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Association of Weight Status with Mortality in Adults with Incident Diabetes

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Abstract

Context—Type 2 diabetes in normal weight (body mass index [BMI] <25kg/m^2) adults is an intriguing representation of the metabolically obese normal weight phenotype with unknown mortality consequences.

Objective—To minimize the influence of diabetes duration and voluntary weight loss on mortality, we tested the association of weight status with mortality in adults with new onset diabetes.

Design—Pooled analysis of five 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; Multi-Ethnic Study of Atherosclerosis, 2002–2011. Participants contributed 27,125 person-years of follow-up.

Setting—2,625 participants with incident diabetes

Participants—Men and women (age>40 years) who developed incident diabetes based on fasting glucose ≥ 126 mg/dL or newly-initiated diabetes medication and who had concurrent measurements of body mass index (BMI). Participants were classified as normal weight if their BMI was 18.5 to 24.99kg/m^2 or overweight/obese if BMI≥25 kg/m^2.

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Main Outcome Measures—Total, cardiovascular, and non-cardiovascular mortality

Results—The proportion of adults who were normal weight at the time of incident diabetes ranged from 9–21% (overall=12%). Over follow-up, 449 participants died, 178 from cardiovascular causes and 253 from non-cardiovascular causes (18 were not classified). The rate of total, cardiovascular and non-cardiovascular mortality was higher in normal weight participants (248.8, 99.8, and 198.1 per 10,000 person-years, respectively) than overweight/obese participants (152.1, 67.8, and 87.9 per 10,000 person-years, respectively). Following adjustment for demographic characteristics and blood pressure, lipids, waist circumference and smoking status, hazard ratios comparing normal weight participants to overweight/obese participants for total, cardiovascular, and non-cardiovascular mortality were 2.08 (95% confidence interval [CI]: 1.52, 2.85), 1.52 (95% CI: 0.89, 2.58) and 2.32 (95% CI: 1.55, 3.48), respectively.

Conclusions—Adults who are normal weight at the time of incident diabetes have higher mortality than adults who are overweight or obese.

Keywords

type 2 diabetes; obesity; cardiovascular disease; longitudinal studies

Type 2 diabetes in normal weight adults is an intriguing and understudied representation of the metabolically obese normal weight (MONW) 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 two 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.

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 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

Study Population

Our study included 2,625 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 and medication use, a comprehensive set of commonly measured covariates and longitudinal follow-up for events and mortality.[9–13] Supplementary table 1 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 de-identified for our analysis and the Northwestern University IRB approved the research.

Diabetes and Weight Status

Diabetes was determined as fasting (≥ 8 hours) glucose ≥126 mg/dL (7 mmol/L)[9, 11–15] or reported use of oral hypoglycemic medications or insulin. Incident diabetes was determined among participants who were free from diabetes at baseline and who met one of the above criteria at a subsequent follow-up examination.

Body mass index (BMI) was determined as the ratio of measured weight (kg) to height (in meters squared). Normal weight, overweight and obese were defined as 18.5 –24.9 kg/m^2, 25–29.9 kg/m^2 and ≥ 30 kg/m^2, respectively.[16] Participants' weight status was assigned at the examination when diabetes was identified (i.e., baseline of this analysis sample).

Follow-up Time and Mortality

Participants were followed 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 (i.e., 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 non-cardiovascular 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 (i.e., 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 (SD) 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 becomes 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 to overweight/obese participants with diabetes (referent).

We used two strategies to generate pooled estimates: 1) 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; and, 2) 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 (non-white vs. white), sex and education (< high school vs. ≥ high school). Model 2 was adjusted for Model 1 and waist circumference, total cholesterol, high density lipoprotein

cholesterol, 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) 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: 1. The association between BMI per standard deviation higher and total mortality; 2. The association between waist circumference per standard deviation higher and total mortality; 3. 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 on medications to control diabetes; 4. To test whether defining diabetes using a single glucose measurement contributed to misclassification, we restricted the definition of diabetes to participants taking medications only; 5. Because Asians are more likely to develop diabetes at a lower BMI, we excluded Asians; 6. 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 for <2 years after diabetes identification; 7. We excluded 162 participants whose BMI decreased by more than two units from the baseline examination, which may have reflected other illnesses that might predispose to death. 8. Given prior reports that overweight adults have the lowest mortality risk (particularly among older adults), we calculated mortality hazard ratios comparing normal weight and obese participants to overweight.

All analyses were carried out using Statistical Analysis Software version 10 (SAS Institute, Cary NC). Statistical significance was determined at $p<0.05$ (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 (11.2%) participants 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 non-white and the mean age of participants ranged from 41 years (SD=6) in CARDIA to 76 years (SD=5) 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 non-cardiovascular 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 non-cardiovascular mortality than overweight/obese participants.

Table 2 displays the crude and mulitivariable adjusted association of weight status with mortality in the pooled sample and by cohort. In the pooled sample, total, cardiovascular and non-cardiovascular 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, 87.9 per 10,000 person-years, respectively). These patterns are consistent for total and non-cardiovascular 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 (hazard ratio [HR]=2.08, 95% CI: 1.52, 2.85) and non-cardiovascular 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, though not always statistically significant. Participants with normal weight diabetes had higher mortality from all causes than overweight/obese participants across strata of gender, age, race and smoking (Figure 2).

The findings from each of our sensitivity analyses are presented in Table 3. BMI (per standard deviation higher) was not associated with total mortality but waist circumference was significantly positively associated with mortality Normal weight status was positively associated with mortality in each of the additional analyses. When we stratified weight at the time of diabetes into three 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.

DISCUSSION

In our pooled longitudinal study, participants who were normal weight at the time of incident diabetes experienced higher total and non-cardiovascular mortality as compared with those who were overweight or obese. Cardiovascular mortality was non-significantly 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 following 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 hazard ratios from fully adjusted models reflect elevated mortality. Consequently, we interpreted the absence of statistical significance as a byproduct 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 hypertensives (the cutpoint for “lean” varies across studies)[22] and persons with heart failure[3] have worse health outcomes than their heavier counterparts. Even among persons without known chronic diseases, heavier weight may only be positively associated with long-term (>15 years) mortality.[23] Our findings are consistent with the existing literature in other prevalent disease cohorts, including those of persons with diabetes.[6, 7, 24, 25]

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,[23] and so our findings could reflect higher mortality among persons who were already ill for reasons unrelated to diabetes. Statistical adjustment for demographic characteristics (e.g., socioeconomic status) and health behaviors (e.g., smoking) associated with other causes of mortality, did not change our findings. Despite having a leaner body habitus, cigarette smokers are more insulin resistant[26], more likely to develop diabetes,[27] and have increased mortality as compared with non-smokers.

However, we report that the elevated mortality in normal weight participants is not entirely attributable to higher smoking as findings are similar among smokers and non-smokers.

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[24, 25]) are that we 1) defined weight status at the time of incident diabetes; and, 2) identified an elevated risk of mortality in normal weight adults who did not have comorbid cardiovascular diseases (e.g., 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 other cardiovascular disease risk factors.[28] 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)[29] is phenotypically similar to type 1 diabetes because of apparent β cell destruction and presentation in normal weight adults. Some normal weight adults with diabetes may have LADA, but it is not possible identify LADA without measuring autoantibodies such as GAD 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,[30–32] 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. Waist circumference was directly positively associated with 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 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 (i.e., 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.[33] Although we did not directly assess frailty, we excluded underweight participants from our analyses, tested for interaction by age, excluded participants who died within two 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 healthcare providers. Consequently, cardiovascular disease risk factors may have gone untreated or under-treated. 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 healthcare complaints 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 comprised of adults with incident disease (an inception cohort) is the strongest design to investigate our question because the likelihood of developing complications is positively associated with diabetes duration and because participants may have initiated weight loss because of their diagnosis. While participants could have developed diabetes in between study intervals, the length between exams 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 are 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 (e.g., duration, timing and amount) was hindered by the inconsistent methods of capturing smoking across cohorts. As a result, we could only crudely stratify to compare participants who ever (comprised of current and former) reported smoking to those who never smoked. Because these cardiovascular disease cohort studies did not commonly validate non-cardiovascular causes of morbidity or mortality, and so we were unable to determine the specific causes of elevated non-cardiovascular mortality or of 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 (e.g., 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 non-cardiovascular illnesses predisposing them to mortality.

Conclusion

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.[34] If those same genetic variants that predispose to diabetes are associated with other illnesses, these individuals may be “genetically loaded” towards 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. In summary, findings from our observational study that adults who are normal weight at the time of diabetes incidence experienced higher mortality than overweight or obese adults with diabetes are relevant to growing segments of our population including older adults and non-whites (e.g., Asian[35], black[36]) who are more likely to experience normal weight diabetes.

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Mr. Peter de Chavez carried out all statistical analyses in the study under the direction of the Principal Investigator.

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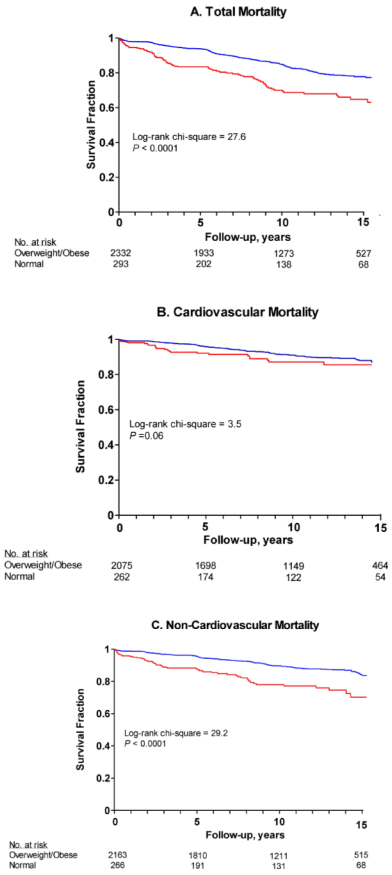

Figure 1. Kaplain-Meier Survial Estimates Comparing Mortality in Participants Stratified by Weight Status at the Time of Incident Diabetes

Red Line = Normal Weight (BMI 18.5 – 24.9 kg/^{2})

Blue Line=Overweight/Obese (BMI > 25 kg/m^2)

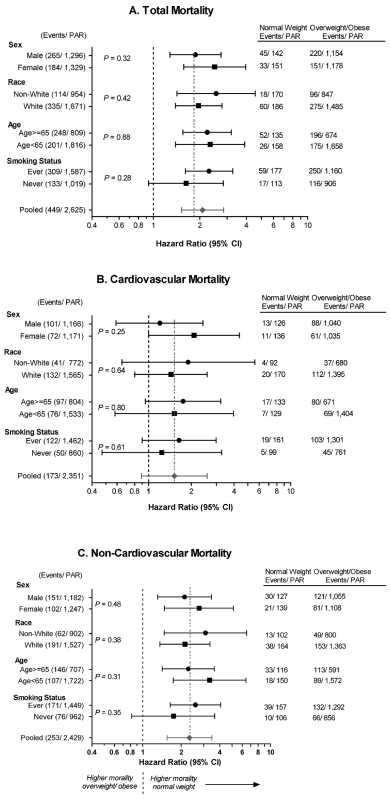

Figure 2. Adjusted hazard ratios (95% confidence intervals) of mortality by weight status (normal weight vs. overweight/obese), stratified by subgroup

Adjusted for age, race, gender, education, waist circumference, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status (ever. vs. never).

Statistical significance (P-value) for interaction term based on the maximum likelihood χ^2 from a proportional hazards model that included a multiplicative interaction term.

PAR= Population at Risk. Normal weight = BMI 18.5 – 24.99 kg/m^2; Overweight/Obese = BMI >= 25 kg/m^2.

Table 1

Distribution of Covariates Stratified by Normal Weight Status

	ARIC			CARDIA			CHS		
Mean (SD) or No. (%)	**Normal (BMI 18.5 – 24.99 kg/m^2)**	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**p***	**Normal (BMI 18.5 – 24.99 kg/m^2)**	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**P**	**Normal (BMI 18.5 – 24.99 kg/m^2)**	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**P**
Participant Number (%)	108 (8.7)	1132 (91.3)		28 (10.2)	246 (89.8)		37 (20.6)	143 (79.4)	
Age (y)	59.8 (6.1)	59.1 (5.9)	0.23	39.4 (6.4)	41.0 (5.8)	0.16	78.6 (5.6)	75.1 (4.7)	<0.001
Non-white race (%)	34 (31.5)	384 (33.9)	0.61	14 (50.0)	164 (66.7)	0.08	5 (13.5)	25 (17.5)	0.56
Gender (% Female)	51 (47.2)	584 (51.6)	0.38	14 (50.0)	139 (56.5)	0.51	20(54.1)	79 (55.2)	0.90
Education (% < High School)	21 (19.4)	316 (28.0)	0.06	3 (10.7)	26 (10.6)	>.99	16 (43.2)	43 (30.1)	0.13
SBP (mmHg)	126.1 (19.3)	128.9 (18.5)	0.14	111.6 (13.3)	121.4 (16.5)	0.003	133.7 (20.3)	134.4 (20.0)	0.85
DBP (mmHg)	72.0 (11.1)	73.9 (10.4)	0.07	71.8 (10.8)	79.2 (12.0)	0.002	67.6 (9.9)	70.1 (11.6)	0.24
Hypertension (%)†	51 (47.2)	671 (59.3)	0.02	6 (21.4)	112 (45.5)	0.01	19 (51.4)	92 (64.3)	0.15
Ever smoking (%)	69 (63.9)	704 (62.5)	0.77	15 (55.6)	100 (41.2)	0.15	24 (68.6)	82 (58.6)	0.28
BMI (kg/m^2)	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
Waist circ (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
Total chol (mg/dL)	205.5 (49.8)	208.8 (42.3)	0.51	180.4 (50.6)	188.7 (38.9)	0.42	200.0 (51.6)	204.2 (41.8)	0.61
HDL chol (mg/dL)	45.5 (13.2)	42.7 (13.0)	0.03	58.3 (26.8)	42.7 (11.4)	0.006	51.7 (11.2)	47.9 (11.6)	0.08
Triglycerides (mg/dL)‡	126.9 (69.9)	152.4 (104.9)	<.001	90.0 (83.0)	121.5 (109.0)	0.005	118.0 (122.0)	159.0 (122.0)	0.02
LDL cholesterol (mg/dL)	131.0 (45.2)	130.8 (37.0)	0.96	97.2 (40.3)	114.7 (34.5)	0.02	122.1 (38.0)	122.9 (32.1)	0.89

	FOS			MESA		
	Normal (BMI 18.5 – 24.99 kg/m^2)	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**p***	**Normal (BMI 18.5 – 24.99 kg/ m^2)**	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**P**
Mean (SD) or No. (%)	48 (10.4)	413 (89.6)		72 (15.3)	398 (84.7)	
Age (y)	59.5 (10.7)	58.5 (9.0)	0.47	68.9 (10.0)	63.6 (9.5)	<.001
Non-white race (%)	0 (0.0)	0 (0.0)	-	54 (75.0)	274 (68.8)	0.30
Gender (% Female)	22 (45.8)	174 (42.1)	0.62	44 (61.1)	202 (50.8)	0.11
Education (% < High School)	5 (12.8)	36 (10.5)	0.59	22 (30.6)	76 (19.1)	0.03
SBP (mmHg)	129.8 (21.9)	136.3 (18.8)	0.03	123.9 (21.3)	126.8 (19.8)	0.26
DBP (mmHg)	76.0 (10.2)	79.4 (12.1)	0.06	68.1 (10.4)	71.5 (10.6)	0.01

	FOS			MESA		
	Normal (BMI 18.5 – 24.99 kg/m^2)	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**P***	**Normal (BMI 18.5 – 24.99 kg/ m^2)**	**Overweight/ Obese (BMI ≥ 25 kg/m^2)**	**P**
Hypertension (%)†	25 (52.1)	285 (69.0)	0.02	43 (59.7)	272 (68.3)	0.15
Ever smoking (%)	38 (79.2)	290 (70.2)	0.20	31 (43.1)	234 (59.5)	0.009
BMI (kg/m^2)	23.1 (1.7)	32.6 (5.5)	<.001	23.2 (1.5)	33.0 (5.8)	<.001
Waist circ (cm)	88.3 (10.5)	109.7 (12.8)	<.001	87.5 (6.7)	109.7 (14.2)	<.001
Total chol (mg/dL)	194.2 (46.0)	209.8 (39.5)	0.01	182.9 (43.3)	182.6 (35.7)	0.96
HDL chol (mg/dL)	45.6 (16.8)	40.6 (11.9)	0.05	52.7 (15.7)	46.5 (12.4)	0.002
Triglycerides (mg/dL)‡	136.5 (112.0)	181.0 (135.5)	0.001	108.0 (83.0)	131.0 (103.0)	0.002
LDL cholesterol (mg/dL)	117.1 (37.8)	142.1 (36.3)	0.01	106.2 (33.8)	104.8 (31.2)	0.73

*P value based on t-test for continuous variables and χ^2 test for categorical variables

†Systolic blood pressure ≥140 or diastolic blood pressure ≥90 or reported use of anti-hypertensive medications

‡Triglycerides are presented as median and interquartile range; statistical significance is determined using a Wilcoxin rank sum test

Table 2

Association between weight status at the time of diabetes incidence and mortality

	Total Mortality		Cardiovascular Mortality		Non-Cardiovascular Mortality	
Weight Status at time of Diabetes Incidence	**Overweight/ Obese (BMI≥ 25 kg/m^2)**	**Normal Weight (BMI 18.5 – 24.99 kg/m^2)**	**Overweight/ Obese (BMI≥ 25 kg/m^2)**	**Normal Weight (BMI 18.5 – 24.99 kg/m^2)**	**Overweight/ Obese (BMI≥25 kg/m^2)**	**Normal Weight (BMI 18.5 – 24.99 kg/m^2)**
Full Sample						
N	2332	293	2086	265	2163	266
N Events	371	78	149	24	202	51
Event Rate (per 10,000 P–Y)	152.1	284.8	67.8	99.8	87.9	198.1
Pooled analysis [*]						
Unadjusted hazard ratio (95% CI)	1 (Referent)	1.70 (1.33, 2.18)	1 (Referent)	1.31 (0.85, 2.02)	1 (Referent)	2.03 (1.49, 2.77)
Multivariable Model 1[†]	1 (Referent)	1.49 (1.15, 1.93)	1 (Referent)	1.04 (0.65, 1.66)	1 (Referent)	1.79 (1.30, 2.47)
Multivariable Model 2[‡]	1 (Referent)	2.08 (1.52, 2.85)	1 (Referent)	1.52 (0.89, 2.58)	1 (Referent)	2.32 (1.55, 3.48)
Meta-analysis [§]						
Unadjusted hazard ratio (95% CI)	1 (Referent)	1.72 (1.33, 2.21)	1 (Referent)	1.24 (0.78, 1.97)	1 (Referent)	1.97 (1.40, 2.76)
Multivariable Model 1	1 (Referent)	1.54 (1.18, 2.02)	1 (Referent)	0.98 (0.59, 1.64)	1 (Referent)	1.78 (1.25, 2.55)
Multivariable Model 2	1 (Referent)	2.01 (1.44, 2.81)	1 (Referent)	1.29 (0.71, 2.33)	1 (Referent)	2.18 (1.39, 3.42)
Cohort-Specific						
ARIC						
N	1132	108	1132	108	1060	102
N Events	129	16	66	5	57	10
Event Rate (per 10,000 P–Y)	95.6	121.2	49.2	38.1	44.3	78.6
Unadjusted hazard ratio (95% CI)	1 (Referent)	1.23 (0.73, 2.07)	1 (Referent)	0.76 (0.31, 1.89)	1 (Referent)	1.73 (0.88, 3.39)
Multivariable Model 1	1 (Referent)	1.20 (0.71, 2.02)	1 (Referent)	0.74 (0.30, 1.84)	1 (Referent)	1.68 (0.85, 3.32)
Multivariable Model 2	1 (Referent)	1.55 (0.86, 2.79)	1 (Referent)	0.99 (0.37, 2.62)	1 (Referent)	2.10 (0.96, 4.58)
CARDIA			--	--		
N	246	28	--	--	237	28
N Events	14	4	--	--	5	4
Event Rate (per 10,000 P–Y)	60.9	131.7	--	--	22.4	131.7
Unadjusted hazard ratio (95% CI)	1 (Referent)	1.96 (0.64, 6.00)	--	--	1 (Referent)	5.48 (1.45, 20.71)
Multivariable Model 1	1 (Referent)	--	--	--	1 (Referent)	--

Weight Status at time of Diabetes Incidence	Total Mortality		Cardiovascular Mortality		Non-Cardiovascular Mortality	
	Overweight/ Obese (BMI≥ 25 kg/m^2)	Normal Weight (BMI 18.5 – 24.99 kg/m^2)	Overweight/ Obese (BMI≥ 25 kg/m^2)	Normal Weight (BMI 18.5 – 24.99 kg/m^2)	Overweight/ Obese (BMI≥25 kg/m^2)	Normal Weight (BMI 18.5 – 24.99 kg/m^2)
Multivariable Model 2	1 (Referent)	--	--	--	1 (Referent)	--
CHS						
N	143	37	143	37	101	27
N Events	94	31	41	10	52	21
Event Rate (per 10,000 P–Y)	661.6	1230.9	289.0	397.1	451.8	995.9
Unadjusted hazard ratio (95% CI)	1 (Referent)	2.01 (1.33, 3.02)	1 (Referent)	1.42 (0.71, 2.83)	1 (Referent)	2.43 (1.46, 4.05)
Multivariable Model 1	1 (Referent)	1.60 (1.05, 2.43)	1 (Referent)	1.04 (0.51, 2.14)	1 (Referent)	1.84 (1.08, 3.12)
Multivariable Model 2	1 (Referent)	1.81 (1.08, 3.03)	1 (Referent)	1.26 (0.56, 2.87)	1 (Referent)	1.98 (1.02, 3.84)
FOS						
N	413	48	413	48	372	40
N Events	115	20	38	6	74	12
Event Rate (per 10,000 P–Y)	211.1	350.6	70.4	108.9	147.6	236.6
Unadjusted hazard ratio (95% CI)	1 (Referent)	1.69 (1.05, 2.71)	1 (Referent)	1.56 (0.66, 3.69)	1 (Referent)	1.61 (0.87, 2.96)
Multivariable Model 1	1 (Referent)	1.82 (1.04, 3.16)	1 (Referent)	1.36 (0.41, 4.54)	1 (Referent)	1.80 (0.91, 3.56)
Multivariable Model 2	1 (Referent)	3.26 (1.47, 7.21)	1 (Referent)	3.45 (0.57, 20.80)	1 (Referent)	2.89 (1.08, 7.78)
MESA						
N	398	72	--	--	393	69
N Events	19	7	--	--	14	4
Event Rate (per 10,000 P–Y)	109.0	239.6	--	--	80.9	142.5
Unadjusted hazard ratio (95% CI)	1 (Referent)	2.25 (0.95, 5.36)	--	--	1 (Referent)	1.80 (0.59, 5.47)
Multivariable Model 1	1 (Referent)	1.79 (0.72, 4.41)	--	--	1 (Referent)	--
Multivariable Model 2	1 (Referent)	3.50 (1.06, 11.61)	--	--	1 (Referent)	--

*Pooled analysis: total mortality includes all cohorts (n=2,625); cardiovascular mortality includes ARIC, CHS, FOS and MESA (n=2,351); non-cardiovascular mortality includes all cohorts (n=2,429)

†Multivariable model 1 includes statistical adjustment for age, race, gender and education

‡Multivariable model 2 includes statistical adjustment for age, race, gender, education, waist circumference, total cholesterol, HDL-cholesterol, SBP and smoking status (ever vs. never)

§Fixed effects meta-analysis for total mortality includes ARIC, CHS, FOS and MESA; cardiovascular mortality includes ARIC, CHS and FOS; non-cardiovascular mortality includes ARIC, CHS and FOS

Table 3

Association of BMI and Weight Status with Total Mortality in the Pooled Cohort: Results of Sensitivity Analyses

	N	N Events	Event Rate	Unadjusted	Multivariable Model 1 *	Multivariable Model 2 †
1. 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)
2. 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)
3. Diagnosis by fasting glucose only ‡						
Overweight/ Obese (BMI ≥ 25 kg/m^2)	1657	193	110.3	1 (Referent)	1 (Referent)	1 (Referent)
Normal weight (BMI 18.5 – 24.9 kg/m^2)	181	35	190.5	1.60 (1.12, 2.30)	1.38 (0.95, 2.00)	2.20 (1.43, 3.38)
4. Diagnosis by medication alone ‡						
Overweight/Obese (BMI ≥ 25 kg/m^2)	1,344	204	164.4	1 (Referent)	1 (Referent)	1 (Referent)
Normal weight (BMI 18.5 – 24.9 kg/m^2)	161	30	222.8	1.32 (0.89, 1.94)	1.38 (0.91, 2.08)	1.96 (1.16, 3.31)
5. Excluding Asians						
Overweight/ Obese (BMI ≥ 25 kg/m^2)	2,307	368	138.4	1 (Referent)	1 (Referent)	1 (Referent)
Normal weight (BMI 18.5 – 24.9 kg/m^2)	268	77	291.4	1.73 (1.35, 2.21)	1.47 (1.14, 1.91)	2.06 (1.50, 2.83)
6. Follow-up for < 2 years						
Overweight/ Obese (BMI ≥ 25 kg/m^2)	2,285	337	138.4	1 (Referent)	1 (Referent)	1 (Referent)
Normal weight (BMI 18.5 – 24.9 kg/m^2)	279	67	246.2	1.65 (1.27, 2.15)	1.46 (1.11, 1.92)	2.05 (1.46, 2.87)
7. BMI decreased by < 2 units from baseline						
Overweight/ obese (BMI ≥ 25 kg/m^2)	2,217	344	147.1	1 (Referent)	1 (Referent)	1 (Referent)
Normal weight (BMI 18.5 – 24.9 kg/m^2)	245	60	261.1	1.66 (1.26, 2.19)	1.48 (1.11, 1.97)	2.07 (1.47, 2.92)
8. Weight status						
Normal weight (BMI 18.5 – 24.9 kg/m^2)	293	78	284.8	1.68 (1.28, 2.20)	1.65 (1.24, 2.19)	2.02 (1.47, 2.77)
Overweight (BMI 25.0 – 29.9 kg/m^2)	858	163	174.9	1 (Referent)	1 (Referent)	1 (Referent)
Obese (BMI ≥ 30 kg/m^2)	1,474	208	138.0	0.97 (0.79, 1.20)	1.22 (0.98, 1.52)	0.86 (0.64, 1.16)

*Multivariable model 1 includes statistical adjustment for age, race, gender and education

†Multivariable model 2 includes statistical adjustment for age, race, gender, education, waist circumference, total cholesterol, HDL-cholesterol, SBP and smoking status (ever vs. never)

‡Includes ARIC, CARDIA, FOS and MESA