### Title

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ORIGINAL RESEARCH

# Associations of Abdominal Muscle Density and Area and Incident Cardiovascular Disease, Coronary Heart Disease, and Stroke: The Multi-Ethnic Study of Atherosclerosis

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**BACKGROUND:** Muscle density is inversely associated with all-cause mortality, but associations with cardiovascular disease (CVD) risk are not well understood. This study evaluated the association between muscle density and muscle area and incident total CVD, coronary heart disease (CHD), and stroke in diverse men and women.

**METHODS AND RESULTS:** Adult participants (N=1869) in the Multi-Ethnic Study of Atherosclerosis Ancillary Body Composition Study underwent computer tomography scans of the L2-L4 region of the abdomen. Muscle was quantified by density (Hounsfield units) and area in $cm^2$. Sex-stratified Cox proportional hazard models assessed associations between incident total CVD, incident CHD, and incident stroke across sex-specific percentiles of muscle area and density, which were entered simultaneously into the model. Mean age for men and women at baseline were 64.1 and 65.1 years, respectively, and median follow-up time was 10.3 years. For men, associations between muscle density and incident CVD were inverse but not significant in fully adjusted models (*P* trend=0.15). However, there was an inverse association between density and CHD (*P* trend=0.02; HR, 0.26 for 95th versus 10th percentile), and no association with stroke (*P* trend=0.78). Conversely, for men, there was a strong positive association between muscle area and incident CVD (HR, 4.19 for 95th versus 10th percentile; *P* trend<0.001). Associations were stronger for CHD (HR, 6.18 for 95th versus 10th percentile; *P* trend<0.001), and null for stroke (*P* trend=0.67). Associations for women were mostly null.

**CONCLUSIONS:** For men, abdominal muscle density is associated with lower CHD risk, whereas greater muscle area is associated with markedly increased risk of CHD.

**Key Words:** body composition ■ heart disease ■ lean mass ■ muscle attenuation ■ myocardial infarction ■ myosteatosis

Unfavorable body composition is a known risk factor for cardiovascular disease (CVD) independent of health behaviors, with a large body of research showing associations between excess adiposity and CVD morbidity and mortality.[1,2] Recent studies have highlighted the important role lean muscle may play in preventing morbidity, independent of adiposity. Across studies, muscle has been associated with lower risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.[3–7]

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## CLINICAL PERSPECTIVE

### What Is New?

- Two characteristics of muscle, density and area, were measured in a diverse cohort of men and women and were mutually adjusted for in models predicting incident cardiovascular disease, which was evaluated as total cardiovascular disease and separately for coronary heart disease and stroke.
- For men, associations of muscle density and area were in the opposite direction with total incident cardiovascular disease and coronary heart disease, with the highest density experiencing 74% reduced risk of coronary heart disease, and those with the highest area showing 6 times greater risk of coronary heart disease.
- Neither muscle density nor area was associated with incident stroke.

### What Are the Clinical Implications?

- These findings highlight that abdominal muscle density is a predictor of coronary health specifically and not just a marker of general health or frailty.
- Measures of abdominal muscle quality and quantity could be useful tools to identify patients at greater risk for coronary events.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **MESA** | Multi-Ethnic Study of Atherosclerosis |

Different characteristics of lean muscle may be more relevant to this association. A growing body of evidence has shown that higher muscle density, a proxy measure of intramuscular fat infiltration and indicator of muscle quality,[8] may be more strongly associated with reduced morbidity and mortality than muscle mass or size, which, in some studies, has been associated with greater risk.[9,10] Consistent with this, we recently showed that muscle density predicted markedly lower risk of all-cause mortality in a diverse cohort, whereas those with greater muscle area had greater risk of all-cause mortality over the 12-year follow-up period.[7]

Whether these qualities of muscle are differentially associated with incident CVD is not as well known. A recent study showed that greater muscle density was not associated with risk of CVD (stroke and myocardial infarction [MI]) in a predominantly White cohort.[11] However, follow-up time in this study was relatively short (3.6 years), and stroke and MI were combined into a composite end point. Examining independent associations between both muscle density and area with cardiac and vascular disease, separately, over a longer follow-up period and in diverse populations would expand our understanding of the relationship between muscle and CVD. As such, the purpose of the current analysis was to evaluate the associations between muscle area and muscle density with incident total CVD, coronary heart disease (CHD), and stroke in adults in MESA (Multi-Ethnic Study of Atherosclerosis). We hypothesized that greater abdominal muscle density would be associated with lower risk of CVD.

## METHODS

### Data Set and Code Availability

Comprehensive data, including follow-up data, are available from the MESA study with proposals approved by the publishing committee. Code for the current analysis will be made available upon request.

### Study Overview and Participants

MESA is a diverse prospective cohort study of 6814 US men and women without clinical cardiovascular disease at baseline. The study included Non-Hispanic White (38%), non-Hispanic Black (28%), Latinx or Hispanic (22%), and Chinese American (12%) participants. Participants were recruited from the following 6 communities: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan, New York; and St Paul, Minnesota. Details of the study design have been previously published.[12] Baseline visits were conducted in 2000, with follow-up exams occurring every 18 to 24 months and telephone interviews every 9 to 12 months.

The Abdominal Body Composition, Inflammation, and Cardiovascular Disease ancillary study was a random and roughly representative sample of the MESA cohort. Approximately one-third of MESA participants (2202) were randomly selected and invited to participate in the body composition study; 1974 participants agreed and underwent an abdominal computed tomography (CT) scan at either visit 2 (2002–2004) or visit 3 (2004–2005). All MESA participants with a completed abdominal CT scan as part of the body composition ancillary study were included in this analysis.

Of the 1974 with an abdominal CT scan, 1869 participants with complete outcome and covariate data were included in the analysis. Institutional review boards at the 6 participating centers approved the study, and all participants gave written informed consent before the study.

### Exposure Measures

Abdominal CT scans were performed using either an Imatron C-150 electron-beam (Imatron Inc., San

Francisco, CA), Siemens S4+ Volume Zoom (Siemens, Erlangen, Germany), or General Electric Hi Speed LX CT (General Electric Medical Systems, Waukesha, WI). Imatron scanners have shown a markedly high degree of agreement with multidetector CT scanners (>99%).[13–15] Six cross-sectional slices were taken with 2 each at L2/L3, L3/L4, and L4/L5 intervertebral disc spaces. Scan collimations were set to 3 mm, with a 6-mm slice thickness. Within the 35-cm field of view, scans were reconstructed using 25 slices of 6 mm each.

Measures of total tissue, lean muscle, and adipose tissue were computed using semiautomated Medical Imaging Processing analysis and Visualization software (version 4.1.2, National Institutes of Health, Bethesda, MD). Pixel density of the cross-sectional CT scans was calculated to determine density of each tissue compartment, which was measured in Hounsfield units. Tissue with Hounsfield unit values between 0 and 100 were considered lean muscle, and those between –190 and –30 were classified as adipose tissue.[16] Abdominal muscle groups included the psoas, paraspinous, oblique, and rectus muscles. The inter- and intrarated reliability measures for overall abdominal area and for each muscle group was excellent, ranging from 0.93 to 0.99.

Abdominal muscle density was defined as the average attenuation (Hounsfield unit) measurement within the fascial plane of each muscle group. Abdominal muscle area was defined as the summation of pixels within the muscle group's fascial plane. Total muscle area was calculated by summing the area of all individual muscle groups. A similar approach was used to quantify area of visceral fat (adipose tissue within the abdominal wall).

## Cardiovascular Disease Outcome Measures

Events were primarily identified by self-report from participants or relatives from repeated follow-up telephone interviews at 9 to 12-month intervals administered to gather information about interim hospital admissions and cardiovascular outpatient diagnoses. Participants also self-reported events at clinic visits or by directly calling the field center after event occurrence. Classification of cardiovascular diagnoses and deaths were verified by medical records, autopsy reports, death certificates, and administered interviews or questionnaires with participants' physicians, relatives, or friends. At least 2 physicians reviewed each event's case materials and differing diagnoses were resolved by the 2 reviewers. Additional details on the MESA study's follow-up methods and event adjudication are available on the MESA website and published elsewhere.[12,17,18] Follow-up time was measured from the time of the CT scan until events occurred.

## Cardiovascular Disease Events

CVD events included MI, resuscitated cardiac arrest, stroke, and cardiovascular death (secondary to stroke, CHD, other atherosclerotic death or other CVD death) and was the primary outcome studied.

## Coronary Heart Disease Events

Hard CHD events included MI, resuscitated cardiac arrest, and CHD death. MI was classified as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. Resuscitated cardiac arrest was designated to participants who successfully recovered from a full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). CHD death required a documented MI within the previous 28 days, chest pain within the 72 hours before death, or a history of CHD and the absence of a known nonatherosclerotic or noncardiac cause of death.

## Stroke Events

Stroke events included stroke and stroke deaths. Stroke events were categorized as hemorrhagic, ischemic, other, or undetermined. For hemorrhagic strokes, subtypes were classified as subarachnoid hemorrhage, intraparenchymal hemorrhage, and other hemorrhage with the source of the hemorrhage specified. Ischemic stroke types were classified as large vessel, extracranial; large vessel, intracranial; cardioembolic; small vessel; other specific mechanisms; multiple mechanisms; or undetermined. *Other* was assigned for conditions that do not clearly meet criteria for either hemorrhagic or ischemic type, for example a venous sinus occlusion. *Undetermined* indicates that not enough information was available to categorize as hemorrhagic, ischemic, or other. Transient ischemic attacks were not included.

## Covariates

All covariates obtained from the participant's abdominal CT scan visit (2 or 3) were defined as baseline for this study. Age, sex, race and ethnicity, smoking status, and medication use were self-reported and collected through standardized questionnaires administered at their CT scan visit. Physical activity (metabolic equivalent of task-min/wk) and sedentary behavior (h/d) were self-reported and calculated from data collected during the participant's CT scan visit using the MESA Typical Week Physical Activity Survey, an adaptation of the Cross-Cultural Activity Participation Study.[19]

Objective measures used in the study were also obtained from the visit (2 or 3) at which the participant's abdominal CT scan was taken. Height and weight

without shoes and with minimal clothing were measured via stadiometer, and body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Resting systolic blood pressure measured by automated sphygmomanometer (Dinamap automated oscillometric sphygmomanometer model Pro 100) was recorded 3 times after a 5-minute resting period. The last 2 measurements were averaged and used for analysis. Total cholesterol and high-density lipoprotein cholesterol were assessed using fasting venous blood samples with cholesterol esterase/cholesterol oxidase reaction (Roche Diagnostics, Indianapolis, IN) and triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN). Diabetes status was categorized by fasting glucose level: normal (<100 mg/dL), impaired fasting glucose (100–125 mg/dL), or diabetic (≥126 mg/dL)[20] measured from fasting blood samples using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY) or by use of diabetes medication.[20]

## Statistical Analysis

There was minimal overlap between men and women in distributions of muscle area. Therefore, and consistent with previous studies[9,21–23], all analyses were stratified by sex. Descriptive characteristics and events for men and women were compared using *t* tests, chi-square, incident rate ratios, and log rank tests as appropriate.

Cox proportional hazard models were used to study the associations between both muscle area and density as separate exposure variables with CVD events as the outcome variable. Associations were evaluated across percentiles of muscle density and area (10, 25, 50, 75, 95) in case the associations were not linear. To determine independent associations, muscle area and density were entered into all models simultaneously. In Model 1, we adjusted for age, height (as a proxy measure of body size), and race or ethnicity. Model 2 adjusted for Model 1 variables in addition to type 2 diabetes, systolic blood pressure, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, statin use, cigarette smoking (current, former, never), physical activity, and sedentary time. To account for adiposity as a possible confounder, in Model 3 we additionally adjusted for visceral fat and BMI.

We examined a dose–response relationship between the exposures (muscle density and area) and outcomes (CVD, CHD, stroke) by repeating Model 3 and including restricted cubic spline functions to test for nonlinearity, using the Regression Modeling Strategies package for R (R Foundation for Statistical Computing; Vienna, Austria). Models were run with 3 knots used at the 10th, 50th, and 90th percentiles and again with 4 knots at the 5th, 35th, 65th, and 95th percentiles to evaluate whether shapes of the dose–response curves were sensitive to knot placement and number, and $\chi^2$ tests for nonlinearity were performed. We found no meaningful differences when plots used 3 or 4 knots; therefore, we used 3 knots to maximize statistical power. In order to show muscle density and area overlaid on the same plot, both were converted to *Z* scores. For both exposures, the 10th percentile was designated as the reference category.

Possible interaction with age and race and ethnicity was evaluated using a multiplicative interaction term for each exposure in the fully adjusted model. None were significant.

# RESULTS

Characteristics of the study sample at baseline are shown in Table 1, stratified by sex. Women were slightly older (65.1 versus 64.1 years), had higher blood pressure, were more likely to use antihypertensives and statins, had higher total cholesterol, engaged in less physical activity, and were more sedentary. Conversely, women had higher high-density lipoprotein cholesterol (56.4 versus 45.8 mg/dL), had lower prevalence of diabetes (11.9% versus 14.9%), and were much more likely to have never smoked (57.8% versus 38.3%). Muscle area and visceral fat were markedly lower in women, and subcutaneous fat was much higher.

The mean (SD) follow-up time for incident cardiovascular disease was 10.3 (2.9) years. During follow-up, there were 81 CVD events for women (8.6%), compared with 108 for men (11.7%; see Table 2). Women also had fewer CHD events (44, 4.7%) than men (70, 7.6%). The incidence of stroke was similar between men (4.2%) and women (4.6%).

## Incident Cardiovascular Disease

The associations between percentiles of muscle density with CVD events in men are shown in Table 3. Compared with the 10th percentile (reference), risk of CVD events was lower in all higher percentiles of muscle density in minimally adjusted models. Each increasing percentile was associated with decreasing odds of CVD events, with the 95th percentile showing less than half the risk compared with the 10th percentile (HR, 0.43; *P* overall=0.04). After adjusting for cardiovascular risk factors and behavior (Model 2) and visceral fat and BMI (Model 3), associations were attenuated (*P*-overall=0.15), but the increasing association across percentiles remained (see Figure 1A).

The associations between muscle area and CVD events in men were markedly different (see Table 3). Compared with the 10th percentile, each increasing percentile of muscle area was associated with greater risk of CVD events, with those in the 50th percentile

**Table 1. Baseline Sociodemographic, Health, and Abdominal Body Composition Characteristics (n=1869), by Sex: MESA Body Composition (2002–2005)**

| | Male sex | Female sex | |
|---|---|---|---|
| | n=924 | n=945 | *P* value |
| Age, y, mean (SD) | 64.1 (9.9) | 65.1 (9.4) | 0.03 |
| Race or ethnicity, n (%) | | | |
| Non-Hispanic White | 384 (41.6) | 363 (38.4) | 0.18 |
| Chinese | 132 (14.3) | 118 (12.5) | |
| Black | 171 (18.5) | 223 (23.6) | |
| Hispanic | 237 (25.6) | 241 (25.5) | |
| Health/behavior characteristics | | | |
| Systolic blood pressure, mm Hg, mean (SD) | 123.7 (19.2) | 126.0 (22.8) | 0.018 |
| Antihypertensive use, n (%) | 350 (37.9) | 404 (42.8) | 0.032 |
| Total cholesterol, mg/dL, mean (SD) | 184.3 (34.3) | 198.0 (34.7) | <0.001 |
| High-density lipoprotein cholesterol, mg/dL, mean (SD) | 45.8 (12.0) | 56.4 (15.8) | <0.001 |
| Statin use, n (%) | 172 (18.6) | 196 (20.8) | 0.25 |
| Diabetes, n (%) | | | <0.001 |
| Normal | 638 (69.0) | 729 (77.1) | |
| Impaired fasting glucose | 148 (16.0) | 104 (11.0) | |
| Diabetes | 138 (14.9) | 112 (11.9) | |
| Cigarette use, n (%) | | | |
| Never | 354 (38.3) | 546 (57.8) | <0.001 |
| Former | 446 (48.3) | 302 (32.0) | |
| Current | 124 (13.4) | 97 (10.3) | |
| Physical activity, MET-min/wk, mean (SD) | 5662.0 (5359.6) | 4248.5 (3947.9) | <0.001 |
| Sedentary time, h/d, mean (SD) | 3.2 (2.0) | 3.5 (2.2) | 0.002 |
| Abdominal body composition measures | | | |
| Muscle density, HU, mean (SD) | 44.5 (4.9) | 40.1 (5.2) | <0.001 |
| Muscle area, $cm^2$, mean (SD) | 116.7 (23.9) | 80.4 (17.4) | <0.001 |
| Visceral fat area, $cm^2$, mean (SD) | 161.2 (71.6) | 130.7 (60.8) | <0.001 |
| Body mass index, $kg/m^2$, mean (SD) | 27.7 (4.3) | 28.3 (5.7) | 0.01 |
| Subcutaneous fat area, $cm^2$, mean (SD) | 211.3 (95.0) | 295.7 (122.4) | <0.001 |
| Height, cm, mean (SD) | 173.0 (7.6) | 159.9 (7.2) | <0.001 |

HU indicates Hounsfield units; and MESA, Multi-Ethnic Study of Atherosclerosis.

experiencing more than twice the risk in minimally adjusted models (HR, 2.13; *P* overall <0.001) and those at the 95th percentile experiencing nearly a 5-fold increased risk (HR, 4.92; *P* overall <0.001). Adjusting for confounders slightly attenuated the relationship, but the association across percentiles remained highly significant (*P* overall <0.001; see Figure 1A).

Associations between muscle density and CVD events for women are shown in Table 3 and Figure 1B. Similar to men, women showed lower risk of CVD events with greater muscle density. Compared with those in the 10th percentile for density, women in the 95th percentile had less than half the risk of CVD events in minimally adjusted models (HR, 0.46) and the relationship decreased across percentiles (*P* overall=0.05). The association attenuated after adjusting for covariates and confounders; those in the 95th percentile still had one-third less risk of CVD events (HR, 0.64), but the linear relationship was no longer significant (*P*=0.30).

Again similar to men, associations between muscle area and CVD events went in the opposite direction for women as those for muscle density, but the association was not as strong (Table 3). Those in the 95th percentile had a 63% greater risk of CVD events than those in the 10th percentile for muscle area in minimally adjusted models, but the trend across percentiles was not significant (*P* overall=0.41). In the fully adjusted model those in the 25th to 75th percentiles had slightly lower risk of CVD events (HR, 0.83–0.89); however, none of the associations were statistically significant.

## Incident Coronary Heart Disease

Figure 2A shows associations between muscle density and area and CHD events for men. For muscle density, there was a strong inverse linear association, with risk of CHD events decreasing with each increasing percentile of density. In fully adjusted models, those in the 95th percentile had a 74% lower risk of CHD events (HR, 0.26 [95% CI, 0.09–0.74]), and the overall trend across percentiles remained statistically significant (*P* overall=0.02; see Figure 2A and Table S1 for quartile analyses).

Associations with muscle area and CHD events were, again, in the opposite direction of density and showed a strong positive linear relationship (see Figure 2B; Table S1). Risk increased with each higher percentile of muscle area, such that men in the 95th

**Table 2. CVD, CHD, and Stroke Events During Follow-Up, by Sex: MESA Body Composition (2002–2015)**

| | Male sex | Female sex | *P* value |
|---|---|---|---|
| CVD events, n (%) | 108 (11.7) | 81 (8.6) | 0.025 |
| CVD events per 1000 y | 11.8 | 8.2 | 0.015 |
| CHD events, n (%) | 70 (7.6) | 44 (4.7) | 0.01 |
| CHD events per 1000 y | 7.5 | 4.4 | 0.006 |
| Strokes, n (%) | 39 (4.2) | 43 (4.6) | 0.12 |
| Strokes per 1000 y | 4.2 | 4.3 | 0.86 |

CHD indicates coronary heart disease; and CVD, cardiovascular disease.

**Table 3. Associations of Abdominal Muscle Density and Muscle Area With CVD Events, by Sex: MESA Body Composition (2002–2015)**

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| | n=924 | n=921 | n=915 |
| Male sex | Events=108 | Events=107 | Events=105 |
| Percentile (density, HU) | | | |
| 10th (37.5) | 1 (ref) | 1 (ref) | 1 (ref) |
| 25th (41.2) | 0.79 (0.60–1.04) | 0.81 (0.61–1.08) | 0.78 (0.57–1.06) |
| 50th (45.1) | 0.62 (0.40–0.96) | 0.68 (0.44–1.07) | 0.63 (0.38–1.03) |
| 75th (48.1) | 0.53 (0.32–0.87) | 0.64 (0.38–1.07) | 0.56 (0.31–1.00) |
| 90th (50.4) | 0.46 (0.24–0.88) | 0.62 (0.32–1.18) | 0.52 (0.25–1.07) |
| 95th (51.6) | 0.43 (0.21–0.91) | 0.61 (0.29–1.29) | 0.50 (0.22–1.15) |
| *P* trend | 0.03 | 0.13 | 0.17 |
| Percentile (area, $cm^2$) | | | |
| 10th (86.6) | 1 (ref) | 1 (ref) | 1 (ref) |
| 25th (99.7) | 1.42 (1.07–1.90) | 1.33 (1.00–1.77) | 1.33 (1.00–1.78) |
| 50th (115.6) | 2.13 (1.25–3.63) | 1.86 (1.10–3.15) | 1.88 (1.09–3.22) |
| 75th (133.4) | 3.14 (1.72–5.73) | 2.57 (1.41–4.68) | 2.69 (1.44–5.00) |
| 90th (148.2) | 4.21 (2.24–7.92) | 3.30 (1.74–6.26) | 3.59 (1.84–7.02) |
| 95th (156.2) | 4.92 (2.50–9.67) | 3.77 (1.89–7.52) | 4.19 (2.03–8.65) |
| *P* trend | <0.001 | 0.002 | 0.002 |
| | Model 1 | Model 2 | Model 3 |
| | n=945 | n=939 | n=938 |
| Female sex | Events=81 | Events=81 | Events=81 |
| Percentile (density, HU) | | | |
| 10th (33.3) | 1 (ref) | 1 (ref) | 1 (ref) |
| 25th (36.4) | 0.76 (0.60–0.98) | 0.84 (0.65–1.09) | 0.81 (0.62–1.06) |
| 50th (40.4) | 0.57 (0.37–0.90) | 0.73 (0.45–1.16) | 0.67 (0.40–1.11) |
| 75th (43.9) | 0.50 (0.28–0.90) | 0.71 (0.39–1.33) | 0.64 (0.32–1.25) |
| 90th (46.6) | 0.47 (0.21–1.08) | 0.74 (0.31–1.75) | 0.64 (0.25–1.62) |
| 95th (48.4) | 0.46 (0.16–1.26) | 0.76 (0.26–2.19) | 0.64 (0.21–2.00) |
| *P* trend | 0.45 | 0.40 | 0.30 |
| Percentile (area, $cm^2$) | | | |
| 10th (59.3) | 1 (ref) | 1 (ref) | 1 (ref) |
| 25th (67.9) | 0.95 (0.74–1.23) | 0.89 (0.68–1.15) | 0.89 (0.69–1.16) |
| 50th (79.2) | 0.96 (0.59–1.56) | 0.81 (0.49–1.34) | 0.83 (0.50–1.37) |
| 75th (92.1) | 1.12 (0.62–2.02) | 0.86 (0.46–1.61) | 0.89 (0.47–1.68) |
| 90th (103.8) | 1.40 (0.66–2.95) | 0.99 (0.45–2.19) | 1.05 (0.47–2.34) |
| 95th (111.2) | 1.63 (0.66–4.02) | 1.10 (0.43–2.83) | 1.17 (0.44–3.08) |
| *P* trend | 0.19 | 0.55 | 0.51 |

Reported are hazard ratios and 95% CIs estimated with multivariable Cox proportional hazard models. Muscle density and area were both modeled using restricted cubic splines with 3 knots (10th, 50th, 90th percentiles). Model 1 adjusts for age, race or ethnicity, and muscle area (for density analyses) or muscle density (for area analyses). Model 2 adjusts for Model 1 + diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, statin use, cigarette smoking, physical activity, and sedentary time. Model 3 adjusts for Model 2 (without height) + visceral fat and body mass index. CVD indicates cardiovascular disease; HU, Hounsfield units; and MESA, Multi-Ethnic Study of Atherosclerosis.

percentile had more than 6-fold greater risk of CHD events than men in the 10th percentile in fully adjusted models (HR, 6.18 [95% CI, 2.51–15.22]). The trend remained statistically significant in fully adjusted models (*P*<0.001; see Figure 2A).

For women, associations between muscle density and CHD events also showed an inverse association (Figure 2B; Table S1). Compared with those in the 10th percentile of density, all other percentiles showed decreased risk of CHD events; however, HRs

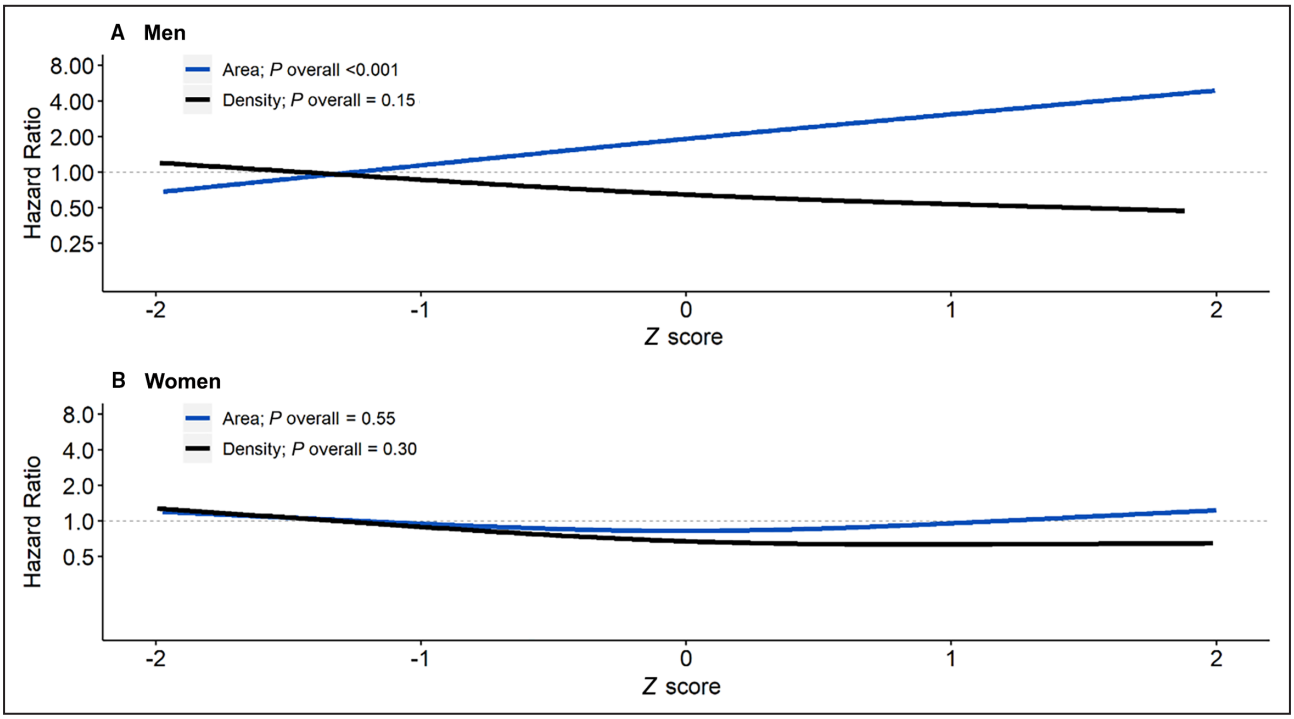


**Figure 1. Continuous dose–response associations of abdominal muscle density and area with CVD events, by sex: MESA Body Composition (2002–2015).**

All associations were estimated with Cox proportional hazard models mutually adjusting for muscle density and muscle area using restricted cubic splines with 3 knots controlling for age, race or ethnicity, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, statin use, diabetes, smoking history, physical activity, sedentary time, visceral fat, and body mass index. Results were trimmed at the 1st and 99th percentiles. Muscle density and area were converted to *Z* scores to allow visual overlay. **A**, Men (n=915, events=105). **B**, Women (n=938, events=81). CVD indicates cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

were smaller than for men (HR, 0.62–0.86), and the overall association was not significant (*P*=0.69). Similar to men, associations between muscle area and CHD events for women were also positive; however, these associations again were much smaller than for men and not significant (*P*=0.41; see Figure 2B).

## Incident Stroke

Associations between muscle density and area and stroke for men are shown in Figure 3A. For both area and density, with slightly greater risk of stroke for each increasing percentile of muscle area and density, though associations were not statistically significant for density or area (*P*=0.78, 0.67, respectively). Conversely, for women, associations between muscle density and area and stroke were both inverse, with greater percentiles of each showing reduced risk of stroke (Figure 3B). However, these again were not statistically significant.

# DISCUSSION

Consistent with hypotheses, the results indicate that greater muscle density and less muscle area were associated with lower risk of overall CVD across 10.3 years of follow-up in the large community-based diverse MESA cohort. These results also emphasize the differential associations of muscle with coronary and vascular morbidity and mortality. When CVD was separated into CHD and stroke, the greater muscle density and less muscle area were associated with lower risk of CHD but there were no significant associations for stroke.

These results are inconsistent with a recent Healthy Ageing Initiative study[11] that found greater muscle density was not associated with increased risk of overall CVD in community-dwelling Swedish men and women. There are several reasons for the inconsistencies, including our sample being more diverse and having a markedly longer follow-up time. Most likely, however, is that the Healthy Ageing Initiative study used a composite outcome that combined MI and stroke, whereas the current investigation examined CHD and stroke separately. When separated, data revealed that the association for overall CVD was primarily driven by strong associations between muscle density and CHD, whereas associations with stroke were null. The high proportion of strokes in the Healthy Ageing composite outcome, along with fewer events overall, could have led to the null findings. Notably, our study also examined associations for men and women separately,

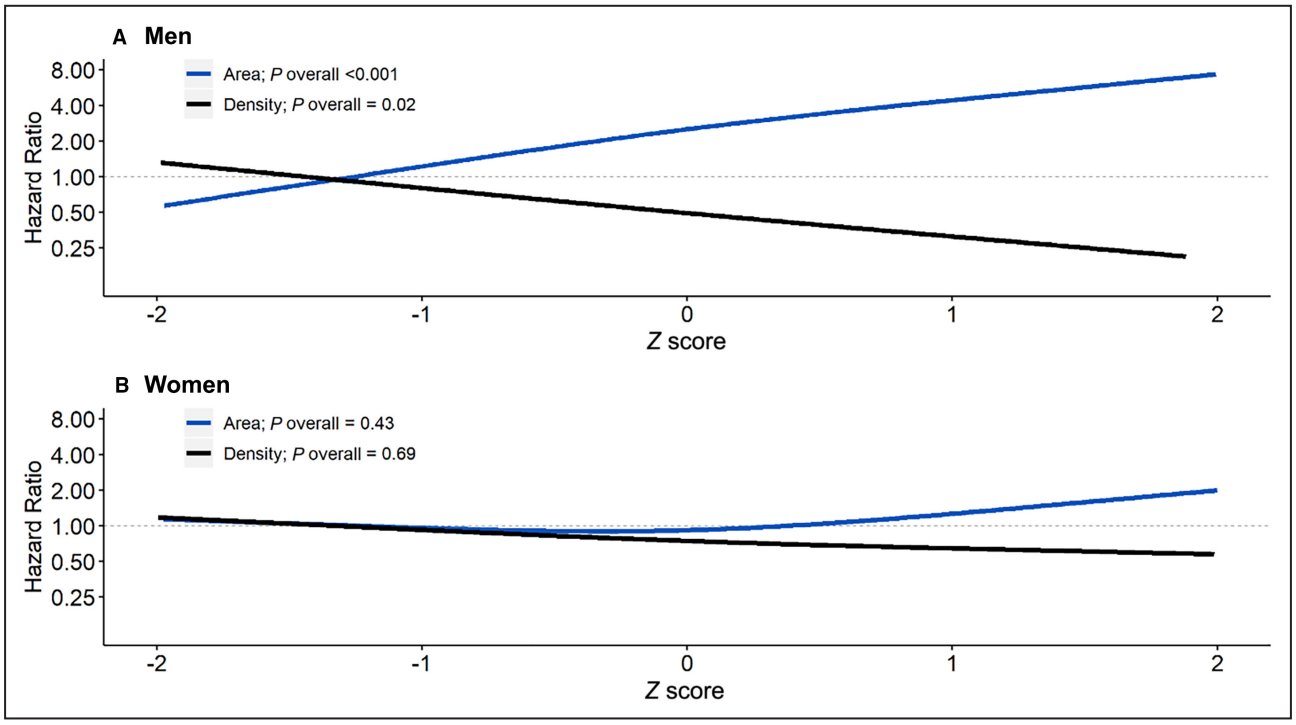


**Figure 2. Continuous dose–response associations of abdominal muscle density and area with coronary heart events, by sex: MESA Body Composition (2002–2015).**

All associations were estimated with Cox proportional hazard models mutually adjusting for muscle density and muscle area using restricted cubic splines with 3 knots controlling for age, race or ethnicity, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, statin use, diabetes, smoking history, physical activity, sedentary time, visceral fat, and body mass index. Results were trimmed at the 1st and 99th percentiles. Muscle density and area were converted to *Z* scores to allow visual overlay. **A,** Men (n=915 events=68). **B,** Women (n=938, events=44). MESA indicates Multi-Ethnic Study of Atherosclerosis.

and associations were significant only for men in fully adjusted models.

The inverse associations between muscle density and CHD are consistent with previous work highlighting muscle density as a protective factor. Our previous work[7] and that by others, also found significant inverse associations between muscle density and all-cause mortality.[5,24,25] As in the present study, other studies also found stronger associations for men than women.[5] Measures of muscle function and strength, such as grip strength, have also shown negative associations with CHD,[26] and fewer CVD events in patients with prediabetes and type 2 diabetes.[27]

The current study found striking positive associations between muscle area and CHD in men, such that those in the 50th percentile for muscle area had double the risk of incident CHD than those in the 10th percentile, and the risk was more than 6 times greater for those in the 95th percentile. This is consistent with previous work showing greater all-cause mortality in those with greater muscle area.[2] Some studies have found muscle area positively associated with morbidity and mortality until adjusting for other measures of body size and composition, such as visceral adipose tissue, suggesting greater muscle size could be a proxy measure for adiposity. It has also been suggested that greater muscle size could be due not to muscle tissue but to greater infiltration of intramuscular fat. However, in the current study, these associations remained consistent after adjusting for adiposity and for muscle density, which has been validated as a reliable proxy measure of intramuscular fat,[8] suggesting greater muscle size is an independent risk factor. More work is needed to determine the mechanisms linking greater muscle area and morbidity and mortality.

The finding that muscle density and area were associated with CHD but not stroke could suggest the mechanisms linking muscle and health outcomes are more atherosclerotic than hypertensive. Consistent with this, Lee et al showed that a higher proportion of muscle with normal attenuation was associated with lower prevalence of coronary artery calcification.[28] Similarly, we previously showed that greater muscle density and lower muscle area were both associated with greater density and lower volume of coronary artery calcium,[29] a profile that has been shown to be cardioprotective.[30] As a growing body of literature has illuminated the association between muscle density and coronary health, the next steps in this line of research are examining the nature and direction of the mechanisms governing this relationship.

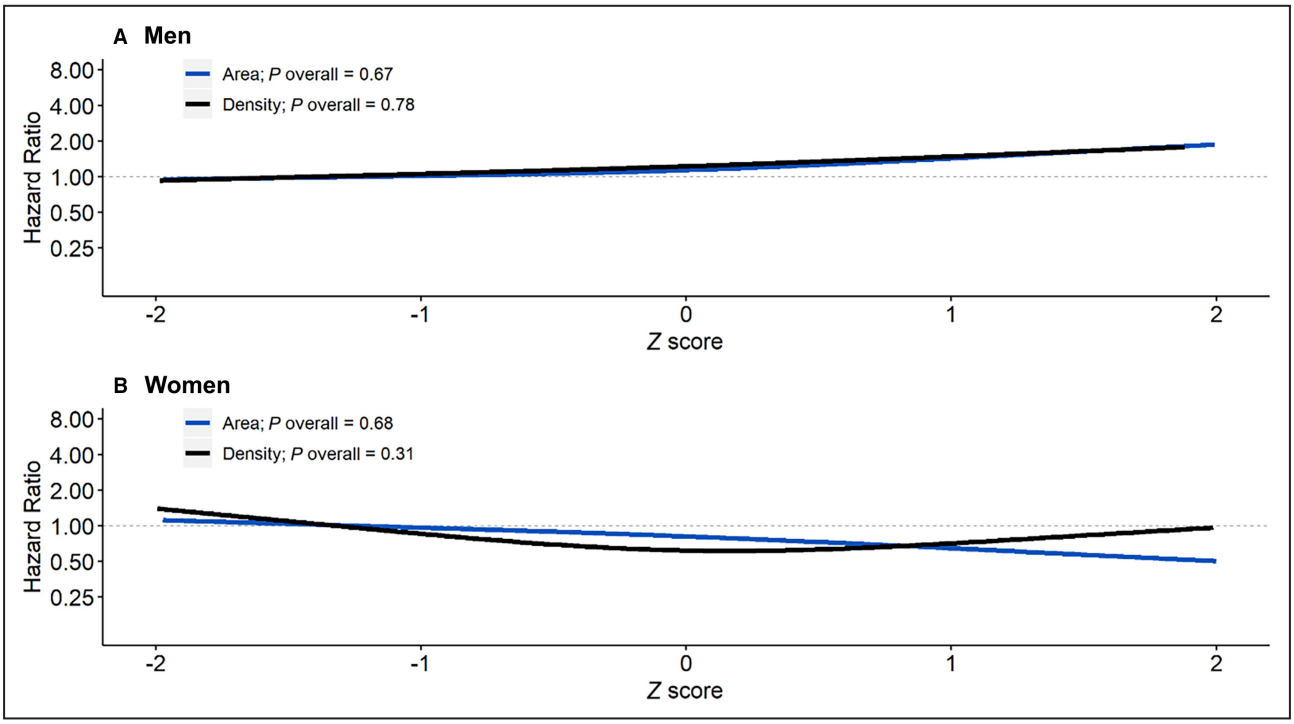


**Figure 3. Continuous dose–response associations of abdominal muscle density and area with stroke events, by sex: MESA Body Composition (2002–2015).**

All associations were estimated with Cox proportional hazard models mutually adjusting for muscle density and muscle area using restricted cubic splines with 3 knots controlling for age, race or ethnicity, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, statin use, diabetes, smoking history, physical activity, sedentary time, visceral fat, and body mass index. Results were trimmed at the 1st and 99th percentiles. Muscle density and area were converted to *Z* scores to allow visual overlay. **A**, Men (n=915, events=38). **B,** Women (n=938, events=43). MESA indicates Multi-Ethnic Study of Atherosclerosis.

In the current study, risk of stroke was not significantly associated with muscle density and muscle area. These results are consistent with a previous study[31] that found abdominal fat-free muscle mass was not an independent predictor of stroke in men. Our study, which used gold-standard CT scans, showed that this finding remained null even when adjusting for muscle density. The differing associations between CHD and stroke suggest abdominal muscle density is not simply a proxy measure of health or frailty but is specifically linked to coronary health. The Tobago Health Study, conversely, found an inverse association between muscle density and incident hypertension.[32] Muscle density in that study was measured in the calf rather than the abdomen; thus, it is also possible that vascular health is related specifically to muscle density in the extremities.

Associations in women were generally null, with greater muscle density and lower area showing associations with CVD only in minimally adjusted models. One possible reason could be that women had fewer events and a smaller range of muscle area and density, which may have reduced statistical precision in finding an association for women. Also, although density was similar between men and women, men had markedly greater muscle area, such that the 95th percentile in area for women was below the 50th percentile for men. Associations with coronary outcomes may been seen only at higher levels of muscle area, despite women having smaller overall body size. One study found that a higher proportion of high-quality muscle in the abdomen had an inverse association with coronary artery calcium in women but not in men.[28] Few studies of muscle density and morbidity and mortality, however, have done sex-stratified analyses, and more research is needed to determine the consistency of these differences between men and women and the possible mechanisms explaining them.

This study includes several strengths, including gold-standard CT scan measurements of body composition, an ethnically and age diverse cohort, thorough measures of lifestyle and CVD confounders, mutually adjusting for muscle density and muscle area, a relatively long follow-up time (median 10.3 years), and separating incident CHD from strokes. We were also able to perform sex-stratified analyses, which is important given the differing distributions in muscle density and area in men and women as well as the potential influence of sex-specific visceral and subcutaneous fat distributions on CVD.

Limitations include self-reported measures of physical activity and sedentary behavior covariates. Although the sample was free of known CVD at baseline, the relatively high baseline prevalence of diabetes and hypertension may limit generalizability to healthy, nonclinical populations.

## CONCLUSIONS

In this longitudinal study of a diverse cohort free of CVD at baseline, we showed that abdominal muscle density and muscle area show inverse associations with incident CHD events, with muscle density potentially playing a protective role, and muscle area associated with a striking increase in risk of CHD. Conversely, we found no association with incident stroke, suggesting muscle density is not simply a marker of overall health. Next steps in this line of research include determining if association between muscle and CHD are causal, and what biological mechanisms of action may be responsible.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Table S1.

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