

# Central Obesity and Visceral Adipose Tissue Are Not Associated With Incident Atherosclerotic Cardiovascular Disease Events in Older Men

John T. Schousboe, MD, PhD; Allyson M. Kats, MS; Lisa Langsetmo, PhD; Tien N. Vo, MS; Brent C. Taylor, PhD, MPH; Ann V. Schwartz, PhD; Peggy M. Cawthon, PhD; Cora E. Lewis, MD, MSPH; Elizabeth Barrett-Connor, MD; Andrew R. Hoffman, MD; Eric S. Orwoll, MD; Kristine E. Ensrud, MD, MPH

**Background**—Visceral adipose tissue (VAT) and other measures of central obesity predict incident atherosclerotic cardiovascular disease (ASCVD) events in middle-aged individuals, but these associations are less certain in older individuals age 70 years and older. Our objective was to estimate the associations of VAT and the android–gynoid fat mass ratio, another measure of central obesity, with incident ASCVD events among a large cohort of older men.

**Methods and Results**—Two thousand eight hundred ninety-nine men (mean [SD] age 76.3 [5.5] years) enrolled in the Outcomes of Sleep Disorders in Older Men study had rigorous adjudication of incident ASCVD events (myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke). We used proportional hazards models to estimate the hazard ratios for incident ASCVD per SD increase of VAT or android–gynoid fat mass ratio (measured at baseline with dual-energy absorptiometry), adjusted for age, race, education, systolic blood pressure, smoking status, oxidized low-density lipoprotein level, treatment for hypertension, statin use, aspirin use, presence of diabetes mellitus, and study enrollment site. Over a mean (SD) follow-up period of 7.9 (3.4) years, 424 men (14.6%) had an incident ASCVD event. Neither VAT nor android–gynoid fat mass ratio were associated with incident ASCVD events, either unadjusted or after multivariable-adjustment (hazard ratios [95% confidence interval] per SD increase 1.02 [0.92–1.13] and 1.05 [0.95–1.17], respectively).

**Conclusions**—Central adipose tissue, as measured by VAT or android–gynoid fat mass ratio, was not associated with incident ASCVD events in this study of older men. (*J Am Heart Assoc.* 2018;7:e009172. DOI: 10.1161/JAHA.118.009172.)

**Key Words:** android gynoid fat mass ratio • cardiovascular outcomes • central obesity • dual energy x-ray absorptiometry • visceral adipose tissue

Previous studies have linked central obesity (around the abdomen rather than appendicular) with metabolic syndrome, dyslipidemia, and a higher risk of incident atherosclerotic cardiovascular disease (ASCVD).<sup>1</sup> Central adipose tissue is composed of both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) compartments. VAT may be particularly detrimental<sup>2–5</sup> because it is infiltrated with macrophages and other inflammatory cells associated with higher levels of serum inflammatory markers,<sup>6</sup> and is also associated with metabolic syndrome and markers of insulin resistance (including raised fasting insulin concentrations).<sup>7–9</sup>

We have previously shown that higher levels of VAT, measured by either computed tomography (CT) or dual energy X-ray absorptiometry (DXA), are associated with a detrimental ASCVD risk factor profile among older men including lower high-density lipoprotein cholesterol, higher triglycerides, and greater insulin resistance.<sup>10</sup> In spite of this, it is unclear whether VAT or other measures of central adiposity predict ASCVD events in the older population, given that adipose tissue may be a marker of vitality and a low burden of comorbid illness in this age group.<sup>11</sup> Although obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) is associated with increased

From the Park Nicollet Clinic & HealthPartners Institute, Minneapolis, MN (J.T.S.); University of Minnesota, Minneapolis, MN (J.T.S., A.M.K., L.L., T.N.V., B.C.T., K.E.E.); VA Health Care System, Minneapolis, MN (B.C.T., K.E.E.); University of California, San Francisco, CA (A.V.S.); California Pacific Medical Center Research Institute, San Francisco, CA (P.M.C.); University of Alabama at Birmingham, AL (C.E.L.); University of California, San Diego, CA (E.B.-C.); Stanford University, Stanford, CA (A.R.H.); Oregon Health & Sciences University, Portland, OR (E.S.O.).

Accompanying Tables S1 and S2 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009172>

**Correspondence to:** John T. Schousboe, MD, PhD, HealthPartners Institute, 3311 Old Shakopee Rd, Bloomington, MN 55425. E-mail: scho0600@umn.edu

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## Clinical Perspective

### What Is New?

- Visceral adipose tissue was not associated with incident clinical atherosclerotic cardiovascular disease (ASCVD) events in older men, without or with adjustment for age and other ASCVD clinical risk factors, even among those without any major pre-existing comorbid medical conditions, overweight men, or men with normal body mass index.
- Android-to-gynoid fat mass ratio (measured using dual energy x-ray absorptiometry) was also not associated with incident clinical ASCVD events in older men.

### What Are the Clinical Implications?

- Dual energy x-ray absorptiometry measures of central adipose tissue depots are not clinically useful for ASCVD risk stratification in older men.
- Weight loss among older men to reduce central obesity may not reduce their risks of incident ASCVDs.
- Since weight loss can result in loss of muscle mass and functional capabilities, the risks and benefits of weight for older men need to be carefully considered on a case-by-case basis.

mortality among adult men and women age 64 years or younger, this association is much weaker or absent among those age 65 and older,<sup>12,13</sup> a phenomenon referred to as the “obesity paradox.”<sup>11</sup> Some have postulated that this paradox is caused by increasing comorbid illness burden in older adults being associated with both weight loss and incident ASCVD.

Only 1 other study has examined the association of VAT with any type of incident ASCVD events in adults older than age 70 years; this study reported that higher VAT was associated with a higher risk of myocardial infarction in older women but not older men. Other ASCVD outcomes were not assessed.<sup>3</sup> Therefore, our primary study aim was to estimate the association of VAT with incident ASCVD events in older men.

Other measures of central adipose tissue (eg, greater waist circumference) have been associated with increased risks of all-cause and ASCVD mortality, but greater gluteofemoral adipose tissue (operationally defined as hip circumference) may be associated with decreased risks.<sup>14,15</sup> Therefore, our second aim was to also estimate the association of another measure of central obesity, the android–gynoid fat mass ratio, with incident ASCVD events.

Given the hypothesis that the obesity paradox is related to a much higher incidence of multimorbidity in those over age 70 years, a third aim was to estimate the association of VAT with incident ASCVD events in the subset without key

common comorbid medical conditions, on the supposition that these men biologically may resemble those who are chronologically younger. Finally, data from the National Health and Nutritional Examination Survey suggest that central obesity may be particularly associated with ASCVD mortality in adult men without obesity as defined by BMI.<sup>16,17</sup> Hence, we also performed all of the above analyses for the subsets of overweight men (BMI 25.0–29.9 kg/m<sup>2</sup>), and men with normal BMI (18.5–24.9 kg/m<sup>2</sup>).

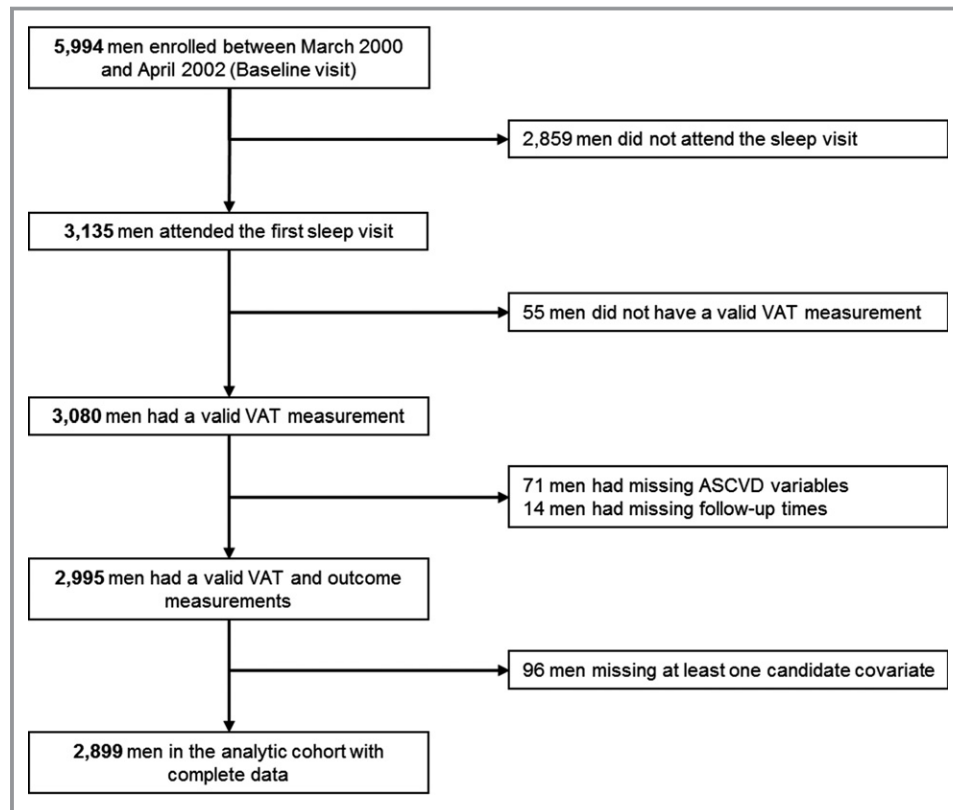
## Methods

MrOS (Osteoporotic Fractures in Men) data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedures in this study.<sup>18</sup> Between 2000 and 2002, the MrOS study enrolled 5994 community-dwelling ambulatory men age 65 years and older at 6 geographic sites in the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA), as described in previous publications,<sup>19,20</sup> after Institutional Review Board approval at each of the 6 study sites. All participants signed informed consent documents. Between December 2003 and March 2005, 3135 of these men were also enrolled in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) ancillary study. Men with the following characteristics were excluded: (1) use of oxygen therapy in the past 3 months; (2) a history of an open tracheotomy; or (3) sleeping with a mouthpiece, continuous positive airway pressure, or bilevel positive airway pressure for snoring or sleep apnea in the prior 3 months. Of these men, 2899 had valid VAT measurements on a DXA body composition study at the MrOS Sleep baseline visit, adjudication of incident ASCVD events, and complete covariate data (Figure 1). Over half of the 236 excluded men did not have a valid VAT measurement on DXA and/or had missing data with respect to an incident ASCVD event. There was no difference in other baseline characteristics between the 2899 men included in and the 236 men excluded from these analyses (Table S1).

## Ascertainment of Incident ASCVD Events

We used the composite outcome of ASCVD events as defined by the American Heart Association–American College of Cardiology guidelines (coronary heart disease death, myocardial infarction, fatal stroke, or nonfatal stroke). This excludes events that have poor reliability (such as angina) and those that are influenced by clinical practice preferences (such as revascularization procedures).<sup>21</sup>

Participants were contacted by postcard and/or telephone every 4 months after the baseline MrOS Sleep substudy visit until February 28, 2015 (mean [SD] follow-up 7.9 [3.4] years),



**Figure 1.** Flow diagram of men selected for analytic cohort. ASCVD indicates atherosclerotic cardiovascular disease; VAT, visceral adipose tissue.

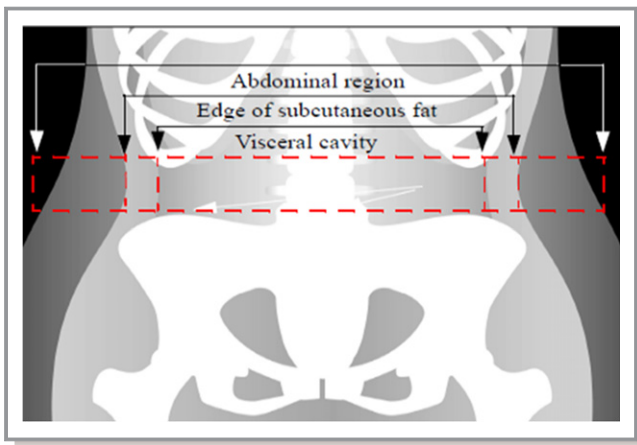
and queried regarding possible ASCVD events; 99% of these follow-up contacts were successfully completed among active surviving participants. Relevant medical records and supporting documentation from any potential incident clinical events identified by phone or postcard contact were obtained by the clinical center and forwarded to the data coordinating center. For fatal events, the death certificate and hospital records from the time of death (if available) were collected. For fatal events that did not occur in hospital, a proxy interview with next of kin and hospital records from the most recent hospitalization in the past 12 months were obtained. These documents were used to determine the underlying cause of death. Documentation for potential nonfatal and fatal ASCVD events were reviewed and adjudicated by a centrally trained board-certified cardiologist using a prespecified adjudication protocol that had been successfully used for both prior randomized trials and epidemiological studies of ASCVD. Only events confirmed by the adjudicator are included for analysis.

### Measurement of Regional Fat Mass Depots on DXA

At the MrOS Sleep baseline visit, DXA whole body composition studies were performed using Hologic QDR4500A densitometers. A whole body phantom was circulated among

the 6 study sites to cross-calibrate regional fat and lean tissue mass measurements. The variability across study enrollment sites was within acceptable limits, and cross-calibration correction factors were not required. To adjust for study site differences, statistical models include indicator variables for the individual scanners.

The whole body DXA scans were re-analyzed centrally in 2016 with Hologic APEX software version 5.5 to obtain VAT measurements, using a standard algorithm.<sup>22</sup> The software calculated the total adipose tissue within a 5-cm transverse slice on the 2-dimensional projection of the abdominal-pelvic region, the inferior border of which is placed at the top of the iliac crests (at about the L4 vertebral level). The lateral and medial edges of the abdominal wall musculature are identified (Figure 2); all of the adipose tissue in the areas outside of the lateral edges is SAT. VAT is contained in the visceral cavity inside the medial edges of the abdominal wall musculature, but this area also includes SAT anterior and posterior to the abdominal wall musculature superimposed on the 2-dimensional projection. The amount of SAT in the medial VAT area can be estimated from the SAT lateral to the abdominal wall musculature, and the estimated visceral fat area (cm<sup>2</sup>) is then calculated as total adipose tissue overlying and within the visceral cavity minus the SAT overlying this area.



**Figure 2.** Measurement of visceral adipose tissue on dual energy x-ray absorptiometry.

The android region of interest was situated above the line between the right and left iliac crests and below the horizontal line 20% of the distance between the inferior boundary and the chin. Fat mass measurements in the android region included both VAT and SAT. The upper boundary of the gynoid region was a line drawn a distance 1.5 times the height of the android region below the iliac crests, and the gynoid region lower boundary was a line 2 times the height of the android region below the upper boundary.<sup>23</sup>

### Other Covariates

Height was measured with a Harpenden stadiometer, weight recorded with a balance beam or electronic scale, and BMI calculated as weight (kg) divided by height squared ( $m^2$ ) at the MrOS Sleep baseline visit. Participants self-reported if they were a current or a past smoker, if they were currently taking aspirin or a statin medication, whether or not they were using medications for hypertension, and whether or not they had been diagnosed previously by a physician with a myocardial infarction, stroke, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, Parkinson's disease, rheumatoid arthritis, liver disease, or renal disease. Systolic blood pressure was measured in the right arm twice with the participant sitting, and averaged. Oxidized low-density lipoproteins were measured on Beckman Coulter Biomek NXp (Beckman Coulter, Inc, Fullerton, CA) using a direct sandwich enzyme immunoassay (Oxidized LDL ELISA; Mercodia AB, Uppsala, Sweden).

### Statistical Analyses

Baseline characteristics of participants were compared in 2 groups, stratified by incident ASCVD outcome (yes versus no) using  $\chi^2$  statistics for categorical variables, Student *t* test for

normally distributed continuous variables, and Mann–Whitney *U* test for continuous variables with a non-normal distribution. Separate Cox proportional hazards models were used to estimate the hazard ratios (per SD increase) of BMI (model 1), VAT (model 2), android-to-gynoid fat mass ratio (model 3), with incident ASCVD events, adjusted for age, education, race, systolic blood pressure, smoking (ever versus never), oxidized LDL level, treatment for hypertension, statin use, aspirin use, and presence of diabetes mellitus, censoring for ASCVD event, mortality for any cause, and loss to follow-up. To test whether the associations of our primary adipose tissue varied by age, additional models were run including the appropriate interaction term (BMI\*age, VAT\*age, or [android/gynoid]\*age). Schoenfeld residuals were used to test that the proportional hazards assumption was not violated.

Gluteofemoral adipose tissue may be protective against incident ASCVD and mortality, and some have therefore recommended that prediction models include measures of central and gluteofemoral adipose tissue as separate covariates in order to capture their independent effects, adjusted for each other, on outcome events.<sup>14,15</sup> Therefore, we also estimated the separate associations of android and gynoid fat mass, adjusted for each other (model 4).

Given that weight loss is associated with and can even begin shortly before the onset of a variety of illnesses in older people,<sup>24</sup> the “obesity paradox” may be a function of comorbid conditions that become more prevalent with age, rather than age per se. Hence, we repeated these analyses in men without major self-reported physician diagnosed pre-existing comorbid illness (prior myocardial infarction, stroke, atrial fibrillation, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, Parkinson's disease, rheumatoid arthritis, liver disease, or renal disease). For all models, postdiagnostic tests were done to ensure that the proportional hazards assumption for the adipose tissue predictor variables was not violated.

### Results

Over a mean follow-up period of 7.9 (SD 3.4) years, 424 men (14.6%) experienced 1 or more incident ASCVD events; 102 (3.5%) died of coronary heart disease, 223 (7.7%) had an acute myocardial infarction, 133 (4.6%) had a nonfatal stroke, and 39 (1.3%) had a fatal stroke. Men who had an incident ASCVD event were older, had a higher systolic blood pressure, and were more likely to self-report that they were using medication for hypertension at baseline (Table 1). None of the crude, unadjusted associations of baseline VAT, android fat mass, gynoid fat mass, and android–gynoid fat mass ratio with incident ASCVD events were statistically significant (Table 1).

**Table 1.** Patient Characteristics Stratified by ASCVD Incident Event Status

Characteristic	All (N=2899)	≥1 ASCVD Event (N=424)	No ASCVD Event (N=2475)	P Value
VAT area (cm <sup>2</sup> ), mean (SD)	182.2 (69.18)	186.9 (71.30)	181.4 (68.79)	0.13
Android fat mass (g), mean (SD)	2253.5 (913.14)	2292.9 (914.57)	2246.7 (912.92)	0.24
Gynoid fat mass (g), mean (SD)	3151.5 (1056.87)	3155.6 (1092.10)	3150.8 (1050.94)	0.83
Android/gynoid fat mass ratio, mean (SD)	0.714 (0.19)	0.728 (0.19)	0.711 (0.18)	0.05
Age (y) at sleep visit, mean (SD)	76.3 (5.53)	78.1 (5.64)	76.0 (5.45)	<0.0001
Educational status, N (%)				
High school or less	611 (21.1)	104 (24.5)	507 (20.5)	0.06
Some college	649 (22.4)	106 (25.0)	543 (21.9)	
College	538 (18.6)	78 (18.4)	460 (18.6)	
Some graduate school	320 (11.0)	40 (9.4)	280 (11.3)	
Graduate school	781 (26.9)	96 (22.6)	685 (27.7)	
Race, N (%)				
White	2616 (90.2)	387 (91.3)	2229 (90.1)	0.44
Other	283 (9.8)	37 (8.7)	246 (9.9)	
Cigarette smoking status, N (%)				
Never	1151 (39.7)	163 (38.4)	988 (39.9)	0.57
Ever	1748 (60.3)	261 (61.6)	1487 (60.1)	
BMI at sleep visit, N (%)				
<18.5 kg/m <sup>2</sup>	9 (0.3)	1 (0.2)	8 (0.3)	0.83
18.5 to 24.9 kg/m <sup>2</sup>	874 (30.1)	122 (28.8)	752 (30.4)	
25 to 29.9 kg/m <sup>2</sup>	1427 (49.2)	209 (49.3)	1218 (49.2)	
≥30 kg/m <sup>2</sup>	589 (20.3)	92 (21.7)	497 (20.1)	
Systolic blood pressure (mm Hg), mean (SD)	126.9 (16.18)	131.0 (18.38)	126.2 (15.67)	<0.0001
oxLDL (U/L), mean (SD)	44.1 (12.25)	43.8 (12.00)	44.1 (12.30)	0.65
Diabetes mellitus, N (%)				
No	2522 (87.0)	362 (85.4)	2160 (87.3)	0.28
Yes	377 (13.0)	62 (14.6)	315 (12.7)	
Current blood pressure medication, N (%)				
No	1249 (43.1)	138 (32.5)	1111 (44.9)	<0.0001
Yes	1650 (56.9)	286 (67.5)	1364 (55.1)	
Current statin medication, N (%)				
No	1698 (58.6)	253 (59.7)	1445 (58.4)	0.62
Yes	1201 (41.4)	171 (40.3)	1030 (41.6)	
Aspirin, N (%)				
No	1208 (41.7)	174 (41.0)	1034 (41.8)	0.78
Yes	1691 (58.3)	250 (59.0)	1441 (58.2)	

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; OxLDL, oxidized low-density lipoprotein; VAT, visceral adipose tissue.

There was no association between VAT, android-to-gynoid fat mass ratio, or BMI with incident ASCVD events among the overall cohort, adjusted for age, study enrollment site, race, education, systolic blood pressure, current hypertension medication use, current aspirin use, current

statin use, oxidized low-density lipoproteins, diabetes mellitus, and smoking status (Table 2, Table S2). Interaction terms between age and BMI category, age and VAT, and age and android-gynoid ratio were all not significant (data not shown). Increasing age, higher systolic blood pressure,

**Table 2.** Multivariable Adjusted Associations\* (HR [95% CI]) of DXA-VAT and Android–Gynoid Fat Mass Ratios Both With Major ASCVD Events

Characteristic	Model 1 (N=2899)	Model 2 (N=2899)	Model 3 (N=2899)	Model 4 (N=2899)
<b>BMI at sleep visit</b>				
<18.5 kg/m <sup>2</sup>	1.05 (0.15, 7.49)			
18.5 to 24.9 kg/m <sup>2</sup>	Reference			
25 to 29.9 kg/m <sup>2</sup>	1.04 (0.83, 1.31)			
≥30 kg/m <sup>2</sup>	1.13 (0.85, 1.51)			
VAT area (cm <sup>2</sup> ) (per SD increase)		1.02 (0.92, 1.13)		
Android/gynoid fat mass ratio (per SD increase)			1.05 (0.95, 1.17)	
Android fat mass (per SD)				1.08 (0.91, 1.28)
Gynoid fat mass (per SD)				0.94 (0.80, 1.12)

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; DXA, dual energy x-ray absorptiometry; HR, hazard ratio; LDL, low-density lipoprotein; VAT, visceral adipose tissue.

\*Adjusted for age, education, race, systolic blood pressure, current use of hypertension medication, oxidized LDL, smoking status, diabetes mellitus, use of statin medication, use of aspirin, and study enrollment site; parameter coefficients with CIs are shown in Table S2.

and current medication for hypertension were each independently associated with a higher risk of ASCVD events. There was no association between all other covariates (including oxidized low-density lipoproteins) and incident ASCVD.

Within subsets of men defined by BMI category or the subset without any self-reported major comorbid illness at baseline (Table 3), neither VAT nor android–gynoid fat mass ratio were associated with incident ASCVD events. Sensitivity analyses showed that android fat mass and gynoid fat mass, adjusted for each other, were also not associated with incident ASCVD events among all men (Table 2), overweight men (Table 3), or men with no pre-existing comorbid illness (Table 3). Among men with normal BMI, each SD increase of gynoid fat mass, adjusted for android fat mass and all other covariates, was associated with a 37% reduction of incident ASCVD events (hazard ratio 0.63, 95% confidence interval, 0.41–0.97).

## Discussion

In this large cohort of older men, VAT and android–gynoid fat mass ratio had no significant bivariate (unadjusted) or multivariable-adjusted association with incident ASCVD events. This is consistent with the “obesity paradox” hypothesis that with advancing age adipose tissue depots may be associated with higher vitality reflected in lower burden of comorbid illness. However, we also did not find any association of VAT or android–gynoid fat mass ratio within the subset of older men without any pre-existing major comorbid conditions. With advancing age, adipose tissue may also be associated with better preservation of muscle mass. Whether this, or other positive nutritional factors associated with higher levels of adipose tissue in adults over age 70 years, negate the negative effects of VAT are unknown.

Some have hypothesized that central adipose tissue may be particularly deleterious among those with normal BMI

**Table 3.** Multivariable-Adjusted Associations (HR, 95% CI)\* of Regional Fat Depots With Incident ASCVD Events in Key Subsets of Men

Predictor(s) (per SD Increase)	Subset		
	Normal BMI (18.5–24.9 kg/m <sup>2</sup> ) (n=874)	Overweight BMI (25.0–29.9 kg/m <sup>2</sup> ) (n=1427)	No Pre-Existing Major Comorbid Illness <sup>†</sup> (n=1424)
VAT	0.90 (0.67, 1.21)	1.02 (0.83, 1.24)	1.09 (0.92, 1.28)
Android–gynoid fat mass ratio	1.07 (0.89, 1.28)	1.03 (0.89, 1.19)	1.14 (0.98, 1.33)
Android fat mass	1.17 (0.80, 1.73)	1.04 (0.81, 1.34)	1.25 (0.96, 1.65)
Gynoid fat mass	0.63 (0.41, 0.97)	1.00 (0.78, 1.29)	0.83 (0.63, 1.08)

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; HR, hazard ratio; LDL, low-density lipoprotein; VAT, visceral adipose tissue.

\*Adjusted for age, education, race, systolic blood pressure, current use of hypertension medication, oxidized LDL, smoking status, diabetes mellitus, use of statin medication, use of aspirin, and study enrollment site.

<sup>†</sup>Absence of myocardial infarction, stroke, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, Parkinson's disease, rheumatoid arthritis, liver disease, or renal disease.

(“normal weight obesity”). However, neither VAT nor android–gynoid fat mass ratio were associated with incident ASCVD in this subset of older men. Considered as separate predictors, gynoid fat mass adjusted for android fat mass may be protective against ASCVD events among older men with normal BMI. However, further studies would be required to confirm this and explicate the reason(s) for this association.

Our findings are consistent with those from the Health ABC study where VAT predicted incident myocardial infarction among older women but not older men.<sup>3</sup> That prior study had a relatively small number (71) of outcomes events; our study had a much larger number (424) of outcome events, and suggests that VAT is also not associated with a broader range of ASCVD outcomes in older men.

While our study was not designed to examine the effects of interventions to reduce central obesity in these older men, our findings suggest that it is possible that weight loss to reduce central obesity among older obese individuals may not reduce their risks of incident ASCVD. On the other hand, weight loss results in loss of both fat and lean mass, and can reduce muscular strength and increase functional impairment even among obese individuals<sup>25</sup>; these changes may be particularly detrimental among very old adults who already have experienced significant age-related loss of muscle mass,<sup>26</sup> resulting in further functional decline<sup>27</sup> and incident frailty.<sup>28</sup> Therefore, the risks versus benefit of recommendations to lose weight need to be carefully considered in older men on a case-by-case basis. At the least, intentional weight loss in obese very old individuals should be accompanied by appropriate exercise and nutritional interventions to reduce or prevent the loss of lean mass and muscle strength and to preserve functional status.<sup>29,30</sup>

It is uncertain why associations of central fat depots, including VAT, with incident ASCVD may weaken with age and may be different for older men versus older women. VAT is associated with metabolic risk factors such as high-density lipoprotein cholesterol in both sexes, albeit somewhat more strongly in women.<sup>31</sup> Moreover, higher levels of VAT on DXA were associated with lower high-density lipoprotein cholesterol, higher triglycerides, greater insulin resistance, and lower adiponectin concentrations in this cohort of older men.<sup>10</sup> However, the associations between VAT and inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 are weak in older men.<sup>10</sup> Whether or not the associations of inflammatory cytokines and adipocytokines with central adiposity weaken with advancing age, and whether or not changes of these associations with age varies by sex, is not known.

It is also possible that the excess ASCVD risk conferred by central obesity simply becomes less important relative to other risk factors, known and unknown, associated with advancing age. Consistent with this, development and

validation of the pooled ASCVD risk calculator of the American Heart Association and American College of Cardiology revealed that the associations of high-density lipoprotein and total cholesterol with incident ASCVD weakened with advancing age in whites and blacks of both sexes.<sup>21</sup> Similarly, the association of systolic blood pressure with incident ASCVD weakens with advancing age among black women.<sup>21</sup> While we did not see that the association of VAT or android-to-gynoid fat mass ratio varied by age in these analyses, our cohort did not include men younger than age 65 years, and a larger age range may be necessary for this to be clearly seen.

It is also possible that men who survive to be at least age 70 years have VAT that is less injurious to the arterial vasculature compared with younger men. VAT is not homogeneous. For example, there is individual variability in regard to its density (as measured in Hounsfield units on CT), and less dense VAT is more strongly associated with cardiometabolic risk factors.<sup>31</sup> Whether or not this or other characteristics of central adipose tissue depots are different for middle-age compared with older men, and/or vary by sex is unknown. Further investigations of the associations of VAT characteristics with age and sex are needed.

Finally, it may be that the extent of atherosclerotic vascular damage may be more strongly associated with the duration of exposure to a high level of VAT, rather than a 1-time value. VAT tends to increase with increasing age<sup>32</sup>; hence, many men with a high level of VAT at the baseline MrOS sleep visit may not have had much VAT at earlier stages of their lives. If there is a tendency for middle-aged men with lower levels of VAT to “catch up” to their peers who survive to advanced ages, that could weaken the association of a 1-time VAT measurement at older ages with incident ASCVD events.

There are several important strengths of our study. Our study was conducted in a large cohort of older men with comprehensively assessed measures of cardiovascular disease risk factors and obesity. While enrollment in MrOS was limited to community-dwelling men, characteristics of the MrOS study population resemble those of the older men enrolled in the population-based National Health and Nutritional Examination Survey.<sup>33</sup> Incident ASCVD events were carefully adjudicated using a validated protocol. Our study had a large number (424) of outcome events and was well powered to detect small-to-modest associations of our main central adipose tissue measures with incident ASCVD events.

There are also limitations of this study. The MrOS cohort enrolled only older men and therefore is not generalizable to women or younger men. Furthermore, 90% of the present study cohort was white, and this might also limit generalizability to other racial or ethnic groups. We cannot rule out the possibility that measures of VAT using CT or magnetic resonance imaging are associated with incident ASCVD in older men. However, we think that is unlikely since DXA-VAT

is highly correlated with both CT<sup>34–37</sup> and magnetic resonance imaging<sup>34,38</sup> measures of VAT, and since DXA-VAT is as strongly associated with cardiometabolic ASCVD risk factors as CT-VAT in older men.<sup>10</sup> Finally, we ascertained prior diagnoses of comorbid conditions at baseline by self-report, and did not have medical records available to confirm self-reported diagnoses.

In conclusion, central obesity, measured as VAT or android–gynoid fat mass ratio, was not associated with incident ASCVD events among this cohort of older community-dwelling men.

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## Disclosures

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Comparison of Baseline Characteristics of Men Included in the Analyses vs Men Excluded from the Analyses.**

<b>Characteristic</b>	<b>All N=3135</b>	<b>Included in analysis N=2,899</b>	<b>Not included N=236</b>	<b>p-value</b>
Age (years) at sleep visit, mean (SD)	76.4 (5.56)	76.3 (5.53)	77.4 (5.87)	0.0036
Educational Status, N (%)				0.4596
High school or less	666 (21.2)	611 (21.1)	55 (23.3)	
Some college	701 (22.4)	649 (22.4)	52 (22.0)	
College	580 (18.5)	538 (18.6)	42 (17.8)	
Some graduate school	353 (11.3)	320 (11.0)	33 (14.0)	
Graduate school	835 (26.6)	781 (26.9)	54 (22.9)	
Race, N (%)				0.6799
White	2827 (90.2)	2616 (90.2)	211 (89.4)	
Other	308 (9.8)	283 (9.8)	25 (10.6)	
Cigarette Smoking Status, N (%)	(N=3133)		(N=234)	0.2518
Never	1235 (39.4)	1151 (39.7)	84 (35.9)	
Ever	1898 (60.6)	1748 (60.3)	150 (64.1)	

BMI at sleep visit, N(%)	(N=3132)		(N=233)	
<18.5 kg/m <sup>2</sup>	10 (0.3)	9 (0.3)	1 (0.4)	0.6325
18.5 to 24.9 kg/m <sup>2</sup>	935 (29.9)	874 (30.1)	61 (26.2)	
25 to 29.9 kg/m <sup>2</sup>	1547 (49.4)	1427 (49.2)	120 (51.5)	
≥30 kg/m <sup>2</sup>	640 (20.4)	589 (20.3)	51 (21.9)	
Systolic Blood Pressure (mmHg), mean (SD)	(N=3131) 127.0 (16.39)	126.9 (16.18)	(N=232) 127.8 (18.74)	0.4416
oxLDL (U/L), mean (SD)	(N=3035) 44.1 (12.30)	44.1 (12.25)	(N=136) 44.2 (13.26)	0.8916
Diabetes Mellitus, N (%)	(N=3133)		(N=234)	
No	2716 (86.7)	2522 (87.0)	194 (82.9)	0.0765
Yes	417 (13.3)	377 (13.0)	40 (17.1)	
Current Blood Pressure Medication, N (%)				
No	1333 (42.5)	1249 (43.1)	84 (35.6)	0.0252
Yes	1802 (57.5)	1650 (56.9)	152 (64.4)	

Current Statin Medication, N (%)	(N=3134)		(N=235)	
No	1838 (58.6)	1698 (58.6)	140 (59.6)	0.7641
Yes	1296 (41.4)	1201 (41.4)	95 (40.4)	
Aspirin, N (%)	(N=3134)		(N=235)	
No	1316 (42.0)	1208 (41.7)	108 (46.0)	0.2002
Yes	1818 (58.0)	1691 (58.3)	127 (54.0)	

**Table S2. Multi-variable Adjusted Associations of all Covariates (HR [95% C.I.]) with major ASCVD events, adjusted for each other.**

<b>Characteristic</b>	<b>Model 1 N=2,899</b>	<b>Model 2 N=2,899</b>	<b>Model 3 N=2,899</b>	<b>Model 4 N=2,899</b>
Age (years) at sleep visit (per SD increase)	1.45 (1.32, 1.60)	1.45 (1.31, 1.59)	1.45 (1.32, 1.60)	1.45 (1.31, 1.60)
<b>Educational Status</b>				
High school or less	Reference	Reference	Reference	Reference
Some college	1.04 (0.78, 1.38)	1.04 (0.78, 1.38)	1.04 (0.78, 1.38)	1.04 (0.78, 1.38)
College	1.00 (0.73, 1.36)	1.00 (0.73, 1.36)	1.00 (0.73, 1.36)	1.00 (0.73, 1.36)
Some graduate school	0.76 (0.52, 1.10)	0.75 (0.51, 1.10)	0.76 (0.52, 1.10)	0.75 (0.52, 1.10)
Graduate school	0.80 (0.59, 1.08)	0.79 (0.59, 1.07)	0.80 (0.59, 1.08)	0.80 (0.59, 1.08)
Race (Other vs. White)	0.87 (0.61, 1.23)	0.87 (0.61, 1.24)	0.87 (0.61, 1.23)	0.87 (0.61, 1.24)
Cigarette Smoking Status (Ever vs. Never)	1.07 (0.88, 1.31)	1.07 (0.88, 1.31)	1.07 (0.88, 1.31)	1.07 (0.88, 1.31)
Systolic Blood Pressure (mmHg) (per SD increase)	1.24 (1.13, 1.36)	1.24 (1.13, 1.36)	1.24 (1.13, 1.36)	1.24 (1.13, 1.36)
oxLDL (U/L) (per SD increase)	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)	1.01 (0.90, 1.12)	1.01 (0.91, 1.12)
Diabetes Mellitus (Yes vs. No)	1.19 (0.90, 1.57)	1.20 (0.90, 1.58)	1.19 (0.90, 1.57)	1.19 (0.90, 1.58)

Current Blood Pressure Medication (Yes vs. No)	1.56 (1.26, 1.94)	1.57 (1.26, 1.95)	1.57 (1.26, 1.94)	1.57 (1.26, 1.94)
Current Statin Medication (Yes vs. No)	0.88 (0.71, 1.09)	0.88 (0.71, 1.09)	0.87 (0.71, 1.09)	0.88 (0.71, 1.09)
Aspirin use (Yes vs. No)	1.02 (0.83, 1.24)	1.02 (0.83, 1.25)	1.02 (0.83, 1.24)	1.02 (0.83, 1.24)
BMI at sleep visit				
<18.5 kg/m <sup>2</sup>	1.05 (0.15, 7.49)			
18.5 to 24.9 kg/m <sup>2</sup>	Reference			
25 to 29.9 kg/m <sup>2</sup>	1.04 (0.83, 1.31)			
≥30 kg/m <sup>2</sup>	1.13 (0.85, 1.51)			
VAT Area (cm <sup>2</sup> ) (per SD increase)		1.02 (0.92, 1.13)		
Android/Gynoid fat mass ratio (per SD increase)			1.05 (0.95, 1.17)	
Android Fat Mass (per SD)				1.08 (0.91, 1.28)
Gynoid Fat Mass (per SD)				0.94 (0.80, 1.12)