Association of Weight Status With Mortality in Adults With Incident Diabetes

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Context Type 2 diabetes in normal-weight adults (body mass index [BMI] <25) is a representation of the metabolically obese normal-weight phenotype with unknown mortality consequences.

Objective To test the association of weight status with mortality in adults with new-onset diabetes in order to minimize the influence of diabetes duration and voluntary weight loss on mortality.

Design, Setting, and Participants Pooled analysis of 5 longitudinal cohort studies: Atherosclerosis Risk in Communities study, 1990-2006; Cardiovascular Health Study, 1992-2008; Coronary Artery Risk Development in Young Adults, 1987-2011; Framingham Offspring Study, 1979-2007; and Multi-Ethnic Study of Atherosclerosis, 2002-2011. A total of 2625 participants with incident diabetes contributed 27 125 person-years of follow-up. Included were men and women (age >40 years) who developed incident diabetes based on fasting glucose 126 mg/dL or greater or newly initiated diabetes medication and who had concurrent measurements of BMI. Participants were classified as normal weight if their BMI was 18.5 to 24.99 or overweight/obese if BMI was 25 or greater.

Main Outcome Measures Total, cardiovascular, and noncardiovascular mortality.

Results The proportion of adults who were normal weight at the time of incident diabetes ranged from 9% to 21% (overall 12%). During follow-up, 449 participants died: 178 from cardiovascular causes and 253 from noncardiovascular causes (18 were not classified). The rates of total, cardiovascular, and noncardiovascular mortality were higher in normal-weight participants (284.8, 99.8, and 198.1 per 10 000 person-years, respectively) than in overweight/obese participants (152.1, 67.8, and 87.9 per 10 000 person-years, respectively). After adjustment for demographic characteristics and blood pressure, lipid levels, waist circumference, and smoking status, hazard ratios comparing normal-weight participants with overweight/obese participants for total, cardiovascular, and noncardiovascular mortality were 2.08 (95% CI, 1.52-2.85), 1.52 (95% CI, 0.89-2.58), and 2.32 (95% CI, 1.55-3.48), respectively.

Conclusion Adults who were normal weight at the time of incident diabetes had higher mortality than adults who are overweight or obese.

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TYPE 2 DIABETES IN NORMAL-weight adults is an understudied representation of the metabolically obese normal-weight phenotype[1] that has become increasingly common over time.[2] It is not known whether the "obesity paradox" that has been observed in chronic diseases such as heart failure, chronic kidney disease, and hypertension extends to adults who are normal weight at the time of incident diabetes.[3-5] In 2 contemporary studies, the Translating Research Into Action for Diabetes (TRIAD) study[6] and the PROactive trial,[7] participants with diabetes who were normal weight at the baseline examination or who lost weight during the trial (PROactive) experienced higher mortality than participants who were overweight or obese. Limitations of these prevalent disease studies are that participants had diabetes of unknown duration and participants from the PROactive trial had preexisting cardiovascular disease at baseline.

For editorial comment see p 619.

To minimize the influence of diabetes duration and unintentional or intentional weight loss secondary to diabetes development and diagnosis,[8] we compared mortality between participants who were normal weight and

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overweight/obese at the time of incident adult-onset diabetes. We hypothesized that participants who were normal weight at the time of incident diabetes would experience higher mortality than participants who were overweight or obese.

METHODS

Our study included 2625 participants from the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA) study, Framingham Offspring Study (FOS), and Multi-Ethnic Study of Atherosclerosis (MESA) who developed incident diabetes. We selected these studies because they had repeated measures of body weight, fasting glucose level, and medication use; a comprehensive set of commonly measured covariates; and longitudinal follow-up for events and mortality.[9-13] The eTable, available at http://www.jama.com, summarizes each study's size, follow-up duration, number of examinations, and examination dates.

Institutional review boards at each of the institutions reviewed the protocols and procedures and approved the research. All participants provided written informed consent at each examination. Data were deidentified for our analysis, and the Northwestern University institutional review board approved the research.

Diabetes and Weight Status

Diabetes was determined as fasting (≥8 hours) glucose of 126 mg/dL or greater[9,11-15] or reported use of oral hypoglycemic medications or insulin. (To convert glucose to mmol/L, multiply by 0.0555.) Incident diabetes was determined among participants who were free from diabetes at baseline and who met one of the these 2 criteria at a subsequent follow-up examination.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Normal weight, overweight, and obese were defined as a BMI of 18.5 to 24.9, 25 to 29.9, and 30 or greater, respectively.[16] Participants' weight status was assigned at the examination when diabetes was identified (ie, baseline of this analysis sample).

Follow-up Time and Mortality

Participants were followed up from the examination at which diabetes was identified until they died, reached the end of their cohort surveillance, or were lost to follow-up. Mortality was determined annually using cohort-specific surveillance protocols, and investigators adjudicated cause of death after review of all available medical records. Cardiovascular death (ie, myocardial infarction, stroke) was adjudicated using a combination of review of death certificates for codes indicating cardiovascular disease as an underlying cause of death and proxy interviews.[10-13,17] Causes of noncardiovascular death were not uniformly adjudicated across studies.

Covariates

Demographic characteristics, health behaviors, and clinical factors available in each of the cohort studies were measured using standard protocols.[9-13] We selected covariates that were commonly measured across studies. Race/ethnicity was determined according to self-report and was assessed by each component cohort study because of the known relevance of race/ethnicity to cardiovascular disease. Covariates were determined at the time of incident diabetes (ie, baseline); however, if the measures were not available from that examination, the most recent value from a prior cohort examination was used instead.

Statistical Analysis

We compared means and standard deviations or proportions of study characteristics between normal-weight and overweight/obese participants who had incident diabetes within each cohort using *t* tests and χ^2 tests, respectively. Kaplan-Meier survival curves with log-rank χ^2 are presented to compare mortality by weight status. Because the number of participants remaining after 15 years was small, we truncated the presentation to 15 years of follow-up. Following confirmation of proportional hazards using log-log survival plots, we modeled the mortality hazards comparing normal-weight with overweight/obese participants with diabetes (referent).

We used 2 strategies to generate pooled estimates. First, we performed cohort-specific analyses to generate effect estimates that were pooled together using fixed- and random-effects meta-analysis. Because effect estimates were relatively homogenous across cohorts, there were no differences between fixed and random effects and so we present fixed effects. Second, we performed a pooled cohort analysis using Cox modeling with a stratification term for cohort. Because waist circumference and lipids were measured using different protocols and assays, we transformed them to *z* scores in the pooled analysis.

Model 1 was adjusted for age, race (nonwhite vs white), sex, and education (less than high school vs high school graduate or more). Model 2 was adjusted for model 1 and waist circumference, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, and smoking status (current or former vs never). Variance inflation factor and tolerance statistics indicated that the covariates in the model were not collinear.[18] We tested whether sex, race, age at diabetes incidence (<65 vs ≥65 years), or smoking status modified the association of weight status with mortality using multivariable Cox models with a multiplicative interaction term between each characteristic of interest and normal-weight status. We determined statistical significance for the interaction based on the maximum likelihood χ^2 from a nested model with and without the interaction term. Analyses were repeated for each cause of mortality.

We carried out a series of sensitivity analyses for our primary outcome of total mortality to explore alternative explanations for our findings. We analyzed the association between BMI per standard deviation higher and total

mortality and the association between waist circumference per standard deviation higher and total mortality. In an attempt to reduce variability in the duration of new-onset diabetes, we restricted our analysis to participants who had elevated fasting glucose but who were not taking medications to control diabetes. To test whether defining diabetes using a single glucose measurement contributed to misclassification, we restricted the definition of diabetes to participants taking medications only. Because Asian adults are more likely to develop diabetes at a lower BMI, we performed an analysis excluding Asian participants.

To reduce the possibility that unmeasured illness at the time of diabetes identification resulted in weight loss prior to imminent death, we excluded participants who were followed up for less than 2 years after diabetes identification. We excluded 162 participants whose BMI decreased by more than 2 units from the baseline examination, which may have reflected other illnesses that might predispose to death. Given prior reports that overweight adults have the lowest mortality risk (particularly among older adults), we calculated mortality hazard ratios (HRs) comparing normal-weight and obese participants with overweight participants.

All analyses were carried out using SAS version 10 (SAS Institute). Statistical significance was determined at $P < .05$ (2-sided).

RESULTS

Demographic, clinical, and behavioral characteristics at the time of incident diabetes are stratified by weight status in TABLE 1. Across cohorts, 293 participants (11.2%) had normal-weight diabetes; normal-weight diabetes was most common in CHS (21%) and lowest in ARIC (9%). Half (50%) of the participants were women, 36% were nonwhite, and the mean (SD) age of participants ranged from 41 (6) years

Table 1. Distribution of Covariates Stratified by Weight Status[a]

	ARIC			CARDIA			CHS			FOS			MESA		
	Normal Weight	O/O	*P* Value[b]	Normal Weight	O/O	*P* Value	Normal Weight	O/O	*P* Value	Normal Weight	O/O	*P* Value[b]	Normal Weight	O/O	*P* Value[b]
Participants, No. (%)	108 (8.7)	1132 (91.3)		28 (10.2)	246 (89.8)		37 (20.6)	143 (79.4)		48 (10.4)	413 (89.6)		72 (15.3)	398 (84.7)	
Age, mean (SD), y	59.8 (6.1)	59.1 (5.9)	.23	39.4 (6.4)	41.0 (5.8)	.16	78.6 (5.6)	75.1 (4.7)	<.001	59.5 (10.7)	58.5 (9.0)	.47	68.9 (10.0)	63.6 (9.5)	<.001
Nonwhite race, No. (%)	34 (31.5)	384 (33.9)	.61	14 (50.0)	164 (66.7)	.08	5 (13.5)	25 (17.5)	.56	0	0		54 (75.0)	274 (68.8)	.30
Female sex, No. (%)	51 (47.2)	584 (51.6)	.38	14 (50.0)	139 (56.5)	.51	20 (54.1)	79 (55.2)	.90	22 (45.8)	174 (42.1)	.62	44 (61.1)	202 (50.8)	.11
Less education, No. (%)[c]	21 (19.4)	316 (28.0)	.06	3 (10.7)	26 (10.6)	>.99	16 (43.2)	43 (30.1)	.13	5 (12.8)	36 (10.5)	.59	22 (30.6)	76 (19.1)	.03
Systolic BP, mean (SD), mm Hg	126.1 (19.3)	128.9 (18.5)	.14	111.6 (13.3)	121.4 (16.5)	.003	133.7 (20.3)	134.4 (20.0)	.85	129.8 (21.9)	136.3 (18.8)	.03	123.9 (21.3)	126.8 (19.8)	.26
Diastolic BP, mean (SD), mm Hg	72.0 (11.1)	73.9 (10.4)	.07	71.8 (10.8)	79.2 (12.0)	.002	67.6 (9.9)	70.1 (11.6)	.24	76.0 (10.2)	79.4 (12.1)	.06	68.1 (10.4)	71.5 (10.6)	.01
Hypertension, No. (%)[d]	51 (47.2)	671 (59.3)	.02	6 (21.4)	112 (45.5)	.01	19 (51.4)	92 (64.3)	.15	25 (52.1)	285 (69.0)	.02	43 (59.7)	272 (68.3)	.15
Ever smoked, No. (%)	69 (63.9)	704 (62.5)	.77	15 (55.6)	100 (41.2)	.15	24 (68.6)	82 (58.6)	.28	38 (79.2)	290 (70.2)	.20	31 (43.1)	234 (59.5)	.009
BMI, mean (SD)	23.2 (1.6)	32.8 (5.7)	<.001	22.4 (1.8)	37.0 (7.7)	<.001	22.8 (1.5)	31.1 (4.7)	<.001	23.1 (1.7)	32.6 (5.5)	<.001	23.2 (1.5)	33.0 (5.8)	<.001
Waist circumference, mean (SD), cm	90.4 (9.4)	111.1 (13.3)	<.001	77.6 (7.0)	109.0 (16.7)	<.001	90.3 (9.1)	108.5 (16.9)	<.001	88.3 (10.5)	109.7 (12.8)	<.001	87.5 (6.7)	109.7 (14.2)	<.001
Total cholesterol, mean (SD), mg/dL	205.5 (49.8)	208.8 (42.3)	.51	180.4 (50.6)	188.7 (38.9)	.42	200.0 (51.6)	204.2 (41.8)	.61	194.2 (46.0)	209.8 (39.5)	.01	182.9 (43.3)	182.6 (35.7)	.96
HDL cholesterol, mean (SD), mg/dL	45.5 (13.2)	42.7 (13.0)	.03	58.3 (26.8)	42.7 (11.4)	.006	51.7 (11.2)	47.9 (11.6)	.08	45.6 (16.8)	40.6 (11.9)	.05	52.7 (15.7)	46.5 (12.4)	.002
Triglycerides, median (IQR), mg/dL[e]	126.9 (69.9)	152.4 (104.9)	<.001	90.0 (83.0)	121.5 (109.0)	.005	118.0 (122.0)	159.0 (122.0)	.02	136.5 (112.0)	181.0 (135.5)	.001	108.0 (83.0)	131.0 (103.0)	.002
LDL cholesterol, mean (SD), mg/dL	131.0 (45.2)	130.8 (37.0)	.96	97.2 (40.3)	114.7 (34.5)	.02	122.1 (38.0)	122.9 (32.1)	.89	117.1 (37.8)	142.1 (36.3)	.01	106.2 (33.8)	104.8 (31.2)	.73

Abbreviations: ARIC, Atherosclerosis Risk in Communities study; BP, blood pressure; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults study; CHS, Cardiovascular Health Study; HDL, high-density lipoprotein; IQR, interquartile range; FOS, Framingham Offspring Study; LDL, low-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; O/O, overweight/obese.

SI conversion factors: To convert total, HDL, and LDL cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

[a] BMI is calculated as weight in kilograms divided by height in meters squared. Normal weight was defined as a BMI of 18.5 to 24.9; overweight/obese defined as a BMI of ≥25.

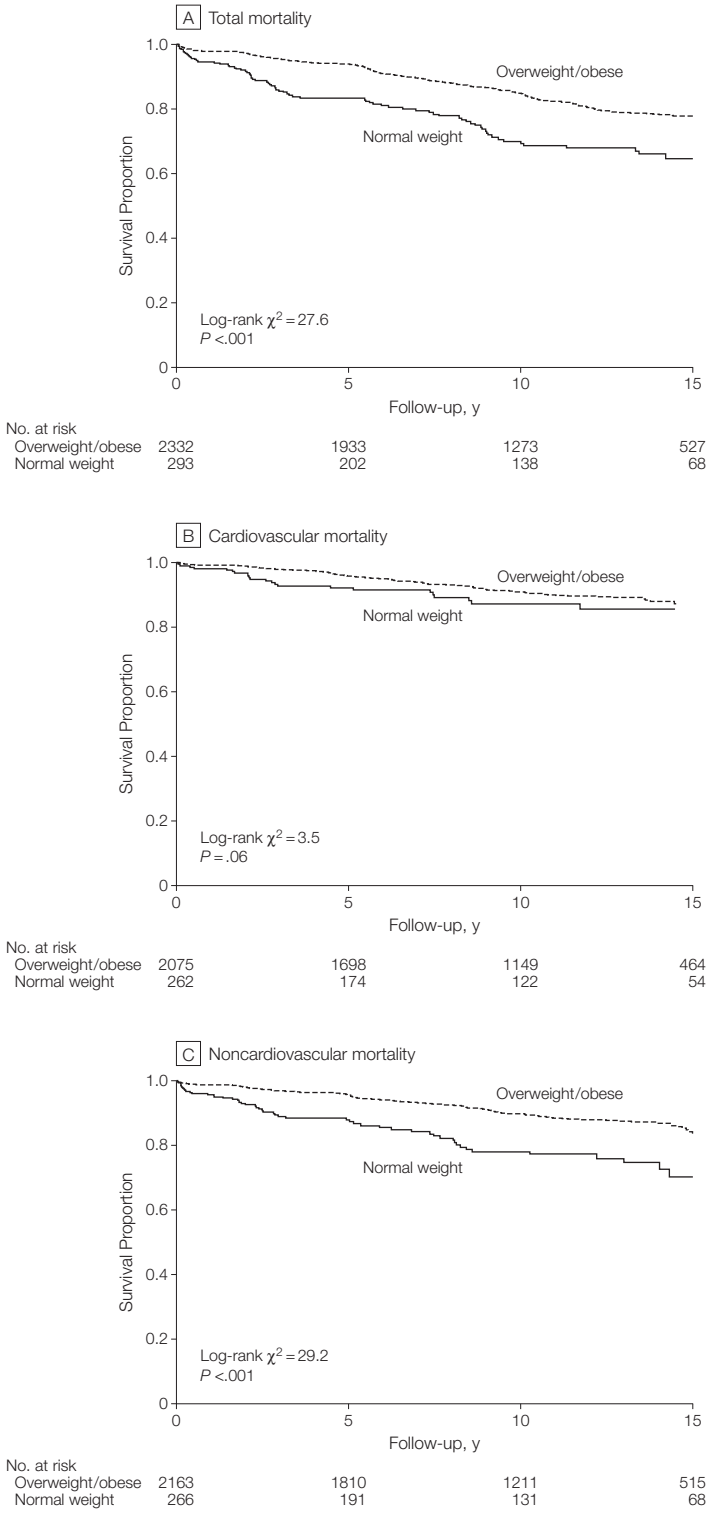
[b] *P* value based on *t* test for continuous variables and χ^2 test for categorical variables.

[c] Did not graduate from high school.

[d] Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or reported use of antihypertensive medications.

[e] Statistical significance determined using a Wilcoxon rank sum test.

Figure 1. Kaplan-Meier Survival Estimates Comparing Mortality in Participants Stratified by Weight Status at the Time of Incident Diabetes



Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Normal weight was defined as a BMI of 18.5-24.9; those categorized as overweight/obese had a BMI of ≥25.

in CARDIA to 76 (5) years in CHS. The distribution of cardiovascular risk factors varied across cohorts.

During follow-up, 449 participants died (165.5 per 10 000 person-years): 178 (6.8%) from cardiovascular causes (66.1 per 10 000 person-years) and 253 (10.4%) from noncardiovascular causes (99.0 per 10 000 person-years); 18 causes of death were unidentified. FIGURE 1 displays Kaplan-Meier estimates of each type of mortality by weight status at the time of diabetes incidence. Normal-weight participants experienced significantly higher total and noncardiovascular mortality than overweight/obese participants.

TABLE 2 displays the crude and multivariable-adjusted association of weight status with mortality in the pooled sample and by cohort. In the pooled sample, total, cardiovascular, and noncardiovascular mortality is higher in normal-weight participants (284.8, 99.8, and 198.1 per 10 000 person-years, respectively) as compared with rates among overweight or obese participants (152.1, 67.8, and 87.9 per 10 000 person-years, respectively). These patterns are consistent for total and noncardiovascular mortality within each cohort and present for cardiovascular mortality in CHS and FOS. Mortality rates were markedly higher in CHS cohort participants who were older, on average, than other cohort participants; further, there were a relatively smaller number of participants from CHS resulting in fewer person-years of follow-up.

Following adjustment for covariates (model 2), participants with normal-weight diabetes experienced a significantly elevated total mortality (HR, 2.08; 95% CI, 1.52-2.85) and noncardiovascular mortality (HR, 2.32; 95% CI, 1.55-3.48). Although the hazard for cardiovascular mortality was elevated, the association was not statistically significant (HR, 1.52; 95% CI, 0.89-2.58). Results generated using meta-analysis demonstrated similar effect estimates. Findings were consistent across cohorts although not always statistically significant. Participants with normal-weight diabetes had higher mortality

Table 2. Association Between Weight Status at the Time of Diabetes Incidence and Mortality[a]

	Total Mortality		Cardiovascular Mortality		Noncardiovascular Mortality	
	Overweight/Obese	Normal Weight	Overweight/Obese	Normal Weight	Overweight/Obese	Normal Weight
Full Sample						
No. of participants	2332	293	2086	265	2163	266
No. of events	371	78	149	24	202	51
Event rate (per 10 000 person-years)	152.1	284.8	67.8	99.8	87.9	198.1
Pooled analysis[b]						
Unadjusted HR (95% CI)	1 [Reference]	1.70 (1.33-2.18)	1 [Reference]	1.31 (0.85-2.02)	1 [Reference]	2.03 (1.49-2.77)
Multivariable model 1[c]	1 [Reference]	1.49 (1.15-1.93)	1 [Reference]	1.04 (0.65-1.66)	1 [Reference]	1.79 (1.30-2.47)
Multivariable model 2[d]	1 [Reference]	2.08 (1.52-2.85)	1 [Reference]	1.52 (0.89-2.58)	1 [Reference]	2.32 (1.55-3.48)
Meta-analysis[e]						
Unadjusted HR (95% CI)	1 [Reference]	1.72 (1.33-2.21)	1 [Reference]	1.24 (0.78-1.97)	1 [Reference]	1.97 (1.40-2.76)
Multivariable model 1	1 [Reference]	1.54 (1.18-2.02)	1 [Reference]	0.98 (0.59-1.64)	1 [Reference]	1.78 (1.25-2.55)
Multivariable model 2	1 [Reference]	2.01 (1.44-2.81)	1 [Reference]	1.29 (0.71-2.33)	1 [Reference]	2.18 (1.39-3.42)
Cohort-Specific						
ARIC						
No. of participants	1132	108	1132	108	1060	102
No. of events	129	16	66	5	57	10
Event rate (per 10 000 person-years)	95.6	121.2	49.2	38.1	44.3	78.6
Unadjusted HR (95% CI)	1 [Reference]	1.23 (0.73-2.07)	1 [Reference]	0.76 (0.31-1.89)	1 [Reference]	1.73 (0.88-3.39)
Multivariable model 1	1 [Reference]	1.20 (0.71-2.02)	1 [Reference]	0.74 (0.30-1.84)	1 [Reference]	1.68 (0.85-3.32)
Multivariable model 2	1 [Reference]	1.55 (0.86-2.79)	1 [Reference]	0.99 (0.37-2.62)	1 [Reference]	2.10 (0.96-4.58)
CARDIA						
No. of participants	246	28			237	28
No. of events	14	4			5	4
Event rate (per 10 000 person-years)	60.9	131.7			22.4	131.7
Unadjusted HR (95% CI)	1 [Reference]	1.96 (0.64-6.00)			1 [Reference]	5.48 (1.45-20.71)
Multivariable model 1	1 [Reference]				1 [Reference]	
Multivariable model 2	1 [Reference]				1 [Reference]	
CHS						
No. of participants	143	37	143	37	101	27
No. of events	94	31	41	10	52	21
Event rate (per 10 000 person-years)	661.6	1230.9	289.0	397.1	451.8	995.9
Unadjusted HR (95% CI)	1 [Reference]	2.01 (1.33-3.02)	1 [Reference]	1.42 (0.71-2.83)	1 [Reference]	2.43 (1.46-4.05)
Multivariable model 1	1 [Reference]	1.60 (1.05-2.43)	1 [Reference]	1.04 (0.51-2.14)	1 [Reference]	1.84 (1.08-3.12)
Multivariable model 2	1 [Reference]	1.81 (1.08-3.03)	1 [Reference]	1.26 (0.56-2.87)	1 [Reference]	1.98 (1.02-3.84)
FOS						
No. of participants	413	48	413	48	372	40
No. of events	115	20	38	6	74	12
Event rate (per 10 000 person-years)	211.1	350.6	70.4	108.9	147.6	236.6
Unadjusted HR (95% CI)	1 [Reference]	1.69 (1.05-2.71)	1 [Reference]	1.56 (0.66-3.69)	1 [Reference]	1.61 (0.87-2.96)
Multivariable model 1	1 [Reference]	1.82 (1.04-3.16)	1 [Reference]	1.36 (0.41-4.54)	1 [Reference]	1.80 (0.91-3.56)
Multivariable model 2	1 [Reference]	3.26 (1.47-7.21)	1 [Reference]	3.45 (0.57-20.80)	1 [Reference]	2.89 (1.08-7.78)
MESA						
No. of participants	398	72			393	69
No. of events	19	7			14	4
Event rate (per 10 000 person-years)	109.0	239.6			80.9	142.5
Unadjusted HR (95% CI)	1 [Reference]	2.25 (0.95-5.36)			1 [Reference]	1.80 (0.59-5.47)
Multivariable model 1	1 [Reference]	1.79 (0.72-4.41)			1 [Reference]	
Multivariable model 2	1 [Reference]	3.50 (1.06-11.61)			1 [Reference]	

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; CHS, Cardiovascular Health Study; FOS, Framingham Offspring Study; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis.

[a] Normal weight was defined as a body mass index of 18.5 to 24.9 (calculated as weight in kilograms divided by height in meters squared); overweight/obese defined as a body mass index of ≥25.

[b] Pooled analysis: total mortality includes all cohorts (n=2625); cardiovascular mortality includes ARIC, CHS, FOS, and MESA (n=2351); noncardiovascular mortality includes all cohorts (n=2429).

[c] Multivariable model 1 includes statistical adjustment for age, race, sex, and education.

[d] Multivariable model 2 includes statistical adjustment for age, race, sex, education, waist circumference, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and smoking status (ever vs never).

[e] Fixed-effects meta-analysis for total mortality includes ARIC, CHS, FOS, and MESA; cardiovascular mortality includes ARIC, CHS, and FOS; noncardiovascular mortality includes ARIC, CHS, and FOS.

from all causes than overweight/obese participants across strata of sex, age, race, and smoking (FIGURE 2).

The findings from each of our sensitivity analyses are presented in TABLE 3. Body mass index (per standard deviation higher) was not associated with total mortality, but waist circumference was significantly associated with increased mortality. Normal-weight status was associated with increased mortality in each of the additional analyses. When we stratified weight at the time of diabetes into 3 levels, we observed higher total mortality in normal-weight as compared with overweight (referent) participants whereas mortality hazards did not differ between obese vs overweight.

COMMENT

In our pooled longitudinal study, participants who were normal weight at the time of incident diabetes experienced higher total and noncardiovascular mortality as compared with those who were overweight or obese. Cardiovascular mortality was nonsignificantly elevated in participants who were normal weight as compared with those who were overweight or obese. Findings were consistent across demographic categories and smoking status and persisted after adjustment for known cardiovascular disease risk factors.

It was unexpected that weight status was not associated with cardiovascular mortality. However, crude cardiovascular mortality rates were higher in normal-weight vs overweight/obese participants, and HRs from fully adjusted models reflect elevated mortality. Consequently, we interpreted the absence of statistical significance as a by-product of low statistical power due to the relatively smaller number of cardiovascular events.

Overweight and obese patients with end-stage renal disease have better health outcomes than leaner patients.[19-21] Similarly, lean persons with hypertension (the cut point for "lean" varies across studies)[4] and persons with heart failure[3] have worse health outcomes than their heavier counterparts. Even among persons without known chronic diseases, heavier weight may be associated with greater long-term (>15 years) mortality.[22] Our findings are consistent with the existing literature in other prevalent disease cohorts, including those of persons with diabetes.[6,7,23,24]

Lower body weight in the presence of obesity-related metabolic disorders may reflect underlying illness that predisposes to mortality. Prior research has attempted to reduce the influence of latent illness by excluding those who died early (2-5 years) during the follow-up period. We did not have an adequate number of events over an extended follow-up period (>15 years) to study long-term mortality,[22] so our findings could reflect higher mortality among persons who were already ill for reasons unrelated to diabetes. Statistical adjustment for demographic characteristics (eg, socioeconomic status) and health behaviors (eg, smoking) associated with other causes of mortality did not change our findings. Despite having a leaner body habitus, cigarette smokers are more insulin resistant,[25] are more likely to develop diabetes,[26] and have increased mortality as compared with nonsmokers. However, we report that the elevated mortality in normal-weight participants is not entirely attributable to smoking because findings are similar among smokers and nonsmokers.

The primary features distinguishing our study from the contemporary PROactive trial[7] and the TRIAD studies[6] (as well as earlier studies addressing this question[23,24]) are that we defined weight status at the time of incident diabetes and identified an elevated risk of mortality in normal-weight adults who did not have comorbid cardiovascular diseases (eg, coronary heart disease, cerebrovascular disease). Although unexplained or unintentional weight loss (despite hunger and regular eating) is most commonly described as a symptom of type 1 diabetes, it is often present in type 2 diabetes.[8] Intentional weight loss is recommended following the identification of type 2 diabetes based on findings that adults who lose weight have better glycemic control and improvement in other cardiovascular disease risk factors.[27] Both of these scenarios could confound the ability to describe the association between weight status and mortality if weight status is determined at the time of prevalent diabetes.

Latent autoimmune diabetes in adults (LADA)[28] is phenotypically similar to type 1 diabetes because of apparent β-cell destruction and disease presentation in normal-weight adults. Some normal-weight adults with diabetes may have LADA, but it is not possible to identify LADA without measuring autoantibodies such as glutamic acid decarboxylase or C-peptide—neither of which were universally measured in these cohort studies. We did not have access to the type of diabetes control medication (oral hypoglycemic vs insulin replacement) across all cohort studies in our analysis. Consequently, we are unable to determine whether participants who were normal weight at the time of diabetes incidence in our study have LADA. Despite this limitation, our findings suggest that regardless of diabetes type, normal-weight status at the time of diabetes incidence may be a straightforward marker to identify elevated mortality risk.

In our epidemiologic study, normal weight is determined based on BMI and not on a direct measure of adiposity. Higher BMI could be the result of more lean muscle mass, which is more insulin sensitive than adipose tissue and consequently metabolically favorable. If, as suggested,[29-31] insulin resistance is the primary underlying factor in cardiovascular disease, then unmeasured fat mass and insulin sensitivity may be a significant source of residual confounding among normal-weight adults. Greater waist circumference was directly associated with increased mortality in our sample, and the strength of association between normal-weight status and total mortality became modestly stronger when waist circumference was included in our models. Our adjusted findings may reflect an adverse role of lower lean mass on

Figure 2. Adjusted Hazard Ratios of Mortality by Weight Status Stratified by Subgroup

A Total Mortality

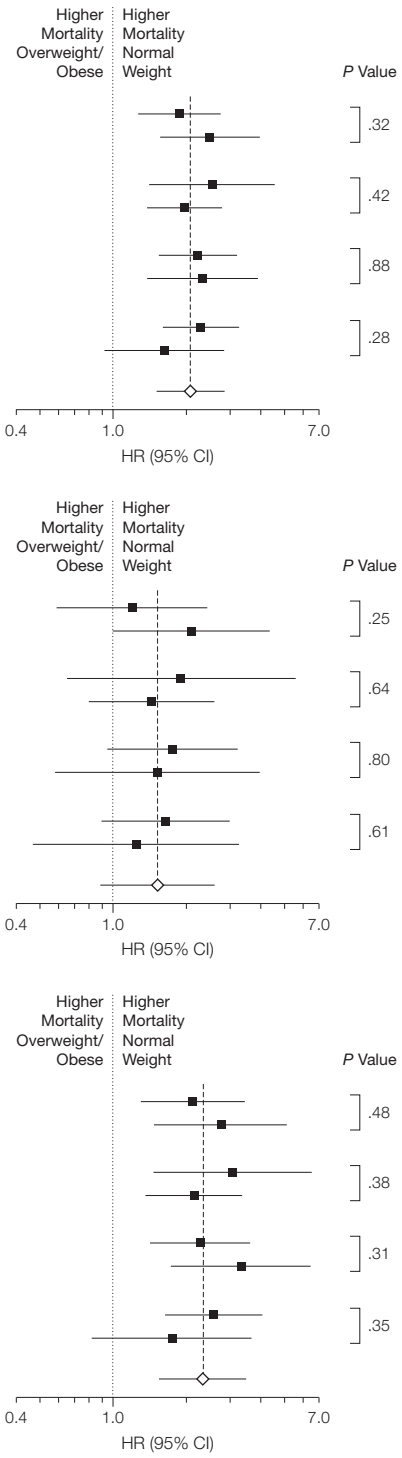
	No. of Events			No. of Participants				
	Total	Normal Weight	Overweight/ Obese	Total	Normal Weight	Overweight/ Obese	HR (95% CI)	*P* Value
Sex								
Male	265	45	220	1296	142	1154	1.87 (1.28-2.74)	.32
Female	184	33	151	1329	151	1178	2.49 (1.57-3.97)	
Race								
Nonwhite	114	18	96	954	170	847	2.55 (1.43-4.57)	.42
White	335	60	275	1671	186	1485	1.96 (1.39-2.78)	
Age, y								
≥65	248	52	196	809	135	674	2.23 (1.55-3.20)	.88
<65	201	26	175	1816	158	1658	2.33 (1.39-3.90)	
Smoking status								
Ever	309	59	250	1587	177	1160	2.29 (1.61-3.26)	.28
Never	133	17	116	1019	113	906	1.63 (0.93-2.84)	
Pooled	449			2625				

B Cardiovascular Mortality

	No. of Events			No. of Participants				
	Total	Normal Weight	Overweight/ Obese	Total	Normal Weight	Overweight/ Obese	HR (95% CI)	*P* Value
Sex								
Male	101	13	88	1166	126	1040	1.20 (0.59-2.41)	.25
Female	72	11	61	1171	136	1035	2.09 (1.00-4.36)	
Race								
Nonwhite	41	4	37	772	92	680	1.90 (0.65-5.60)	.64
White	132	20	112	1565	170	1395	1.44 (0.80-2.58)	
Age, y								
≥65	97	17	80	804	133	671	1.75 (0.95-3.22)	.80
<65	76	7	69	1533	129	1404	1.52 (0.58-3.96)	
Smoking status								
Ever	122	19	103	1462	161	1301	1.64 (0.90-2.99)	.61
Never	50	5	45	860	99	761	1.24 (0.47-3.27)	
Pooled	173			2351				

C Noncardiovascular Mortality

	No. of Events			No. of Participants				
	Total	Normal Weight	Overweight/ Obese	Total	Normal Weight	Overweight/ Obese	HR (95% CI)	*P* Value
Sex								
Male	151	30	121	1182	127	1055	2.12 (1.31-3.44)	.48
Female	102	21	81	1247	139	1108	2.76 (1.48-5.13)	
Race								
Nonwhite	62	13	49	902	102	800	3.09 (1.47-6.51)	.38
White	191	38	153	1527	164	1363	2.14 (1.36-3.36)	
Age, y								
≥65	146	33	113	707	116	591	2.27 (1.42-3.63)	.31
<65	107	18	89	1722	150	1572	3.34 (1.73-6.43)	
Smoking status								
Ever	171	39	132	1449	157	1292	2.58 (1.64-4.07)	.35
Never	76	10	66	962	106	856	1.74 (0.83-3.66)	
Pooled	253			2429				



Hazard ratios (HRs) were adjusted for age, race, sex, education, waist circumference, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and smoking status (ever vs never). Statistical significance (*P* value) for interaction term was based on the maximum likelihood χ^2 from a proportional hazards model that included a multiplicative interaction term. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Normal weight was defined as a BMI of 18.5-24.9; those categorized as overweight/obese had a BMI of ≥25. Dashed line indicates pooled estimate for all participants.

mortality in participants who are normal weight at the time of incident diabetes. Because our initial hypothesis was for a threshold effect of BMI in the normal-weight category, it was not unexpected that when BMI was studied continuously in relation to mortality that the effect we hypothesized was obscured and that there was no association.

Age-related loss of lean muscle mass and bone (ie, sarcopenia) could result in a lower body weight despite greater fat mass in older adults. Older adults who are "frail" have elevated mortality from all causes.[32] Although we did not directly assess frailty, we excluded underweight participants from our analyses, and we tested for interaction by age. Also excluded were participants who died within 2 years of inception into the cohort and participants who lost weight. In each of these sensitivity analyses, normal-weight status remained associated with higher mortality and there was no interaction by age. While the effect estimates for cardiovascular mortality in older adults included the null, our tests for statistical interaction indicate that there is no difference between strata.

Leaner adults with diabetes may have been screened less rigorously for diabetes and its complications by their health care providers. Consequently, cardiovascular disease risk factors may have gone untreated or undertreated. One strength of having carried out our investigation in a cohort study vs a health practice plan is that all participants were examined at regular intervals independent of health care concerns and weight status. By including assessments of cardiovascular disease risk factors in our multivariable models, we were able to statistically adjust for the presence of other cardiovascular risk factors at the time of diabetes identification that could have precipitated mortality.

Strengths and Limitations

A cohort comprising adults with incident disease (an inception cohort) is the strongest design to investigate our question because the likelihood of developing complications is associated with longer diabetes duration and because participants may have initiated weight loss because of their diagnosis. Although participants could have developed diabetes in between study intervals, the length between examinations across studies ranged from 2 to 5 years and variability in diabetes duration at baseline is truncated. Sensitivity analyses excluding participants using medications confirmed our findings. The robustness of our findings is reflected in the consistent associations within each cohort and in subgroups defined by age, race, sex, and smoking status.

Smoking status is a potentially important modifier of the association, and our ability to distinguish smoking burden (eg, duration, timing, and amount)

Table 3. Association of BMI and Weight Status With Total Mortality in the Pooled Cohort: Results of Sensitivity Analyses[a]

	No. of Participants	No. of Events	Event Rate per 10 000 Person-years	Unadjusted	Multivariable Model 1[b]	Multivariable Model 2[c]
BMI (per SD)	2625	449	165.5	0.90 (0.81-1.00)	1.04 (0.93-1.17)	1.00 (0.88-1.13)
Waist circumference (per SD)	2625	449	165.5	1.08 (0.97-1.19)	1.18 (1.06-1.31)	1.14 (1.02-1.28)
Diagnosis by fasting glucose only[d]						
Overweight/obese	1657	193	110.3	1 [Reference]	1 [Reference]	1 [Reference]
Normal weight	181	35	190.5	1.60 (1.12-2.30)	1.38 (0.95-2.00)	2.20 (1.43-3.38)
Diagnosis by medication alone[d]						
Overweight/obese	1344	204	164.4	1 [Reference]	1 [Reference]	1 [Reference]
Normal weight	161	30	222.8	1.32 (0.89-1.94)	1.38 (0.91-2.08)	1.96 (1.16-3.31)
Excluding Asian participants						
Overweight/obese	2307	368	138.4	1 [Reference]	1 [Reference]	1 [Reference]
Normal weight	268	77	291.4	1.73 (1.35-2.21)	1.47 (1.14-1.91)	2.06 (1.50-2.83)
Follow-up for <2 y						
Overweight/obese	2285	337	138.4	1 [Reference]	1 [Reference]	1 [Reference]
Normal weight	279	67	246.2	1.65 (1.27-2.15)	1.46 (1.11-1.92)	2.05 (1.46-2.87)
BMI decreased by <2 units from baseline						
Overweight/obese	2217	344	147.1	1 [Reference]	1 [Reference]	1 [Reference]
Normal weight	245	60	261.1	1.66 (1.26-2.19)	1.48 (1.11-1.97)	2.07 (1.47-2.92)
Weight status						
Normal weight	293	78	284.8	1.68 (1.28-2.20)	1.65 (1.24-2.19)	2.02 (1.47-2.77)
Overweight	858	163	174.9	1 [Reference]	1 [Reference]	1 [Reference]
Obese	1474	208	138.0	0.97 (0.79-1.20)	1.22 (0.98-1.52)	0.86 (0.64-1.16)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; FOS, Framingham Offspring Study; MESA, Multi-Ethnic Study of Atherosclerosis; per SD, per standard deviation higher.

[a] BMI is calculated as weight in kilograms divided by height in meters squared. Normal weight was defined as a BMI of 18.5-24.9, overweight defined as a BMI of 25.0-29.9, and obese defined as a BMI of ≥30.

[b] Multivariable model 1 includes statistical adjustment for age, race, sex, and education.

[c] Multivariable model 2 includes statistical adjustment for age, race, sex, education, waist circumference, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and smoking status (ever vs never).

[d] Includes ARIC, CARDIA, FOS, and MESA.

was hindered by the inconsistent methods of capturing smoking across cohorts. As a result, we could only crudely stratify to compare participants who ever reported smoking (current and former smokers) with those who never smoked. Because these cardiovascular disease cohort studies did not commonly validate noncardiovascular causes of morbidity or mortality, we were unable to determine the specific causes of elevated noncardiovascular mortality or medical conditions that could promote the onset of diabetes in normal-weight adults.

Similarly, we could not study the contributions of medications for other illnesses that are associated with higher mortality and that could promote the onset of diabetes (eg, antidepressants). Despite our attempts to rule out illness through our sensitivity analyses, it is possible that participants who were normal weight at the time of diabetes incidence may have had underlying noncardiovascular illnesses predisposing them to mortality.

Mechanisms to explain our findings of higher mortality in adults who are normal weight at the time of incident diabetes are unknown. However, previous research suggests that normal-weight persons with diabetes have a different genetic profile than overweight or obese persons with diabetes.[33] If those same genetic variants that predispose to diabetes are associated with other illnesses, these individuals may be "genetically loaded" toward experiencing higher mortality. Future research in normal-weight persons with diabetes should test these genetic hypotheses, along with other plausible mechanisms to account for higher mortality, including inflammation, the distribution and action of adipose tissue, atherosclerosis burden and the composition of fatty plaques, and pancreatic β-cell function.

CONCLUSIONS

In summary, adults who were normal weight at the time of diabetes incidence experienced higher mortality than adults who were overweight or obese at diabetes incidence. These findings are relevant to segments of the US population, including older adults and nonwhite persons (eg, Asian,[34] black[35]), who are more likely to experience normal-weight diabetes.

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Study concept and design: Golden, Campbell-Jenkins, Dyer, Carnethon.
Acquisition of data: Lewis, Bertoni, Mukamal.
Analysis and interpretation of data: De Chavez, Biggs, Pankow, Liu, Mukamal, Carnethon.
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Just as the water of the streams we see is small in amount compared to that which flows underground, so the idealism which becomes visible is small in amount compared with what men and women bear locked in their hearts, unreleased or scarcely released. To unbind what is bound, to bring the underground waters to the surface: mankind is waiting and longing for such as can do that.

——Albert Schweitzer (1875-1965)