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The Relationship of Lean Body Mass With Aging to the Development of Diabetes

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Context: Older adults have the greatest burden of diabetes; however, the contribution of age-related muscle loss to its development remains unclear.

Objective: We assessed the relationship of lean body mass with aging to incident diabetes in community-dwelling adults.

Design and Setting: We studied participants in the Baltimore Longitudinal Study of Aging with median follow-up of 7 years (range 1-16). Cox proportional hazard models with age as the time scale were used. Time-dependent lean body mass measures were updated at each follow-up visit available.

Participants: Participants included 871 men and 984 women without diabetes who had ≥ 1 assessment of body composition using dual x-ray absorptiometry.

Main Outcomes: Incident diabetes, defined as self-reported history and use of glucose-lowering medications; or fasting plasma glucose ≥ 126 mg/dL and 2-hour oral glucose tolerance test glucose ≥ 200 mg/dL either at the same visit or 2 consecutive visits.

Results: The baseline mean [standard deviation] age was 58.9 [17.3] years. Men and women with a higher percentage of total lean body mass had lower fasting and 2-hour glucose levels, and less prediabetes (all $P < 0.01$). Among men, comparing highest versus lowest quartiles, percentage of total lean body mass (hazard ratio [HR], 0.46; 95% confidence interval, 0.22-0.97), percentage leg lean mass (HR, 0.38; 0.15-0.96), and lean-to-fat mass ratio (HR, 0.39; 0.17-0.89) were inversely associated with incident diabetes after accounting for race and attenuated after adjustment for height and weight. Conversely, absolute total lean body mass was positively associated with incident diabetes among women, with similar trends in men. No associations were observed with muscle strength or quality.

Conclusions: Relatively lower lean body mass with aging is associated with incident diabetes in men and partially related to anthropometrics, but not so in women.

Abbreviations: A1c, hemoglobin A1c; BLSA, Baltimore Longitudinal Study of Aging; DXA, dual x-ray absorptiometry; FPG, fasting plasma glucose; HR, hazard ratio; OGTT, oral glucose tolerance test.

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Short of dramatic changes in our ability to prevent or cure diabetes, its public health burden will continue to increase as lifespan continues to lengthen. Diabetes prevalence is growing most rapidly among older adults. Although the role of obesity in type 2 diabetes is well established, and efforts to intervene are widespread [1], it remains unclear whether age-related changes in body composition also relate to the development of diabetes. Given previous cross-sectional studies demonstrating that decreased skeletal muscle index and decreased appendicular lean body mass are related to insulin resistance [2, 3], it may be hypothesized that persons with declines in lean body mass with aging also have a higher risk of developing type 2 diabetes. Yet, this hypothesis has not been fully investigated. Further, the degree to which sex differences exist in the relationship of these body composition changes to incident diabetes remains unclear. Understanding the role of lean body mass in the development of diabetes could inform the development of novel preventive strategies, particularly in older adults.

During the adult years, body composition begins to change more dramatically in middle age. Specifically, fat mass increases and lean body mass decreases, although not always in parallel. In late life, fat mass may start declining as well. However, interestingly, the loss of lean body mass that occurs beginning in middle age is typically offset by gains in fat mass [4]. As a result, total body weight in men and women might remain stable or increase only slightly even though the relative proportion of body fat actually increases while proportion of lean body mass decreases [5]. When these changes are overt, they may lead to sarcopenic obesity. In a cross-sectional substudy comparing persons with diabetes to controls in the Look AHEAD clinical trial, those with diabetes had a greater relative fat mass and smaller relative lean mass regardless of ethnicity [6]. However, while this body composition pattern was found in prevalent diabetes, its specific role in the development of new-onset diabetes is not completely understood.

Previous studies have reported that lower lean body mass is related to dysglycemia, possibly through a reduced surface area for glucose transport [7, 8].We have previously demonstrated that persons with dysglycemia (defined as elevated blood glucose levels and/or diabetes) have decreased appendicular lean body mass, knee extensor strength, and leg muscle quality and that those with persistent dysglycemia are more likely to have accelerated loss of muscle function over time [4, 9-11]. Thus, it is possible that a vicious cycle exists where changes in lean body mass may be both a risk factor and a consequence of impaired glucose states, independent of changes in total body fat.

Our hypothesis for the current study is that relatively lower lean body mass with aging is related to the development of diabetes. We hypothesized that participants with a lower percentage of lean body mass during follow-up will be more likely to develop diabetes compared with participants with relatively higher percentages, even after accounting for fat mass, and that similar findings will be observed with other measures such as absolute lean body mass and knee extensor strength. We investigated this relationship among participants in the Baltimore Longitudinal Study of Aging (BLSA), a unique cohort of healthy community-dwelling persons aged 20 years and older, with extensive follow-up over many years.

Materials and Methods

Study population

The BLSA is a longitudinal cohort study conducted by the Intramural Research Program of the National Institutes of Health, National Institute on Aging since 1958. BLSA participants are community-dwelling men and women recruited primarily from the Baltimore–Washington, DC, area with above-average education, income, and access to medical care and with an age range of 20 to 98 years [12]. Participants underwent extensive

evaluations at regular, predefined intervals (on average intervals were every 2.5 ± 1.2 years). Participants in the BLSA currently return for evaluations based on age. Participants aged <60 years are assessed every 4 years; those aged 60 to 79 years are assessed every 2 years, and participants aged 80 years and older are assessed annually. Participants who had at least one dual x-ray absorptiometry (DXA) assessment and did not have diabetes at their initial DXA study were included (n = 1855).

The research protocol was approved by the Intramural Research Program of the National Institute on Aging and the institutional review board of the National Institute of Environmental Health Science. All participants provided written informed consent.

Measures of body composition

Total body composition was assessed using DXA (model DPX-L Lunar Radiation, Madison, WI) to determine fat mass, fat-free mass, and bone mineral content for the total body and lower extremities. DXA measures were available beginning in 1991 until 2015. Entry date for a participant was their first evaluation when DXA was first assessed. All scans were analyzed by one investigator using the Lunar version 1.2i DPX-L program for body composition analyses. These scans were considered reliable with < 2% difference between repeated scans a few weeks apart [13]. The scanner was calibrated daily before testing. For older Lunar instruments, an algorithm has been developed to appropriately standardize measures on older instruments for comparability with measures on the newer Lunar machine that began in 2003.The total number of DXA measurements available for 1855 participants across all visits was 5767. Specifically, the number of participants with DXA measures included in the study is as follows: 1 DXA measure (n = 596), 2 DXA measures (n = 362), 3 DXA measures (n = 258), 4 DXA measures (n = 223), and ≥5 DXA measures (n = 416).

Knee extensor strength was assessed in the BLSA with the Kin-Com isokinetic dynamometer until February 2011 (Kin-Com, model 125E, version 3.2, Chattanooga Group, Chattanooga, TN). Assessment with the Biodex Multi-Joint System-Pro dynamometer (Biodex Medical System, Advantage Software V0.4X, Inc., Shirley, NY, USA) began in 2010. A conversion equation was created using data from 108 participants with knee extensor strength assessed on both dynamometers at the same visit from 2010 through 2011. Knee extensor strength was measured via concentric quadricep peak torque from the right leg measured at an angular velocity of 0.52 rad/s (30°/s). Three graded submaximal practice repetitions preceded the test. These were followed by 3 maximal efforts, separated by 30-second rest intervals. Knee extensor strength was considered as the maximum of 3 trials. Reliability of strength testing by the Kin-Com and Biodex dynamometers has been reported elsewhere [9, 14]. Mean coefficient of variation was 5% [15]. The total number of knee extensor measurements available across all visits for a subset of 1124 participants in our study who also had at least 1 DXA assessed was 2434. To assess muscle quality, knee extensor strength was divided by DXA-derived leg lean body mass of the right leg, similar to other studies [16].

Assessment of glycemic status and incident diabetes

Participants were observed overnight on the research ward, and after a 10-hour overnight fast, they received the oral glucose tolerance test (OGTT) as previously described [17]. Glucose levels were measured using automated glucose oxidase methods (Beckman Instruments, Inc., Fullerton, CA) from 1977 to 2009 and (YSI Incorporated, Yellow Springs, OH) from 2009 until present. There were no systematic differences in glucose concentrations among the various glucose analyzers; hence, it was not necessary to apply a conversion factor. Hemoglobin A_{1C} (A1C) was assessed using the Automated DiaSTAT analyzer between the years of 2003 and 2006 (Bio-Rad Laboratories, Hercules, CA) and then using the Dimension Vista System (Siemens, Camberley, UK) from 2007 onward. The values from both instruments were standardized such that the results were comparable. Diabetes was

defined as self-reported history and taking glucose-lowering medications; or fasting plasma glucose (FPG) ≥ 126 mg/dL and 2-hour OGTT glucose ≥ 200 mg/dL at the same visit; or FPG ≥ 126 mg/dL or 2-hour OGTT glucose ≥ 200 mg/dL at 2 consecutive visits, similar to previous studies in BLSA [18]. The age of diabetes onset was ascertained based on the self-reported duration of diabetes for those with a previous history or by date of the first visit when diabetes was diagnosed for incident cases. Participants with diabetes at baseline were excluded from the current study. Prediabetes was defined in those without diabetes as an FPG between 100 and 125 mg/dL and/or a 2-hour OGTT glucose of 140 to 199 mg/dL at the baseline visit. The number of participants with OGTT visits available in the study was as follows: none (n = 211); 1 OGTT visit (n = 629), 2 OGTT visits (n = 339), 3 OGTT visits (n = 232), 4 OGTT visits (n = 168), and ≥5 OGTT visits (n = 276).

Covariates

Demographics including age, sex, and race were assessed by questionnaire. Height and weight were measured objectively by standard methods [12].

Statistical analysis and interpretation

Quartiles were constructed for each body composition measure from all DXA (or knee extensor strength) measures available from all study visits. Baseline characteristics were defined based on the participant's quartile at the initial study visit where they had a DXA evaluation. Differences in baseline characteristics across quartiles of percentage of total lean body mass (defined as absolute total lean body mass divided by total body weight in kilograms) were summarized as means ± standard deviations and tested by analysis of variance with an F test for continuous variables and by chi-square tests for categorical variables.

Bayesian logistic regression with weakly informative priors was utilized to explore the distribution of probability (also termed posterior density curve) of developing diabetes for each quartile of muscle measure at baseline. The risk of incident diabetes increases as the curve moves from left to right, and the degree of separation of the curves for each quartile horizontally represents the strength of association, with greater separation indicating greater association.

Cox proportional hazard models were used to examine the time to event (participants with the event were then censored from further analysis), with age as the time scale, as described by previous authors [19], for incident diabetes regressed on the primary measure (percentage of total lean body mass) and secondary measures (absolute total lean body mass, percentage of leg lean body mass, absolute leg lean body mass, absolute total lean-to-fat body mass ratio, knee extensor strength, and leg muscle quality) in separate models. The survival model used all longitudinally collected data with a time-dependent approach based on the Anderson-Gill formulation of a counting process using the survival functions developed by Therneau and Grambsch [20]. Cox models with time-dependent covariates allowed for the updating of each participant's quartile of muscle measure based on the DXA (or knee extensor) assessment at each visit it was available during follow-up. For participants who only had baseline measures available, the independent variable was included as a fixed covariate. The lowest quartile of muscle measure was set as the reference category. Four models were fitted, which sequentially included covariates of interest: model 1 was unadjusted; model 2 was adjusted for race; model 3 = model 2 + height + weight; model 4 = model 3 + prediabetes. Sensitivity analyses were performed with an alternative definition of diabetes that required any of the diagnostic criteria for diabetes to be met only at 1 visit. Additional sensitivity analyses were performed with time-dependent weight, total fat mass, or waist-to-hip ratio in separate models (ie, this variable was updated at each visit it was available). All analyses were stratified by sex.

Table 1. Baseline participant characteristics by quartile of percentage of total lean body mass among men[a]

	All	Percentage of Lean Body Mass Quartile 1 (43.6%-62.8%)	Percentage of Lean Body Mass Quartile 2 (62.9%-67.7%)	Percentage of Lean Body Mass Quartile 3 (67.9%-72.8%)	Percentage of Lean Body Mass Quartile 4 (72.8%-91.5%)	*P* Value
n	871	173	206	224	268	
Mean age at baseline (years)	60.6 (17.1)	63.7 (14.6)	62.5 (16.0)	62.1 (15.9)	55.8 (19.3)	<0.0001
Race (% AA)	17.7	17.3	19.9	17.0	16.8	0.82
Mean BMI (kg/m^2)	25.5 (4.5)	30.6 (3.6)	27.8 (2.6)	26.0 (2.3)	23.6 (2.1)	<0.0001
Mean height (cm)	175.8 (7.0)	175.5 (7.1)	175.8 (7.4)	175.8 (6.6)	175.6 (7.1)	0.73
Mean weight (kg)	82.3 (12.7)	94.1 (12.5)	86.2 (11.0)	80.4 (9.7)	73.3 (8.2)	<0.0001
Mean total lean mass (kg)	56.4 (6.6)	55.4 (6.7)	56.3 (7.1)	56.5 (6.7)	57.2 (6.1)	0.06
Mean total fat mass (kg)	22.8 (8.5)	34.0 (6.9)	26.6 (3.8)	21.1 (3.3)	14.0 (3.8)	<0.0001
% Incident diabetes	7.6	8.7	13.1	5.8	4.1	0.002
Median follow-up time (years, range)	6 (1, 14)	9 (2, 16)	7 (1, 15)	6 (1, 13)	4.5 (1, 12)	0.24
Incidence rate of diabetes per 1000 person-years	9.1	12.2	16.2	6.4	4.8	0.02
Mean number of visits	2.9 (2.1)	2.7 (2.2)	2.8 (1.9)	3.0 (2.0)	2.9 (2.1)	0.50
Knee extensor strength (Nm)[b]	138.6 (45.7)	134.3 (50.1)	137.2 (44.0)	141.2 (42.6)	142.0 (46.1)	0.76
Leg lean mass (Right, kg)	9.4 (1.4)	9.3 (1.4)	9.5 (1.5)	9.3 (1.2)	9.5 (1.3)	0.71
Knee extensor strength/leg lean mass (muscle quality; Nm/kg)[b]	14.6 (4.1)	14.3 (4.7)	14.6 (4.1)	15.0 (4.1)	14.7(3.7)	0.39
Mean A_{1C} (%)[c]	5.6 (0.4)	5.6 (0.5)	5.6 (0.4)	5.7 (0.5)	5.4 (0.4)	0.005
Mean fasting plasma glucose (mg/dL)	97.2 (9.5)	99.6 (8.7)	97.9 (9.8)	97.7 (9.4)	94.6 (9.3)	0.0002
Mean 2-hour plasma glucose (mg/dL)[d]	127.2 (38.5)	139.1 (36.0)	126.4 (34.8)	133.0 (40.7)	114.5 (37.8)	<0.0001
Prediabetes (%)	47	61	55	45	34	<0.0001

Abbreviations: A_{1C}, hemoglobin A_{1c}; AA, African American; BMI, body mass index; DXA, dual x-ray absorptiometry; IQR, interquartile range; OGTT, oral glucose tolerance test; SD, standard deviation.

[a]Quartile ranges are defined based on DXA measures available at all visits. Mean (SD) shown unless otherwise indicated.

[b]n = 224 men with knee extensor strength assessed at their baseline visit.

[c]n = 237 men with A_{1C} measured at their baseline visit.

[d]n = 603 men with 2-hour plasma glucose measured during OGTT at their baseline visit.

A P value < 0.05 was used to indicate statistical significance. Analyses were done using packages rethinking, rstan, and survival in R version 3.5.0.

Results

There were 871 men and 984 women included in our study and a total of 134 incident cases of diabetes during follow-up. Median follow-up was 7 years (range 1-16 years) with an average of 3.1 visits. Among men, being in a higher quartile of percentage total lean body mass was associated with significantly younger age; lower body mass index, weight, and total fat body mass at baseline; lower percentage of participants who developed diabetes during follow-up; lower A_{1C}, fasting glucose, and 2-hour glucose levels; and lower prevalence of prediabetes at baseline (Table 1; all $P < 0.05$). Among women, being in a higher quartile of percentage total lean body mass at baseline was associated with significantly younger age; non–African American race; lower body mass index; lower weight, total lean body mass, and total fat body mass; lower mean fasting glucose and 2-hour glucose levels; and lower prevalence of prediabetes (Table 2; all $P < 0.05$).

Total lean body mass, lean-to-fat body mass ratio, and risk of diabetes

The probability of developing diabetes differed by quartile of body composition measure at baseline. For percentage of total lean body mass (Fig. 1A and 1B), those in the highest quartile of percentage of total lean body mass (quartile 4) had the lowest probability of developing diabetes for both men and women. In addition, there was a greater spread across quartiles in men compared with women (ie, less overlap of the quartile distributions). The opposite relationship was seen with absolute total lean body mass (Fig. 1C and 1D); for both men and women, those in the lowest quartile of absolute total lean body mass (quartile 1) had the lowest probability of developing diabetes, while those in the highest quartile (quartile 4) had the highest probability of developing diabetes. The spread in quartile distributions was similar for men and women. For absolute total lean-to-fat body mass ratio (Fig. 1E and 1F), men and women in the highest quartile (quartile 4) at baseline had the lowest probability of developing diabetes, and the spread was greater for men than women. In women, participants in the lowest quartile (quartile 1) had the highest probability of developing diabetes.

Knee extensor strength, leg muscle quality, and risk of diabetes

For knee extensor strength (Fig. 1G and 1H), men in the lowest quartile of knee extensor strength at baseline had the highest probability of developing diabetes, and men in the highest quartiles of strength (quartiles 3 and 4) had the lowest probability. For leg muscle quality (Fig. 1I and 1J), men in the lowest quartile of leg muscle quality (quartile 1) had the highest probability of developing diabetes. Similar relationships were not observed in women.

Body composition measures over time and risk of diabetes in men

In regression analysis modeling the relationship of body composition quartiles to incident diabetes (Table 3), which additionally allowed for the updating of each participant's quartile at each follow-up visit, a relatively higher quartile of percentage of total lean body mass was associated with a lower hazard ratio (HR) of developing diabetes among men in the unadjusted model 1 (P for trend = 0.009). After adjustment for race in model 2, participants in the third quartile of percentage of total lean body mass had 55% lower risk (HR, 0.45; 0.22-0.92) and those in the highest quartile had a 54% lower risk of developing diabetes compared with those in the lowest quartile (HR, 0.46; 0.22-0.97). The P for trend was 0.01. After further adjustment for baseline height and weight in model 3, the risk of developing

Table 2. Baseline participant characteristics by quartile of percentage of total lean body mass among women[a]

	All	Percentage of Lean Body Mass Quartile 1 (37.3%-52.2%)	Percentage of Lean Body Mass Quartile 2 (52.3%-57.6%)	Percentage of Lean Body Mass Quartile 3 (57.6%- 62.2%)	Percentage of Lean Body Mass Quartile 4 (62.2%-86.6%)	*P* Value
N	984	201	240	229	314	
Mean age at baseline (years)	57.4 (17.3)	60.1 (14.4)	59.3 (15.7)	57.5 (18.3)	54.1 (18.9)	0.0002
Sex (% female)	100	100	100	100	100	
Race (% AA)	24.5	34.8	25.0	26.2	16.2	<0.0001
Mean BMI (kg/m^2)	26.6 (3.6)	31.3 (4.1)	26.9 (3.1)	24.4 (2.2)	21.6 (2.0)	<0.0001
Mean height (cm)	162.3 (6.7)	162.5 (6.7)	162.0 (6.2)	162.1 (6.7)	162.7 (7.0)	0.60
Mean weight (kg)	67.3 (13.1)	82.8 (12.8)	70.6 (10.3)	64.0 (6.9)	57.3 (6.9)	<0.0001
Mean total lean mass (kg)	39.0 (4.9)	40.0 (5.5)	38.9 (5.4)	38.4 (4.1)	38.9 (4.6)	0.01
Mean total fat mass (kg)	25.8 (9.8)	39.4 (7.8)	29.3 (5.0)	23.2 (3.2)	16.3 (3.9)	<0.0001
% Incident diabetes	6.9	8.0	6.7	8.7	5.1	0.37
Median follow-up time in years (IQR range)	7 (1, 16)	11 (3, 18)	6 (1, 15)	6 (1, 15)	6 (1, 14)	0.31
Incidence rate of diabetes per 1000 person-years	7.6	8.9	7.5	10.0	5.4	0.41
Mean number of visits	3.3 (2.5)	3.3 (2.3)	3.5 (2.9)	3.2 (2.4)	3.4 (2.4)	0.51
Knee extensor strength (Nm)[b]	91.7 (30.9)	93.0 (33.4)	92.0 (29.7)	91.4 (28.6)	91.0 (28.6)	0.82
Leg lean mass (Right, kg)	6.5 (1.1)	6.7 (1.3)	6.2 (1.2)	6.4 (1.0)	6.6 (1.1)	0.08
Knee extensor strength/leg lean mass (muscle quality; Nm/kg)[b]	13.9 (3.8)	13.6 (3.8)	14.5 (3.3)	13.9 (4.3)	13.7 (3.9)	0.39
Mean A_{1C} (%)[c]	5.6 (0.4)	5.7 (0.4)	5.6 (0.4)	5.6 (0.4)	5.6 (0.5)	0.10
Mean fasting plasma glucose (mg/dL)	93.5 (8.6)	95.4 (8.6)	94.7 (8.2)	93.8 (9.6)	91.0 (7.5)	<0.0001
Mean 2-hour plasma glucose (mg/dL)[d]	119.8 (33.8)	128.4 (35.2)	123.6 (35.5)	118.3 (31.7)	111.8 (31.3)	<0.0001
% Prediabetes	29	35	36	31	18	<0.0001

Abbreviations: A_{1C}, hemoglobin A_{1c}; AA, African American; BMI, body mass index; DXA, dual x-ray absorptiometry; IQR, interquartile range; SD, standard deviation.
[a]Quartile ranges are defined based on DXA measures available at all visits. Mean (SD) shown unless otherwise indicated.
[b]n = 212 women with knee extensor strength assessed at their baseline visit.
[c]n = 237 women with A_{1C} measured at their baseline visit.
[d]n = 691 women with 2-hour plasma glucose measured at their baseline visit.

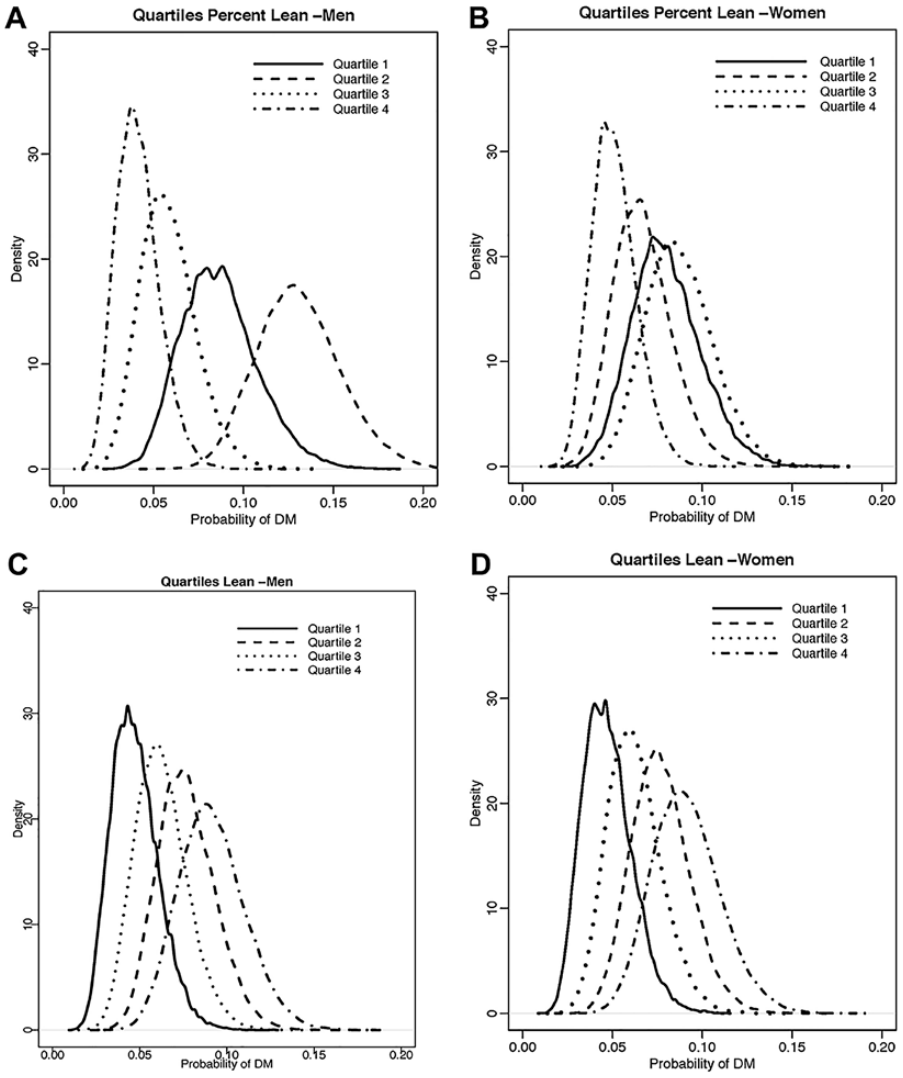

Figure 1. A-J. The probability of developing diabetes by baseline quartile of muscle mass, strength, or quality using a Bayesian logistic regression model. The relationship of baseline quartiles of percentage of total lean body mass (**1A-1B**), absolute total lean body mass (**1C-1D**), absolute total lean-to-fat body mass ratio (**1E-1F**), knee extensor strength (**1G-1H**), and leg muscle quality (**1I-1J**) to the probability of developing diabetes among both men and women. The greater the density on the y-axis at a given probability on the x-a xis, the more likely that is the true probability of developing diabetes for that quartile. The quartile cutoffs for each baseline measure are as follows: **A**) percentage of total lean body mass in men (%): Q1 43.6-63.1; Q2 63.1-68.0; Q3 68.0-73.0; Q4 73.0-92.9; **B**) percentage of total lean body mass in women (%): Q1 37.3-52.4; Q2 52.4-57.8; Q3 57.8-63.3; Q4 63.3-96.1; **C**) total lean body mass in men (kg): Q1 36.8-51.3; Q2: 51.3-55.5; Q3: 55.5-59.9; Q4: 59.9-81.2; **D**) total lean body mass in women (kg): Q1 23.6-35.4; Q2 35.4-38.7; Q3 38.7-42.1; Q4 42.1-75.7; **E**) absolute total lean-to-fat mass ratio in men: Q1 1.1-1.9; Q2 1.9-2.4; Q3 2.4-3.1; Q4 3.1-17.3; **F**) absolute total lean-to-fat mass ratio in women: Q1 0.6-1.2; Q2 1.2-1.5; Q3 1.5-1.9; Q4 1.9-8.3; **G**) knee extensor strength in men (Nm): Q1 27.0-106.8; Q2 106.8-131.8; Q3 131.8-164.3; Q4 164.3-312.6; **H**) knee extensor strength in women (Nm): Q1 18.8-68.9; Q2 68.9-89.2; Q3 89.2-110.7; Q4 110.7-211.3; **I**) leg muscle quality in men (Nm/kg): Q1 3.3-12.0; Q2 12.0-14.6; Q3 14.6-17.3; Q4 17.3-28.1; and **J**) leg muscle quality in women (Nm/kg): Q1 2.9-11.1; Q2 11.1-13.9; Q3 13.9-16.5; Q4 16.5-28.1. DM, diabetes mellitus.

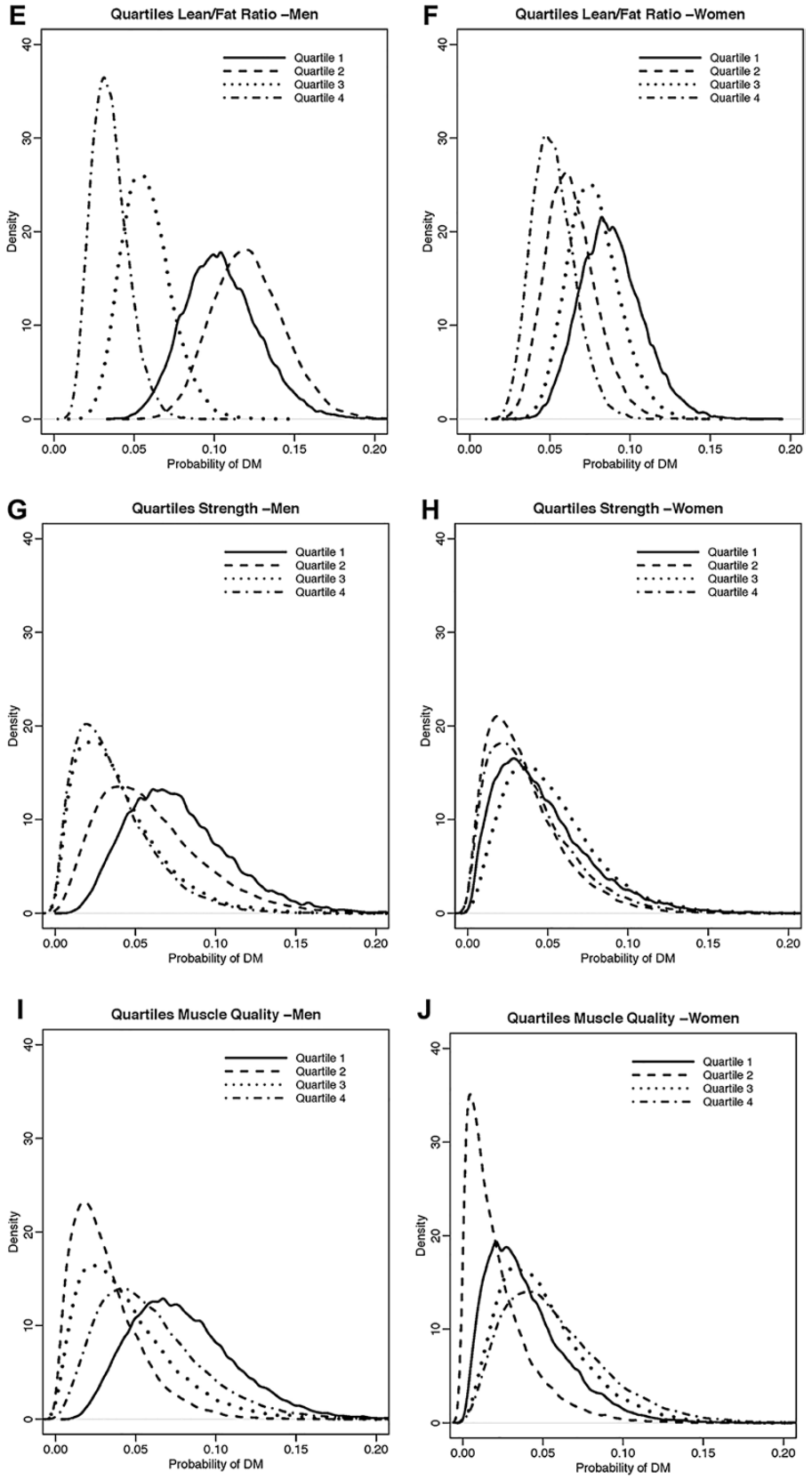

Figure 1. Continued.

Table 3. Cox regression models for the relationship of different measures of muscle mass, strength, and quality to incident diabetes in men[a]

	Model 1	Model 2	Model 3	Model 4
Percentage of total lean body mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.86 (0.48-1.55)	0.87 (0.48-1.56)	0.91 (0.42-1.95)	0.94 (0.44-2.01)
Quartile 3	0.45 (0.22-0.92)[b]	0.45 (0.22-0.92)[b]	0.34 (0.11-0.99)[b]	0.35 (0.12-1.03)
Quartile 4	0.45 (0.21-0.96)[b]	0.46 (0.22-0.97)[b]	0.50 (0.17-1.50)	0.53 (0.18-1.59)
P value for trend	0.009	0.01	0.07	0.09
Absolute total lean body mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.48 (0.20-1.15)	0.47 (0.20-1.13)	0.21 (0.04-0.99)[b]	0.20 (0.04-0.94)[b]
Quartile 3	1.15 (0.56-2.34)	1.10 (0.54-2.26)	1.33 (0.48-3.68)	1.24 (0.44-3.51)
Quartile 4	1.42 (0.69-2.93)	1.32 (0.63-2.75)	2.03 (0.61-6.76)	2.13 (0.63-7.20)
P value for trend	0.10	0.15	0.08	0.07
Absolute total lean-to-fat mass ratio				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	1.01 (0.57-1.79)	1.04 (0.59-1.85)	1.14 (0.53-2.45)	1.16 (0.54-2.50)
Quartile 3	0.49 (0.24-1.01)	0.49 (0.24-1.01)	0.47 (0.17-1.32)	0.51 (0.17-1.44)
Quartile 4	0.39 (0.17-0.88)[b]	0.39 (0.17-0.89)[b]	0.50 (0.16-1.61)	0.53 (0.16-1.72)
P value for trend	0.005	0.005	0.10	0.15
Knee extensor strength				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	1.0 (0.29-3.48)	1.06 (0.31-3.71)	0.82 (0.18-3.76)	0.81 (0.18-3.73)
Quartile 3	0.97 (0.28-3.43)	1.03 (0.29-3.65)	0.71 (0.15-3.35)	0.72 (0.15-3.43)
Quartile 4	1.86 (0.56-6.23)	1.99 (0.60-6.61)	1.27 (0.29-5.46)	1.27 (0.29-5.51)
P value for trend	0.34	0.29	0.78	0.78
Percentage of leg lean mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.66 (0.30-1.44)	0.64 (0.29-1.40)	0.54 (0.22-1.35)	0.54 (0.22-1.35)
Quartile 3	0.37 (0.14-0.93)	0.33 (0.13-0.84)	0.34 (0.12-1.00)	0.36 (0.12-1.04)
Quartile 4	0.40 (0.16-1.02)	0.38 (0.15-0.96)	0.50 (0.18-1.44)	0.54 (0.19-1.56)
P value for trend	0.02	0.01	0.10	0.12
Absolute leg lean mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.41 (0.14-1.15)	0.39 (0.14-1.11)	0.30 (0.08-1.09)	0.29 (0.08-1.07)
Quartile 3	0.67 (0.27-1.66)	0.64 (0.25-1.60)	0.81 (0.31-2.14)	0.76 (0.29-2.04)
Quartile 4	1.11 (0.49-2.51)	0.94 (0.41-2.19)	0.91 (0.34-2.41)	0.92 (0.35-2.42)
P value for trend	0.67	0.94	0.91	0.89
Leg muscle quality				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.80 (0.24-2.63)	0.83 (0.25-2.75)	0.95 (0.25-3.63)	0.96 (0.25-3.66)
Quartile 3	0.88 (0.28-2.74)	0.94 (0.30-2.94)	0.76 (0.20-2.94)	0.78 (0.20-3.04)
Quartile 4	0.99 (0.31-3.19)	1.11 (0.34-3.61)	0.57 (0.13-2.55)	0.55 (0.12-2.45)
P value for trend	0.98	0.83	0.44	0.43

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile; Ref, reference.
[a]Model 1: unadjusted. Model 2: model 1 + race. Model 3: model 2 + height and weight; Model 4: model 3 + prediabetes. Quartiles for muscle measures were updated for participants at each follow-up visit when available. (HR, 95% CI)
[b]$P < 0.05$.

diabetes remained significantly lower for those in the third quartile (HR, 0.34; 0.11-0.99) and the *P* value for trend was borderline significant at 0.07. After further adjustment for prediabetes in fully adjusted model 4, the *P* for trend remained borderline significant at 0.09. Interestingly, similar findings for percentage of leg lean mass were observed in men comparing those in the highest with the lowest quartile (HR, 0.38; 0.15-0.96; model 2), with results attenuated after further adjustment in subsequent models.

However, when absolute total lean body mass was considered instead, results were in the opposite direction. The highest versus lowest quartile of absolute total lean body mass was associated with a greater risk for developing diabetes, though the relationship was not

Table 4. Cox regression models for the relationship of different measures of muscle mass, strength, and quality to incident diabetes in women[a]

	Model 1	Model 2	Model 3	Model 4
Percentage of total lean body mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.87 (0.45-1.67)	0.90 (0.47-1.73)	1.16 (0.48-2.77)	1.10 (0.46-2.64)
Quartile 3	1.09 (0.57-2.09)	1.13 (0.58-2.17)	1.48 (0.55-4.01)	1.39 (0.51-3.78)
Quartile 4	0.64 (0.32-1.29)	0.68 (0.34-1.39)	1.08 (0.36-3.27)	1.03 (0.34-3.14)
P value for trend	0.33	0.43	0.84	0.89
Absolute total lean body mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	2.40 (1.04-5.50)	2.39 (1.04-5.50)[b]	2.42 (0.84-6.96)	2.35 (0.82-6.75)
Quartile 3	1.67 (0.69-4.07)	1.63 (0.67-3.97)	2.43 (0.72-8.13)	2.31 (0.69-7.76)
Quartile 4	3.19 (1.39-7.34)[b]	3.04 (1.31-7.04)[b]	6.82 (1.93-24.2)[b]	6.40 (1.80-22.77)[b]
P value for trend	0.02	0.03	0.003	0.005
Absolute total lean-to-fat mass ratio				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.91 (0.47-1.74)	0.93 (0.49-1.79)	1.18 (0.49-2.81)	1.11 (0.46-2.68)
Quartile 3	1.09 (0.59-2.03)	1.13 (0.61-2.11)	1.52 (0.58-4.03)	1.42 (0.53-3.78)
Quartile 4	0.55 (0.25-1.19)	0.58 (0.26-1.27)	0.90 (0.27-3.02)	0.86 (0.26-2.89)
P value for trend	0.26	0.34	0.97	0.96
Knee extensor strength				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	1.38 (0.44-4.33)	1.29 (0.41-4.07)	1.75 (0.43-7.18)	1.71 (0.42-7.05)
Quartile 3	1.61 (0.53-4.89)	1.50 (0.49-4.60)	2.47 (0.65-9.39)	2.29 (0.60-8.77)
Quartile 4	1.37 (0.41-4.56)	1.21 (0.36-4.09)	1.45 (0.33-6.47)	1.39 (0.31-6.23)
P value for trend	0.60	0.74	0.60	0.67
Percentage of leg lean mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.97 (0.44-2.14)	0.97 (0.44-2.14)	0.82 (0.35-1.94)	0.78 (0.33-1.83)
Quartile 3	0.55 (0.22-1.38)	0.56 (0.22-1.41)	0.56 (0.20-1.50)	0.53 (0.20-1.46)
Quartile 4	0.93 (0.41-2.13)	0.93 (0.41-2.14)	0.82 (0.30-2.24)	0.83 (0.30-2.24)
P value for trend	0.55	0.57	0.54	0.53
Absolute leg lean mass				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	0.60 (0.21-1.71)	0.60 (0.21-1.69)	0.50 (0.16-1.51)	0.49 (0.16-1.47)
Quartile 3	1.47 (0.62-3.48)	1.43 (0.60-3.41)	1.12 (0.43-2.94)	1.06 (0.40-2.78)
Quartile 4	1.51 (0.62-3.67)	1.37 (0.55-3.39)	1.36 (0.47-3.99)	1.34 (0.46-3.89)
P value for trend	0.15	0.23	0.38	0.40
Leg muscle quality				
Reference (Q1)	Ref	Ref	Ref	Ref
Quartile 2	1.96 (0.67-5.68)	1.87 (0.64-5.42)	3.03 (0.82-11.2)	2.98 (0.81-11.00)
Quartile 3	1.17 (0.36-3.74)	1.16 (0.36-3.70)	1.69 (0.41-6.89)	1.65 (0.40-6.77)
Quartile 4	1.30 (0.40-4.17)	1.27 (0.39-4.09)	1.84 (0.43-7.78)	1.74 (0.41-7.41)
P value for trend	0.99	0.98	0.80	0.87

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile; Ref, reference.
[a]Model 1: unadjusted. Model 2: model 1 + race. Model 3: model2 + height and weight. Model 4: model 3 + prediabetes. Quartiles for muscle measures were updated for participants at each follow-up visit when available. (HR, 95% CI).
[b]$P < 0.05$.

statistically significant in any of the models. In sensitivity analyses that also adjusted for absolute total fat mass or waist-to-hip ratio, with these measures updated at each follow-up visit, the results were significant with fat mass (*P* value for trend = 0.01) and borderline significant with waist-to-hip ratio (*P* value for trend = 0.07).

In regard to absolute total lean-to-fat body mass ratio, men in relatively higher quartiles were less likely to develop diabetes in models 1 and 2 (both *P* for trend = 0.005). In model 2, men in quartile 4 versus quartile 1 had a 61% lower risk of developing diabetes (HR,

0.39; 0.17-0.89). This relationship was attenuated such that it was no longer significant in model 3 (HR, 0.50; 0.16-1.61) with a *P* value for trend that was borderline significant at 0.10. No significant relationship to the development of diabetes was observed for strength or muscle quality.

In sensitivity analyses using the alternate definition of diabetes, which only required 1 visit for the diagnosis, the results remained similar for percentage of total lean body mass (*P* value for trend = 0.07) and significant for absolute total lean-to-fat body mass ratio (*P* value for trend = 0.03) but nonsignificant for absolute total lean body mass (*P* value for trend = 0.23) among men in the fully adjusted model 4.

Body composition measures over time and risk of diabetes in women

For women, there was no significant relationship of percentage of total lean body mass quartile to incident diabetes (Table 4). However, a relatively higher quartile of absolute total lean body mass was significantly associated with a higher risk of developing diabetes (*P* value for trend < 0.05 in all models). Participants in quartile 4 versus quartile 1 had an almost 7-fold higher risk of developing diabetes in the fully adjusted model (model 4, HR, 6.40; 1.80-22.77). In sensitivity analyses that additionally adjusted for absolute total fat mass or waist-to-hip ratio, with these measures updated at each visit, the results remained significant (both *P* for trend ≤ 0.01). Additionally, in sensitivity analyses with time-dependent weight, the results of the fully adjusted model for absolute total lean body mass remained significant for women (*P* for trend = 0.04). There were no significant relationships found for absolute total lean-to-fat body mass ratio, knee extensor strength, or leg muscle quality with incident diabetes among women. Though a similar positive association of absolute leg lean mass with incident diabetes was observed in women, the results were not significant in any of the models.

In additional sensitivity analyses using the alternate definition of diabetes, which only required 1 visit for the diagnosis, the results remained similar for the positive relationship of absolute total lean body mass to incident diabetes (*P* for trend = 0.03), among women in model 4.

For both men and women, each model was tested using a likelihood ratio test comparing a model that included each muscle measure separately with the same model without the muscle measure. Results were statistically significant in fully adjusted models (model 4) only for absolute total lean body mass in men ($P < 0.01$) and women ($P = 0.02$), suggesting that differences in absolute total lean body mass are related to observed differences in incident diabetes between participants.

Discussion

Our study demonstrated that among men, a higher percentage of total lean body mass over time was associated with a lower risk of developing diabetes during an average 7 years of follow-up, even after accounting for race. Additionally, a higher absolute total lean-to-fat mass ratio over time was also related to a relatively lower risk of diabetes in men. Further adjustment for anthropometrics attenuated these relationships such that they were borderline significant. Interestingly, among both men and women, we unexpectedly found that relatively higher absolute total lean body mass over time was associated with a higher risk of diabetes even after accounting for total body fat mass in sensitivity analyses.

A higher percentage of total lean body mass has been associated with a lower likelihood of current diabetes, prediabetes, insulin resistance, and metabolic syndrome in cross-sectional studies [2, 21]. Similar to our study, an inverse relationship between relative muscle mass (measured by bioelectric impedance analysis) and the incidence of diabetes was found in Korean men and women who had a median age of 39 years at baseline, much younger than our study participants [22]. Findings from the Health, Aging, and Body Composition Study were also consistent with our study where higher absolute total lean body mass was

associated with a higher incidence of diabetes only in the unadjusted model; however, in that study, the association disappeared after adjusting for measures of fat mass in both sexes [23]. The average age of participants in that study was 73 years at baseline, much older than our study participants. Taken together, the findings of these previous studies suggest that relative versus absolute measures of lean body mass may have discordant relationships to the development of diabetes depending on the method of body composition utilized.

The results of our study demonstrated an unexpected divergence in the direction of the relationship of relative versus absolute total lean body mass to the development of diabetes. In both sexes, higher absolute total lean body mass was surprisingly related to a higher risk of diabetes. A possible explanation is that total lean body mass measured by DXA is affected by body water and also includes visceral organs such as liver, lungs, and intestinal tract as well and may have contributed to the discordant findings observed in our study. In other words, the actual presence of contractile muscle mass may have been smaller but not detected accurately in these participants using this instrument. In addition, larger individuals have a less favorable body habitus that put them at risk of diabetes. Increased accumulation of fat around and within nonadipose tissue organs that normally contain only small amounts of fat, such as in skeletal muscle, can impair the normal physiological function of those organs [24]. Myosteatosis has been identified as a risk factor for insulin resistance and type 2 diabetes [25, 26] and among otherwise well-functioning older adults is related to decreased muscle strength and mobility loss [27, 28], reduced physical performance [29], and impaired longevity [30, 31]. Previous studies have demonstrated that skeletal muscle fat infiltration increases with advancing age [32-34]. It has been postulated that differences in muscle function among older adults that are not attributed to muscle quantity may instead be related to greater muscle lipid content [27]. In contrast, the percentage of total lean body mass, which additionally accounts for the relative proportion of lean mass to total body mass (including the sum of lean, fat, and bone mass, with bone mass usually being less than 5% of total body mass) and lean-to-fat ratio, were both related to a lower risk of developing diabetes among men in our study, as we hypothesized.

Future studies that use different measures to assess body composition such as proton magnetic resonance spectroscopy may be able to better differentiate the presence of intermuscular (visible fat beneath the fascia lata) and intramuscular fat (fat between muscle fibers and fat within muscle cell) that have both been linked to insulin resistance [35-37], and further disentangle the relationship of lean body mass changes to the development of diabetes. In addition, new and emerging measures that directly assess the muscle contractile component [38] may be able to give a refined measure of skeletal muscle mass and shed further insight into the different relationships of relative versus absolute lean body mass to the development of diabetes in our study.

Strengths of our study included the well-documented protocols over many years including the majority of participants having repeated measures of OGTT to determine the development of diabetes. Cox models with time-dependent covariates were able to account for changes in the independent variable (ie, lean body mass) during follow-up for most participants using rigorous analytic methods. Our cohort included participants of all ages that were otherwise relatively healthy, and thus findings are likely to be generalizable. In contrast to previous studies that included mostly young or mostly older adults, our study included on average middle-aged men and women (mean age of 59 years), the age group when the incidence of diabetes typically occurs.

Limitations of our study included the method of body composition assessment, which may not fully reflect actual muscle contractile content. DXA can noninvasively show total, trunk, arm, or leg fat and lean mass excluding bone mineral content [39, 40]; however, DXA estimates of lean body mass may not be specific to skeletal muscle contractile mass. Nonetheless, we were still able to detect significant inverse relationships of percentage of total lean body mass, percentage of leg lean mass, and absolute total lean-to-fat body mass to the development of diabetes in men in minimally adjusted models. The relationships

remained similar in fully adjusted models but were attenuated such that they were no longer statistically significant, possibly due to sample size considerations. Further, even after accounting for multiple comparisons in regression analyses, the significance of the findings and conclusions of our study did not change. Not all participants had repeated measures of lean body mass available; thus, changes in the independent variable during follow-up for these participants could not be accounted for in models. Participants who only had single visits available contributed to the robustness of estimates at baseline, however did not contribute to the findings in survival analyses. While physical activity measures were not uniformly available for all participants, we found that the results of survival analyses were similar when this variable was imputed in models [results not shown]. We also did not have availability of A_{1C} for all participants as it was a more recently introduced diagnostic criterion for diabetes; this may have led to possible missed diagnoses of diabetes. Additionally, some participants who were not in the full follow-up period may have dropped out of the study before developing diabetes.

In conclusion, we found that lean body mass over time was related to the development of diabetes in our study. While men with a lower percentage of total and leg lean mass had a greater incidence of diabetes as we hypothesized, in part related to anthropometrics such as height and weight, both men and women with higher absolute total lean body mass unexpectedly had a greater incidence of diabetes, too, even after accounting for total fat mass measures. These discordant findings may be related to the method of body composition assessment used in our study. Future studies that use more sophisticated methods for the direct estimation of muscle mass are needed to give further insights into these relationships. Such research can ultimately inform the development of novel preventive strategies to reduce the public health burden of diabetes, particularly in older adults.

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Additional Information

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Data Availability: Data for the BLSA Study are available at https://www.blsa.nih.gov/.

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