



# Adipose Tissue, Muscle, and Function: Potential Mediators of Associations Between Body Weight and Mortality in Older Adults With Type 2 Diabetes

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## OBJECTIVE

Studies in type 2 diabetes report both increased mortality for normal weight and no evidence of an obesity paradox. We aimed to examine whether adipose tissue, muscle size, and physical function, which are known to vary by weight, mediate associations between BMI and mortality.

## RESEARCH DESIGN AND METHODS

The AGES-Reykjavik cohort comprised participants aged 66–96 years with diabetes defined by fasting glucose, medications, or self-report. BMI was determined from measured height and weight and classified as normal (18.5–24.9 kg/m<sup>2</sup>, *n* = 117), overweight (25.0–29.9 kg/m<sup>2</sup>, *n* = 293, referent group) or obese (≥30.0 kg/m<sup>2</sup>, *n* = 227). Thigh muscle area and intermuscular, visceral, and subcutaneous adipose tissues were assessed with computed tomography. Function was assessed from gait speed and knee extensor strength. Hazard ratios (HRs) and 95% CIs were estimated by Cox proportional hazards regression adjusted for demographics and diabetes-related risk factors.

## RESULTS

The median follow-up was 6.66 years, and there were 85, 59, and 44 deaths among normal weight, overweight, and obese participants, respectively. There was no mortality risk for obese participants and an increased risk among normal weight compared with overweight participants (HR 1.72 [95% CI 1.12–2.64]). Associations remained with adjustment for adipose tissues and knee extensor strength; however, mortality risk for normal weight was attenuated following adjustment for thigh muscle (HR 1.36 [95% CI 0.87–2.11]) and gait speed (HR 1.44 [95% CI 0.91–2.27]). Linear regression confirmed with bootstrapping indicated that thigh muscle size mediated 46% of the relationship between normal weight and mortality.

## CONCLUSIONS

Normal weight participants had elevated mortality risk compared with overweight participants. This paradoxical association was mediated in part by muscle size.

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The negative health outcomes of obesity, including elevated mortality risk, are widely documented and accepted (1–3). However, numerous studies in free-living populations (4) and individuals with chronic disease, including chronic kidney disease (5), heart failure (6), and cancer (7), reported that obese individuals have a lower mortality risk than normal weight individuals, a phenomenon termed the “obesity paradox.”

Although type 2 diabetes is typically associated with excess weight, the prevalence among normal weight individuals has increased over the past decade (8) to ~10–20% of individuals with diabetes (8,9). A number of studies suggested that normal weight individuals have increased mortality risk compared with overweight or obese individuals with diabetes (9–11). Conversely, Tobias et al. (12) did not find evidence of an obesity paradox. As a result, the relationship between BMI and mortality is controversial. Questions remain regarding potential confounding of relationships by inflammation, kidney function, physical function, and hypertension (13–15). Also suggested but not tested is that physical function, low muscle, and differences in adipose tissue distribution may mediate the obesity paradox (9) because these factors are related to both BMI and mortality.

Our objective was to provide a deeper understanding of factors underlying associations between BMI and mortality among individuals with type 2 diabetes by investigating mortality risk factors known to vary by weight: adipose tissue, muscle size, and physical function. We hypothesized that normal weight individuals would have a more advanced disease profile, including less muscle, different adipose distribution, and poorer physical function, compared with overweight or obese individuals. Therefore, after comprehensively adjusting for comorbid conditions, adipose tissue, muscle size, and physical function, we hypothesized that risk differences among BMI categories would be minimal and that this conclusion would be supported by mediation analysis.

## RESEARCH DESIGN AND METHODS

### Study Population

The Age, Gene/Environment Susceptibility Study-Reykjavik Study (AGES-Reykjavik) is a random sample of 5,764 men and women nested in the Reykjavik

Study, a single-center population-based cohort begun in 1967 to study heart disease. At study baseline (2002–2006), participants were aged 66–96 years. All variables with the exception of midlife BMI were assessed at baseline. Details of the study design are provided in Harris et al. (16). All participants provided written informed consent, and the study was approved by the institutional review board (VSN: 00-063).

### Diabetes

Type 2 diabetes was determined from self-reported diabetes, diabetes medication use, or fasting plasma glucose  $\geq 7$  mmol/L based on American Diabetes Association diagnosis recommendations (17).

### Assessment of Body Composition and Physical Function

BMI from measured height and weight ( $\text{kg}/\text{m}^2$ ) and waist circumference (cm) were determined using standardized protocols (16). Midlife BMI was available from height and weight measured in the Reykjavik Study (16,18,19). BMI categories of normal weight (18.5–24.9  $\text{kg}/\text{m}^2$ ), overweight (25.0–29.9  $\text{kg}/\text{m}^2$ ), and obese ( $\geq 30.0$   $\text{kg}/\text{m}^2$ ) were used to classify participants.

Computed tomography imaging of the midthigh and abdomen at the L4/L5 vertebrae was performed with a four-row detector system (Sensation; Siemens Medical Systems, Erlangen, Germany). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were estimated from a single 10-mm-thick transaxial section. VAT was distinguished from SAT by tracing along the facial plane defining the internal abdominal wall. Adipose areas ( $\text{cm}^2$ ) were calculated by multiplying the number of pixels by the pixel area using specialized software (University of California, San Francisco). Total thigh muscle cross-sectional area was determined from a single 10-mm-thick transaxial section in the left and right legs as described previously (20). Thigh muscle attenuation (Hounsfield units), an indicator of fat infiltration, was recorded.

Physical function was assessed using baseline measures of gait speed and muscle strength. Usual gait speed was determined over 6 m. Knee extensor strength was assessed as the maximal isometric strength from three trials of the dominant leg (20).

### Mortality

Mortality was ascertained through 31 May 2011 from the Icelandic National Register (33), an adjudicated registry of deaths. Cause-specific mortality was collected from National Health System Records through 31 December 2009. Participants who were not identified as deceased were censored at the date through which vital records were complete.

### Diabetes-Related Covariates

Diabetes duration was calculated as the difference between self-reported age of diabetes diagnosis and age at baseline examination. Medication use was determined from medications brought to the clinic and self-report questionnaire. Blood pressure was assessed in a recumbent position using a mercury sphygmomanometer and large cuff on the right arm after participants had rested for 5 min. Hypertension was determined from self-report, use of hypertensive medication, systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg. Microalbuminuria was defined as urinary albumin/creatinine ratio between 30 and 300 mg/g (21). Total cholesterol, HDL cholesterol, triglycerides, C-reactive protein (CRP), glucose, and HbA<sub>1c</sub> were analyzed from fasting blood samples using reagents from Roche Diagnostics (Mannheim, Germany) on a Hitachi 912 analyzer according to manufacturer instructions. LDL cholesterol was calculated using the Friedewald equation. The coefficients of variation for the entire AGES-Reykjavik study were 1.8% for plasma glucose, 1.4% for total cholesterol, 2.3% for HDL, 4.8% for urinary albumin, and 1.3% for CRP.

### Analytical Cohort

Participants with type 1 diabetes (diabetes before age 25 [ $n = 2$ ]) and incomplete data on diabetes history ( $n = 66$ ) were excluded, leaving 749 participants with diabetes. Participants missing BMI ( $n = 18$ ) and thigh muscle area ( $n = 90$ ) data or with a BMI  $< 18.5$   $\text{kg}/\text{m}^2$  ( $n = 4$ ) were also excluded. Thus, 637 participants (117 normal weight, 293 overweight, and 227 obese) were included. All data presented are from individuals with diabetes except for a comparison of the analytic cohort and the AGES-Reykjavik cohort.

### Statistical Analysis

Differences between groups were assessed using the Kruskal-Wallis test for

continuous variables due to nonnormal distributions or  $\chi^2$  test for categorical variables. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for mortality risk. Overweight was the referent group due to potential positive relationships between obesity and mortality. Proportional hazards were confirmed from examination of Kaplan-Meier curves and Schoenfeld residuals. Model 1 was unadjusted. Model 2 was adjusted for age, sex, education (less than high school, high school graduate, or more than high school), and duration of diabetes. Model 3 was additionally adjusted for midlife BMI, waist circumference, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status (never, current, or former), hypertension, statin use, diabetes medication use, microalbuminuria, and CRP. The effect of VAT, SAT, thigh muscle attenuation, thigh muscle area, and physical function on risk estimates was assessed by adjusting for each variable in model 3. Measures that attenuated risk estimates were assessed with mediation models that progress through four steps/models (22). The models tested whether a variable was a significant mediator of the association between an independent variable (BMI category) and a dependent variable (mortality) and quantified the direct, indirect, and total effect of relationships. The proportion of the effect of BMI category and mortality mediated was then determined. Bootstrapping was used to estimate the 95% CIs of mediators (23).

We conducted multiple sensitivity analyses to assess the strength of risk relationships. Analyses were conducted using an alternative definition of diabetes from self-report, medication use, and  $\text{HbA}_{1c} \geq 6.5\%$  ( $\geq 48$  mmol/mol), which has been suggested as a redefinition of diabetes by an International Expert Committee (24). BMI was analyzed as a continuous value (risk per SD increase in BMI). Analyses excluding participants who died within 2 years of study baseline were conducted to exclude potentially undetected subclinical disease. To minimize confounding of BMI and mortality due to smoking, we restricted analyses to never smokers, although this resulted in only 54 normal weight, 109 overweight, and 84 obese participants. All tests were two-sided, with

significance set at  $P < 0.05$ . Analyses were performed with Stata 12.1 (StataCorp, College Station, TX) and SPSS version 22.0 (IBM Corporation, Chicago, IL).

## RESULTS

Compared with the AGES-Reykjavik population, participants with diabetes were more likely to be men (54.6 vs. 40.5%,  $P < 0.001$ ), older (77.4 vs. 76.9 years,  $P = 0.03$ ), and heavier (BMI 28.8 vs. 26.8  $\text{kg}/\text{m}^2$ ,  $P < 0.001$ ). The distribution of thigh muscle area in the analytic sample of participants with diabetes is similar to the distribution in the AGES-Reykjavik population (Supplementary Fig. 1). When adjusted for BMI, men but not women with diabetes had lower thigh muscle area than the AGES-Reykjavik population ( $P < 0.001$  vs.  $P = 0.29$ , respectively).

Characteristics of participants according to BMI categories are shown in Table 1. Age, HDL cholesterol, CRP, triglycerides, midlife BMI, waist circumference, VAT, SAT, thigh muscle area, muscle strength, and thigh muscle attenuation increased in a graded manner across BMI categories from normal weight to obese. Conversely, duration of diabetes, current smoking, and HDL cholesterol decreased across BMI categories from normal weight to obese. Self-reported illness-related weight loss of  $\geq 5$  kg in the prior year was present in 7.97% of normal weight, 4.18% of overweight, and 3.52% of obese participants.

Median follow-up was 6.66 years (interquartile range 5.72–7.63 years), during which 188 participants died (46.8 per 1,000 person-years). The number of deaths by smoking status did not differ (nonsmokers 68 [36.4%], former smokers 90 [48.1%], current smokers 29 [15.5%],  $P = 0.12$ ). Among participants with cause-specific mortality ( $n = 143$ ), the main causes of death were cardiovascular disease ( $n = 68$  [47.6%]) and cancer ( $n = 40$  [28.0%]). Eight deaths (5.59%) were attributed to diabetes.

Compared with overweight, normal weight tended to be associated with increased mortality risk in unadjusted models (Supplementary Fig. 2 and Table 2). Associations strengthened after full adjustment for risk factors (model 3, HR 1.72 [95% CI 1.12–2.64]) (Table 2). Within model 3, covariates positively associated with mortality were age, female sex, current smoking, midlife BMI,

and microalbuminuria. When body composition and physical function variables were added to model 3, only thigh muscle area and gait speed attenuated the mortality risk in normal weight participants (HR 1.36 [95% CI 0.87–2.11] and 1.44 [95% CI 0.91–2.27], respectively). When gait speed and thigh muscle area were included in the same model, the risk estimate was attenuated further (HR 1.27 [95% CI 0.80–2.01]). Interactions between BMI and thigh muscle area, BMI and gait speed, and BMI and muscle strength were significant ( $P < 0.05$ ) in the fully adjusted model (model 3).

Sensitivity analyses are shown in Table 3. An alternative diabetes definition similarly showed no mortality risk for obese participants and increased mortality risk for normal weight participants (model 3, HR 1.49 [95% CI 1.06–2.09]), which was attenuated with adjustment for thigh muscle and gait speed. BMI per SD increase was not associated with mortality risk, suggesting a nonlinear relationship. Excluding participants who died within 2 years of baseline to account for undiagnosed underlying chronic disease did not alter associations. Despite losing statistical power, the results from never smokers were consistent with the main analysis in Table 2.

Thigh muscle area met all four criteria for mediation (22), as shown in models 1–4 (Table 4). In the adjusted mediation model, muscle was significantly associated with mortality (model 4,  $\beta = 0.25$ ,  $P < 0.001$ ). However, normal weight BMI no longer significantly accounted for any unique variance (model 4,  $\beta = -0.05$ ,  $P = 0.29$ ), indicating a significant mediating effect of thigh muscle whereby thigh muscle mediated 46% of the effect of normal weight on mortality. This was confirmed by bootstrapping (95% CI 0.01–0.02). Although normal weight was no longer significant in the adjusted mediation model of gait speed (model 4,  $\beta = -0.07$ ,  $P = 0.13$ ), the 95% CI ( $-0.03$  to  $0.06$ ) indicated a nonsignificant mediating effect. Thigh muscle in relation to BMI and mortality was also explored in post hoc analyses. The median thigh muscle for men and women was defined within normal weight and overweight participants, resulting in four groups: 1) normal weight, low muscle (below the respective sex-specific median); 2) normal weight,

**Table 1—Baseline characteristics of participants with diabetes according to BMI**

	Normal weight (n = 117)	Overweight (n = 293)	Obese (n = 227)	P value
Women	51 (43.6)	113 (38.6)	121 (53.3)	0.003
Age (years)	78 (75–81)	76 (72–81)	75 (72–79)	<0.001
Duration of diabetes (years)	10.0 (1.0–20.0)	3.0 (0–14.0)	3.0 (0–10.0)	<0.001
Less than high school education	19 (16.2)	67 (22.9)	52 (22.9)	0.34
Current smoker	20 (17.1)	33 (11.3)	20 (8.8)	0.02
Systolic BP (mmHg)	143 (130–163)	145 (132–159)	143 (131–159)	0.71
Diastolic BP (mmHg)	73.0 (67.0–79.0)	73.0 (67.0–80.0)	74.0 (67.0–80.0)	0.66
Hypertension	104 (88.9)	262 (89.4)	214 (94.3)	0.10
Fasting glucose (mmol/L)	7.40 (6.00–8.90)	7.40 (6.70–8.40)	7.30 (6.60–8.50)	0.80
Hemoglobin A <sub>1c</sub> (%)	6.30 (5.90–7.20)	6.20 (5.80–6.80)	6.20 (5.90–6.60)	0.20
Hemoglobin A <sub>1c</sub> (mmol/mol)	45.4 (41.0–55.2)	44.3 (39.9–50.8)	44.3 (41.0–48.6)	
Insulin medication	8 (7.08)	12 (4.24)	9 (4.04)	0.41
Hypoglycemia medication	62 (54.9)	149 (52.7)	109 (48.9)	0.53
Total cholesterol (mg/dL)	197 (162–230)	197 (170–232)	201 (166–232)	0.88
HDL cholesterol (mg/dL)	57.9 (45.2–72.4)	49.4 (42.9–59.9)	47.9 (41.3–57.5)	<0.001
LDL cholesterol (mg/dL)	114 (87.1–139)	119 (91.5–149)	118 (85.7–147)	0.50
Triglycerides (mg/dL)	91.2 (65.9–137)	114 (83.2–159)	136 (104–177)	<0.001
CRP (mg/L)	1.55 (0.75–3.40)	2.00 (1.00–4.40)	2.60 (1.30–5.00)	<0.001
Cancer	20 (17.1)	40 (13.8)	32 (14.2)	0.68
Coronary heart disease	38 (32.5)	76 (25.9)	64 (28.2)	0.41
Microalbuminuria	16 (13.7)	38 (13.0)	36 (15.9)	0.64
BMI (kg/m <sup>2</sup> )	23.8 (22.4–24.5)	27.4 (26.4–28.6)	32.8 (31.2–35.1)	<0.001
Midlife BMI (kg/m <sup>2</sup> )	24.3 (22.2–26.5)	26.1 (23.8–27.8)	28.6 (26.7–31.4)	<0.001
Waist circumference (cm)	93.0 (87.0–97.0)	104 (99.0–107)	116 (110–123)	<0.001
VAT (cm <sup>2</sup> )	253 (223–299)	325 (280–376)	405 (338–461)	<0.001
SAT (cm <sup>2</sup> )	281 (241–320)	354 (316–410)	465 (411–532)	<0.001
Thigh muscle (cm <sup>2</sup> )	226 (208–239)	238 (222–256)	242 (227–270)	<0.001
Thigh muscle attenuation (HU)	168 (165–171)	167 (163–171)	165 (161–169)	<0.001
Gait speed (m/s)	0.95 (0.80–1.05)	0.94 (0.81–1.07)	0.88 (0.76–1.01)	0.004
Muscle strength (N · m)	112 (88.7–155)	134 (96.8–184)	120 (90.5–168)	0.006

Data are median (interquartile range) or n (%). BP, blood pressure; HU, Hounsfield unit; N · m, newton meter.

high muscle; 3) overweight, low muscle; and 4) overweight, high muscle. The first three groups had increased mortality risk relative to overweight, high muscle (Supplementary Fig. 3). Risk appeared to increase in a graded manner related to muscle, whereas normal weight, low muscle, and overweight, low muscle, had the highest risks of mortality.

## CONCLUSIONS

In this study of older adults with type 2 diabetes, normal weight participants had elevated mortality risk compared with overweight participants, whereas obese participants had no mortality risk relative to overweight participants. The results are consistent with previous studies (9–11) and suggest that increased risk of mortality in normal weight participants is not

attenuated, even with adjustment for risk factors, including inflammation and adipose tissue distribution. The results further suggest that the obesity paradox is related to differences in muscle size, whereby muscle size mediates 46% of the effect of normal weight on mortality risk, which is a novel contribution.

Contrary to our hypothesis, adipose tissue distribution did not attenuate mortality risk for normal weight participants, aligning with a study reporting that the obesity paradox in diabetes persists with adjustment for waist circumference, an indirect measure of VAT (9). Physical function and frailty have been hypothesized to mediate relationships between BMI and mortality whereby both lead to weight loss and increased risk of death (9,25). The present results

do not support this notion because muscle strength did not attenuate risk estimates and mediation analysis did not indicate a significant mediating effect of gait speed. However, we did not assess frailty directly because the study population was not characterized by overt frailty; >60% met gait speed thresholds for poor performance, but the prevalence of illness-related weight loss and weakness (grip strength) was low (data not shown). Further studies that address frailty directly in older populations with a wider range of physical functioning are warranted.

The finding of muscle as a mediating factor of relationships between BMI and mortality in diabetes is a step forward in our understanding of risk factors. However, potential mechanisms need to be investigated, particularly because the

**Table 2—BMI and mortality risk in participants with diabetes**

	No. participants	No. events	Event rate	Model 1	Model 2	Model 3
Overweight	293	85	45.5	1.00	1.00	1.00
Obese	227	59	40.8	0.90 (0.65–1.26)	1.13 (0.81–1.60)	0.89 (0.58–1.38)
Normal weight	117	44	62.5	1.39 (0.97–2.01)	1.34 (0.93–1.95)	1.72 (1.12–2.64)
Adjustment for adipose tissue, muscle tissue, and/or function in model 3						
Normal weight + thigh muscle area						1.36 (0.87–2.11)
Normal weight + gait speed						1.44 (0.91–2.27)
Normal weight + gait speed + thigh muscle area						1.27 (0.80–2.01)
Normal weight + muscle strength						1.59 (1.00–2.52)
Normal weight + thigh muscle attenuation						1.93 (1.25–2.99)
Normal weight + VAT and SAT <sup>a</sup>						1.60 (1.03–2.49)

Data are HR (95% CI) unless otherwise indicated. Events per 1,000 person-years. Model 1 unadjusted. Model 2 adjusted for age, sex, education, and duration of diabetes. Model 3 adjusted for model 2 covariates plus midlife BMI, waist circumference, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, hypertension, statin use, diabetes medication type, microalbuminuria, and CRP. HRs are shown only for covariates that were significant in the fully adjusted model. <sup>a</sup>Model excluded waist circumference due to collinearity with VAT.

effect of muscle does not seem to reflect muscle function or quality (no attenuating effect of intermuscular fat). Muscle mass is inversely associated with insulin resistance (26). Because insulin resistance is an etiologic factor for cardiovascular disease (27) and cancer (28), this may help to explain the elevated mortality risk among normal weight participants who had less muscle than overweight or obese participants. However, the results provide conflicting support that overweight or obese participants have more-favorable metabolic profiles than normal weight participants. Fasting glucose, HbA<sub>1c</sub>, and type of diabetes medication

did not differ, but the duration of diabetes was longer among normal weight participants.

An alternative explanation for the obesity paradox in diabetes is that of selection bias (29,30). It has been suggested that conditioning on a variable (diabetes) that is affected by exposure (BMI) may induce associations with mortality (31). However, the notion that restricting analyses to populations with diabetes results in normal weight individuals with more risk factors for mortality than overweight or obese individuals is not supported by the present data. The distribution of baseline factors suggests differences that would

be expected to be both risk and protective factors. For example, relative to overweight or obese participants, normal weight participants were older and had longer duration of diabetes and higher prevalence of current smoking but had higher HDL cholesterol, lower triglycerides, lower CRP, and similar HbA<sub>1c</sub>. Furthermore, although current smoking was more prevalent among normal weight individuals, the positive direction of the association between normal weight and mortality persisted when the analysis was restricted to never smokers.

Strengths of this study are the measures of physical function and body

**Table 3—BMI and mortality risk in participants with diabetes: sensitivity analysis**

	No. participants	No. events	Event rate	Model 1	Model 2	Model 3
Diabetes from self-report, medications, and HbA <sub>1c</sub> ≥6.5%						
Overweight	408	115	40.7	1.00	1.00	1.00
Obese	247	63	37.6	0.94 (0.69–1.28)	1.23 (0.90–1.69)	0.95 (0.64–1.42)
Normal weight	263	84	45.6	1.12 (0.85–1.48)	1.8 (0.82–1.44)	1.49 (1.06–2.09)
Normal weight + thigh muscle						1.21 (0.86–1.71)
Normal weight + gait speed						1.39 (0.98–1.96)
BMI per SD increment	637	188	46.8	0.95 (0.83–1.09)	1.09 (0.94–1.27)	0.98 (0.71–1.36)
Excluding participants who died within first 2 years						
Overweight	278	70	37.8	1.00	1.00	1.00
Obese	108	52	36.2	1.04 (0.91–1.18)	1.29 (0.89–1.88)	0.99 (0.62–1.59)
Normal weight	108	35	50.5	1.35 (1.21–1.50)	1.38 (0.91–2.08)	1.63 (1.02–2.62)
Normal weight + thigh muscle						1.33 (0.81–2.17)
Normal weight + gait speed						1.39 (0.85–2.27)
Excluding participants reporting current or former smoking						
Overweight	109	32	45.1	1.00	1.00	1.00
Obese	85	19	33.9	0.75 (0.43–1.32)	1.08 (0.60–1.95)	0.73 (0.36–1.51)
Normal	54	17	51.0	1.15 (0.64–2.07)	1.28 (0.70–2.33)	1.83 (0.90–3.70)

Data are HR (95% CI) unless otherwise indicated. Events per 1,000 person-years. Model 1 unadjusted. Model 2 adjusted for age, sex, education, and duration of diabetes. Model 3 adjusted for model 2 covariates plus midlife BMI, waist circumference, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, hypertension, statin use, diabetes medication type, microalbuminuria, and CRP.

**Table 4—Mediating effects of muscle and function on the association of normal weight BMI and mortality**

	Effect	$\beta$	P value
Model 1	Normal weight on mortality risk	−0.10	0.04
Thigh muscle area as mediator			
Model 2	Normal weight on muscle	−0.18	<0.001
Model 3	Muscle on mortality	0.25	<0.001
Model 4	Normal weight and muscle on mortality		
	Muscle on mortality	0.25	<0.001
	Normal weight on mortality	−0.05	0.29
Gait speed as mediator			
Model 2	Normal weight on gait speed	−0.03	0.58
Model 3	Gait speed on mortality	0.21	<0.001
Model 4	Normal weight and gait speed on mortality		
	Gait speed on mortality	0.21	<0.001
	Normal weight on mortality	−0.07	0.13

Overweight BMI as referent group vs. normal weight, standardized  $\beta$ . Models adjusted for age, sex, education, duration of diabetes, midlife BMI, waist circumference, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, hypertension, statin use, diabetes medication type, microalbuminuria, and CRP. The four models tested whether muscle size and gait speed mediate/drive increased mortality risk in normal weight individuals. Model 1 shows that normal weight participants have 0.10 units less of life. Model 2 shows that normal weight participants have 0.18 units less muscle but not significantly different gait speed than overweight participants. Model 3 shows that for a 1-unit increase in muscle, survival increases by 0.25 units (0.21-unit increase for each 1-unit increase in gait speed). When thigh muscle and normal weight are included in a model, the effect of normal weight on mortality is no longer significant, suggesting that the effect is explained in part by thigh muscle (model 4). The 95% CI for thigh muscle was (0.01–0.02) as estimated by the bootstrapping method—confirmed significant mediation (23). When gait speed and normal weight on mortality are included in a model, the effect of normal weight on mortality is no longer significant, but the 95% CI (−0.03 to 0.06) indicated nonsignificant mediation.

composition from radiographic imaging, which enabled novel examination of factors known to vary by BMI. Another strength is the availability of measured midlife BMI. A criticism of previous studies has been that BMI often is assessed up to several decades after diabetes diagnosis, thereby increasing the risk of reverse causation (12). In the present analysis, normal weight participants had lost weight since midlife, but adjustment for midlife BMI did not attenuate mortality risk. Excluding deaths within 2 years of study baseline also did not attenuate risk, suggesting that the results were not driven by early mortality from undetected subclinical disease at baseline. We were also able to address the possibility of survival bias by referencing a comparative analysis by Olafsdottir et al. (32) of type 2 diabetes in the Reykjavik Study and the AGES-Reykjavik study (survivors from the Reykjavik Study) who were examined 11 years apart. The rate for all-cause and cardiovascular mortality was lower in the AGES-Reykjavik study, but the decline in mortality was similar to that in the general Icelandic population

over that time period (33). Thus, it does not appear that individuals with type 2 diabetes in the present cohort had a survival bias relative to the general type 2 diabetes population.

The main limitation of this study is the small sample size, which did not permit us to restrict the study population to those with incident diabetes. Thus, we were unable to avoid reverse causation or possible differences in mortality that reflect complications from longer diabetes duration in normal weight participants. The study was undertaken with the aim of examining the effects of weight-related measures from imaging and clinical tests, which are typically not available in large samples, rather than providing a definitive answer regarding the presence or absence of an obesity paradox in type 2 diabetes. Although we adjusted for diabetes duration, we cannot rule out possible residual confounding from self-reported age at diabetes diagnosis. It is noteworthy that the prevalence of diabetes complications, such as cardiovascular disease and peripheral neuropathy, in old age is similar for individuals

diagnosed with diabetes in midlife versus old age (34), and chronic diseases did not differ by BMI despite differences in diabetes duration. Also possible is that we had residual bias from adjusting for smoking status rather than stratifying by smoking status, but the number of deaths did not vary by smoking status, and analyses restricted to never smokers indicated increased mortality risk for normal weight participants, although the sample size was limited. The finding of muscle as a mediating factor was tested in a statistical model that provides insight into causal relationships but is not a substitute for clinical studies. It is also important to test the possible mediating effect of muscle in younger populations that may have a different body composition from older adults (35).

In conclusion, the results illustrate the importance of identifying type 2 diabetes among normal weight individuals and suggest that muscle size may help to explain relationships between BMI and mortality in type 2 diabetes. The divergence of muscle size and muscle function as mediators of relationships is likely to spur additional debate on the importance of muscle size versus physical function in old age (36–38), and further studies in this area are warranted.

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