diabetes population, we also investigated the relationship between BMI and mortality in the SCCS population without diabetes

Table 3 Multivariable Adjusted Association of BMI Category with Mortality in Younger- and Older-Onset Diabetes, Stratified by Race

	Young-Onset		**Older-Onset**	
	African Americans	**Whites**	**African Americans**	**Whites**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	
BMI category, kg/m^2				
<25	Ref	Ref	Ref	Ref
25–29.9	0.73 (0.54–1.00)	0.55 (0.34–0.90)	0.70 (0.63–0.77)	0.86 (0.73–1.02)
30–34.9	0.82 (0.60–1.15)	0.62 (0.37–1.06)	0.65 (0.58–0.72)	0.99 (0.84–1.17)
35–39.9	0.67 (0.47–0.96)	0.51 (0.28–0.92)	0.76 (0.68–0.85)	1.04 (0.87–1.24)
≥40	0.78 (0.55–1.11)	0.98 (0.58–1.67)	0.95 (0.85–1.07)	1.45 (1.22–1.73)
Sex, female	0.62 (0.50–0.77)	0.60 (0.42–0.85)	0.60 (0.56–0.65)	0.69 (0.63–0.76)
Diabetes duration	0.94 (0.93–0.95)	0.95 (0.93–0.96)	1.00 (1.00–1.00)	1.00 (1.00–1.01)
Hypercholesterolemia				
No	Ref	Ref	Ref	Ref
Treated	0.99 (0.79–1.23)	1.07 (0.74–1.56)	0.82 (0.77–0.88)	0.69 (0.62–0.77)
Not treated	0.98 (0.75–1.28)	1.08 (0.65–1.80)	0.95 (0.86–1.04)	0.85 (0.73–0.98)
Hypertension	1.11 (0.88–1.41)	1.63 (1.07–2.47)	1.05 (0.96–1.15)	0.99 (0.88–1.12)
Hx of CHD	1.34 (1.05–1.72)	1.56 (1.08–2.26)	1.38 (1.26–1.50)	1.32 (1.18–1.47)
Hx of TIA/stroke	1.30 (1.01–1.67)	1.03 (0.68–1.57)	1.30 (1.19–1.42)	1.22 (1.07–1.39)
Hx of smoking	1.15 (0.94–1.41)	2.17 (1.47–3.21)	1.48 (1.39–1.59)	1.61 (1.45–1.79)
<high school graduate	0.97 (0.72–1.31)	1.49 (0.91–2.44)	0.73 (0.66–0.80)	0.93 (0.81–1.07)
Household income <$15,000/yr	1.48 (1.18–1.84)	1.21 (0.84–1.75)	1.40 (1.30–1.50)	1.62 (1.46–1.79)
Health insurance	1.18 (0.95–1.46)	0.82 (0.57–1.18)	0.78 (0.72–0.83)	0.64 (0.57–0.71)
	BMI by race p-interaction = 0.24		BMI by race p-interaction = 0.0001	

Table 4 Multivariable Adjusted Association of BMI Category with Mortality in Younger- and Older-Onset Diabetes, Stratified by Sex

	Young-Onset		Older-Onset		No Diabetes	
	Men	Women	Men	Women	Men	Women
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
BMI category, kg/m^2						
<18.5	5.56 (1.69–18.31)	3.37 (0.81–14.07)	1.57 (1.06–2.32)	2.83 (1.91–4.20)	1.29 (1.11–1.51)	1.71 (1.48–1.98)
18.5–24.9	Ref	Ref	Ref	Ref	Ref	Ref
25–29.9	0.75 (0.53–1.07)	0.68 (0.48–0.98)	0.66 (0.59–0.74)	0.87 (0.76–0.99)	0.75 (0.71–0.79)	0.78 (0.73–0.84)
30–34.9	0.78 (0.53–1.16)	0.85 (0.60–1.21)	0.65 (0.58–0.73)	0.85 (0.75–0.97)	0.72 (0.67–0.77)	0.75 (0.70–0.81)
35–39.9	0.76 (0.45–1.28)	0.65 (0.45–0.94)	0.79 (0.69–0.90)	0.91 (0.80–1.04)	0.88 (0.79–0.98)	0.82 (0.75–0.89)
≥40	1.04 (0.62–1.75)	0.84 (0.59–1.20)	0.99 (0.85–1.15)	1.24 (1.10–1.41)	1.19 (1.04 (1.36)	1.01 (0.92–1.11)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
African American	0.85 (0.61–1.19)	0.96 (0.75–1.22)	1.05 (0.96–1.15)	0.89 (0.83–0.96)	0.94 (0.90–1.00)	0.95 (0.90–1.00)
Other race	0.64 (0.29–1.42)	0.95 (0.58–1.57)	1.06 (0.88–1.29)	0.90 (0.75–1.08)	0.87 (0.76–1.00)	0.86 (0.75–0.99)
Diabetes duration	0.94 (0.93–0.96)	0.94 (0.93–0.95)	0.99 (0.99–1.00)	1.00 (1.00–1.01)	–	–
Hypercholesterolemia						
No	Ref	Ref	Ref	Ref	Ref	Ref
Treated	1.24 (0.90–1.70)	0.94 (0.75–1.19)	0.74 (0.68–0.81)	0.82 (0.76–0.88)	0.65 (0.60–0.70)	0.69 (0.65–0.74)
Not treated	1.16 (0.79–1.71)	0.90 (0.67–1.20)	0.95 (0.84–1.06)	0.92 (0.84–1.02)	0.84 (0.78–0.90)	0.74 (0.69–0.79)
Hypertension	1.09 (0.77–1.53)	1.35 (1.05–1.73)	1.15 (1.03–1.27)	0.95 (0.87–1.05)	1.26 (1.20–1.32)	1.11 (1.05–1.17)
Hx of CHD	1.03 (0.72–1.46)	1.72 (1.35–2.18)	1.37 (1.25–1.51)	1.35 (1.23–1.48)	1.29 (1.20–1.39)	1.61 (1.47–1.75)
Hx of TIA/stroke	1.08 (0.74–1.57)	1.33 (1.03–1.70)	1.30 (1.17–1.45)	1.28 (1.16–1.40)	1.19 (1.09–1.30)	1.31 (1.21–1.43)
Hx of smoking	1.35 (0.99–1.85)	1.39 (1.12–1.70)	1.27 (1.16–1.40)	1.72 (1.61–1.84)	1.59 (1.49–1.69)	2.06 (1.95–2.18)
<high school graduate	1.06 (0.70–1.60)	1.09 (0.79–1.50)	0.71 (0.63–0.79)	0.86 (0.78–0.95)	0.79 (0.73–0.85)	0.87 (0.80–0.94)
Household income <$15,000/year	1.77 (1.31–2.39)	1.25 (0.99–1.58)	1.59 (1.46–1.72)	1.37 (1.27–1.48)	1.78 (1.69–1.87)	1.67 (1.58–1.77)
Health insurance	0.79 (0.60–1.05)	1.32 (1.05–1.67)	0.68 (0.62–0.74)	0.76 (0.70–0.82)	0.75 (0.71–0.79)	0.81 (0.77–0.86)

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(Appendix Table 1). A total of 14,054 (22.6%) of the 62,295 without diabetes at cohort entry had died. Among those without diabetes, the inverted J-shaped relationship between BMI and mortality was also observed, though the relationship between BMI in the underweight category and mortality was not as strong as among those with diabetes.

In sensitivity analyses, we tested the relationship of BMI with mortality among those with and without control for insulin therapy restricted to those with data on insulin therapy (Appendix Table 2). Accounting for insulin therapy had no effect on the relationship of BMI with mortality among those with young-onset diabetes but attenuated the excess risk associated with being underweight among those with older-onset diabetes. As an additional sensitivity analysis, we also tested the relationship between BMI and mortality, stratified by smoking status (Appendix Table 3). Results were essentially similar by smoking status, though there were no individuals without a history of smoking in the underweight category among those with young-onset diabetes. Results were also essentially similar with or without control for comorbidities or cardiovascular complications (Appendix Table 4).

Discussion

In our study of over 17,000 largely low-income and predominately African American and White adults with diabetes at cohort entry, we observed a protective relationship between overweight and obesity and mortality risk. The protective relationship was observed for every overweight and obese category up through a BMI of 40 kg/m2 or higher among those with young-onset diabetes, and up through a BMI of 35-<40 kg/m2 among those with older-onset diabetes. We observed some racial variation in these findings, with a stronger protective relationship associated with higher BMI among Whites with young-onset diabetes and among Blacks with older-onset diabetes. Being underweight was associated with excess mortality among both those with younger- and older-onset diabetes that was attenuated after adjustment for being on insulin therapy, but still remained 3-fold higher compared to normal weight among those with young-onset diabetes. Overweight and obesity class I and II status were associated with lower mortality among those with adult-onset diabetes, whereas these weight categories are strong risk factors for prospectively ascertained diabetes onset in the SCCS population studied here.[29] Thus, we also observed the obesity paradox. However, the inverted J-shaped relation between BMI and mortality among those with diabetes was similar to the BMI-mortality pattern observed among our population without diabetes. Our findings are consistent with the observation that among populations with limited lifespans and diseases with accelerated mortality, increased body fat seems to be a protective mechanism extending survival.

The patterns we observed in this large population in the southeastern United States have been seen elsewhere. In the Madrid Diabetes study, 3443 outpatients with Type 2 diabetes were followed for up to five years. All-cause mortality was inversely related to BMI, with the lowest risk observed among those in the 33–39.4 kg/m^2 range and the highest risk among those with a BMI <23 kg/m^2.[12] No difference in mortality was observed among those with a BMI ≥39.4 kg/m^2 compared to their normal weight reference of 23.0–26.8 kg/m^2. These findings remained essentially unchanged even after excluding the first two years of follow-up. A Chinese study followed 11,449 participants for an average of 7 years and found the lowest mortality rates to be among those in the two highest BMI quartiles.[13] This varied slightly by age, with the strongest protective relationship observed among those 60 years and older; however, being in the top 2 BMI quartiles was protective in all age groups. By contrast, having a BMI of <18.5 kg/m^2 only increased risk, and increased it markedly, among the two age groups less than 60 years of age; no difference in risk was observed among the underweight compared to a BMI of 18.5–23.9 among those age 60 years and older. In a meta-analysis of 21 studies including 414,587 participants with diabetes, Zaccardi et al found the lowest mortality risk to be associated with a BMI of 33kg/m^2.[14] A dose-response meta-analysis by Liu et al of 13 cohorts, including 161,984 participants with diabetes, found a 5% decrease in mortality for every 5 kg/m2 increase in BMI, with the lowest mortality risk among those with a BMI ≥30.[15] However, Liu et al's study has been criticized for including participants with comorbid complications such as cardiovascular disease,[14] suggesting that including individuals with pre-existing disease biases the results. However, unless these comorbidities preceded the onset of diabetes, they are not pre-existing diseases.

While we were not able to investigate the relationship of BMI at the time of diabetes diagnosis (as opposed to BMI at cohort entry, although the two BMI measurements should be highly correlated) with mortality, Carnethon et al examined this in a pooled analysis of 2,625 people from the ARIC, CHS, CARDIA, Framingham Offspring Study, and MESA.[3] They found that people who were overweight/obese at the time of diabetes diagnosis had a lower all-cause mortality than

those who were normal weight at diabetes diagnosis. All-cause and non-cardiovascular mortality rates were twice as high among the normal weight, while cardiovascular mortality was non-significantly 50% higher compared to those who were overweight/obese.

The inverse relationship often observed between diabetes and mortality has been attributed by some to collider bias. Collider bias is a theory in causal inferencing in which the conditioning variable, in this case diabetes, is related to downstream factors that are associated with the outcome of interest, in this case mortality. Just what these factors may be is unclear, but it has been speculated that non-obesity related causes of diabetes may have worse outcomes, so obesity-related causes appear to have favorable outcomes.[12,13] However, we have previously shown that obesity is the predominant risk factor for adult-onset incident diabetes in the population studied.[29] Further, in the current analysis, we stratified by age at onset, ie young-onset vs older-onset, and by insulin therapy use within age strata (we have previously shown a two-fold higher mortality risk among those with young-onset insulin treated diabetes compared to those not treated with insulin and a four-fold higher risk compared to those without diabetes) and saw similar patterns across all groups. We also stratified by the risk factors of race and smoking history status and saw similar patterns. Thus, neither collider bias specifically nor selection bias more broadly appears to account for our results.

Although BMI with outcomes of Type 1 diabetes has not been as extensively studied as outcomes in Type 2 diabetes, U- and inverted J-shaped relationships have also been observed for Type 1 diabetes or insulin-treated young-onset diabetes.[21,30–33] While increased all-cause mortality rates were observed among the overweight and obese and an increased risk among those with a BMI below 22 in a large Swedish population with Type 1 diabetes after excluding smokers, people with HbA1c >7.6%, ie not in optimum glycemic control, or who either died or had a cardiovascular event/or diagnosis of a cardiovascular complication within the first five years of follow-up,[31] Conway et al observed a strong U-shaped relationship between BMI and mortality in the US Pittsburgh Epidemiology of Diabetes Complications study population even after accounting for HbA1c, smoking and late complications of diabetes in updated mean and time varying analyses.[32] The similar, though attenuated, findings we observed between BMI and mortality in our SCCS population without diabetes suggest that our results are not due to reverse causation or late diabetes complications among our SCCS participants with diabetes.

Impaired insulin signaling rather than insulin resistance has been shown to play a more predominant role in Type 2 diabetes among those who are lean at diagnosis compared to those who are overweight or obese.[34] This has been suggested by some as a more pernicious form of diabetes.[12] While we were unable to account for glycemic control, the similar results observed among those without diabetes suggest that our findings are not due to greater beta cell failure/impaired insulin secretion among the lean. Furthermore, we have previously shown that coronary heart disease, which is strongly characterized by insulin resistance, is the leading cause of death among those with or without diabetes in this population.[35]

While our study focused predominately on low-income African American and non-Hispanic White people in the US, our results may be generalizable to other populations as well. For example, Zheng et al also observed a strong U-shaped relationship between BMI and mortality in a population of more than one million Asian people of different nationalities. Their findings in the general population are important because Asians and African Americans are more likely to have or develop diabetes at a BMI in the normal weight range. In our population, the inverse relationship between BMI and mortality among those with older-onset diabetes was slightly stronger among African Americans than among non-Hispanic White Americans.

Strengths of our study include our very large sample size of low-income Blacks and Whites, the largest traditional cohort study to date of African Americans with diabetes. We were thus able to, by both study design and statistical analyses, control for socioeconomic status, one of the most important confounding factors in Black–White racial differences in mortality and also an important confounder in the BMI relationship with mortality. This may explain the strong inverse relationship, among both Blacks and Whites, that we observed between BMI and mortality since in the US the very poor, for whom mortality is increased, tend to be overrepresented at both ends of the BMI spectrum. We were also able to control for smoking, an important putative confounder in the BMI relationship with mortality. Finally, the relatively long average follow-up time of 12.3 years was also a major strength of our study, limiting weight loss among those with occult disease and death shortly after follow-up heavily influencing our results.

This study also has a few limitations. The subjects self-reported height and weight may not be accurate, although, among those with measured height and weight, the correlation between self-reported and measured BMI exceeded 95%.

In addition, lack of information of waist circumference or the waist-to-hip ratio for the majority of our population, lack of information on renal failure - a leading cause of death among those with diabetes-, and lack of information on markers of inflammation are a few of the limitations of this study. In addition to BMI, diabetes and age at the time of diabetes diagnosis were based on self-report. Separate validation efforts based on review of medical records and/or A1c levels for random samples of SCCS participants, however, confirmed over 97% of the self-reports.[36] We were not able to separate type 1 from type 2 diabetes in our study population; however, most of those with type 1 diabetes would be in the subgroup diagnosed before the age of thirty while most of those with type 2 diabetes would be found among those diagnosed at or after the age of 30 years. Controlling for insulin therapy in the young-onset population, where all those with type 1 diabetes would be on insulin therapy, did not change the association of BMI with mortality. A major late complication of diabetes is kidney failure, a condition often resulting in weight loss and a very high risk of mortality. In these analyses, we were unable to assess whether the protection associated with high BMI was due to factors such as increased inflammation protecting against mortality among those with renal failure or whether high BMI itself was protective against mortality among those with End-stage renal disease. We were also unable to assess whether increased inflammation among the obese was protecting against common acute infections, especially sepsis, in which people with diabetes are more prone and which increase mortality risk.

Increased mortality risk was found among the underweight and protective or no associations among the overweight and most obese categories compared to the normal weight category among our populations with diabetes. It is common in clinical practice to counsel patients with Type 2 diabetes to lose weight. However, our data, consistent with most of the literature, suggest that such advice is not warranted. Among patients with diabetes, measures other than BMI may be more clinically relevant to morbidity and mortality such as visceral adiposity, ejection fraction, measures of inflammation such as C-reactive protein, triglycerides to high-density lipoprotein-cholesterol ratio and B-type natriuretic peptide. Indeed, given the very high mortality rate in this largely low SES population, clinical attention to risk factors for diabetes complications other than overweight and obesity may be much more prudent.

Data Sharing Statement

Data are available upon an approved request to the Southern Community Cohort Study Biospecimen Committee.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no potential conflicts of interest relevant to this article.

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