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Body Fat Distribution, Cardiometabolic Traits, and Risk of Major Lower-Extremity Arterial Disease in Postmenopausal Women

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OBJECTIVE

To assess the relationship between body fat distribution and incident lower-extremity arterial disease (LEAD).

RESEARCH DESIGN AND METHODS

We included 155,925 postmenopausal women with anthropometric measures from the Women's Health Initiative who had no known LEAD at recruitment. A subset of 10,894 participants had body composition data quantified by DXA. Incident cases of symptomatic LEAD were ascertained and adjudicated through medical record review.

RESULTS

We identified 1,152 incident cases of LEAD during a median 18.8 years follow-up. After multivariable adjustment and mutual adjustment, waist and hip circumferences were positively and inversely associated with risk of LEAD, respectively (both *P*-trend < 0.0001). In a subset (n = 22,561) where various cardiometabolic biomarkers were quantified, a similar positive association of waist circumference with risk of LEAD was eliminated after adjustment for diabetes and HOMA of insulin resistance (*P*-trend = 0.89), whereas hip circumference remained inversely associated with the risk after adjustment for major cardiometabolic traits (*P*-trend = 0.0031). In the DXA subset, higher trunk fat (*P*-trend = 0.0081) and higher leg fat (*P*-trend < 0.0001) were associated with higher and lower risk of LEAD, respectively. Further adjustment for diabetes, dyslipidemia, and blood pressure diminished the association for trunk fat (*P*-trend = 0.49), yet the inverse association for leg fat persisted (*P*-trend = 0.0082).

CONCLUSIONS

Among U.S. postmenopausal women, a positive association of upper-body fat with risk of LEAD appeared to be attributable to traditional risk factors, especially insulin resistance. Lower-body fat was inversely associated with risk of LEAD beyond known risk factors.

Following coronary heart disease (CHD) and ischemic stroke, lower-extremity arterial disease (LEAD) ranks as the third leading atherosclerotic disease worldwide

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(1–3). In the U.S., an estimated 7.2% (~8.5 million) of adults aged ≥40 years are affected by LEAD (3). LEAD is an important complication for diabetes and shares several additional risk factors (i.e., smoking, hypertension, dyslipidemia) with other atherosclerotic cardiovascular disease (CVD) (1,4). While obesity (especially abdominal obesity) is well recognized as a risk factor for atherosclerotic CVD (5), the association of obesity with risk of LEAD remains unclear.

Only a few studies have assessed overall adiposity, as defined by BMI, or abdominal adiposity, as reflected by waist size or waist-to-hip ratio (WHR), in relation to risk of LEAD, and the findings are mixed. Some found that both types of obesity were associated with higher risk of LEAD (6–8) and that the associations appeared to be largely (6) or totally (7) dependent on known clinical risk factors for LEAD. Other studies showed no clear associations between BMI (9–14) or waist circumference and risk of LEAD (12,13). It is notable that biological functions of adipose tissue may be location specific. Upper- and lower-body fat depots have been widely demonstrated to have opposite impacts (i.e., detrimental vs. beneficial) on various metabolic processes, including glycemic control and lipid storage (15–18). Thus, it is important to consider both the amount and the location of body fat when assessing the health consequence of excess body fat accumulation. Furthermore, anthropometric measures are known to have a limited ability to distinguish between fat mass and fat-free mass. Thus, use of DXA-derived data on regional fat mass may improve the understanding of the association between body fat distribution and risk of LEAD.

In the Women's Health Initiative (WHI), a large prospective study of U.S. postmenopausal women (19), we examined the association of body fat distribution with risk of LEAD. In addition to traditional anthropometric measures commonly used in other obesity studies, we further evaluated the relationship between DXA-determined body fat mass and risk of LEAD.

RESEARCH DESIGN AND METHODS

Study Design and Population

Details of the WHI design and study population have been reported elsewhere (19). Briefly, between 1993 and 1998, 161,808 postmenopausal women aged 50–79 years were recruited at 40 clinical centers throughout the U.S. Participants were either enrolled in the WHI Observational Study or in one or more of the WHI clinical trials that evaluated the health effects of hormone therapy (two trials), low-fat diet modification, and/or calcium and vitamin D supplementation. After the end of the initial WHI study in 2005, the first (2005–2010) and the second (2010–2020) WHI extension studies continued follow-up of all women who consented. The study was approved by the institutional review boards of all participating institutions, and all participants provided written informed consent at initial enrollment and for the extension studies.

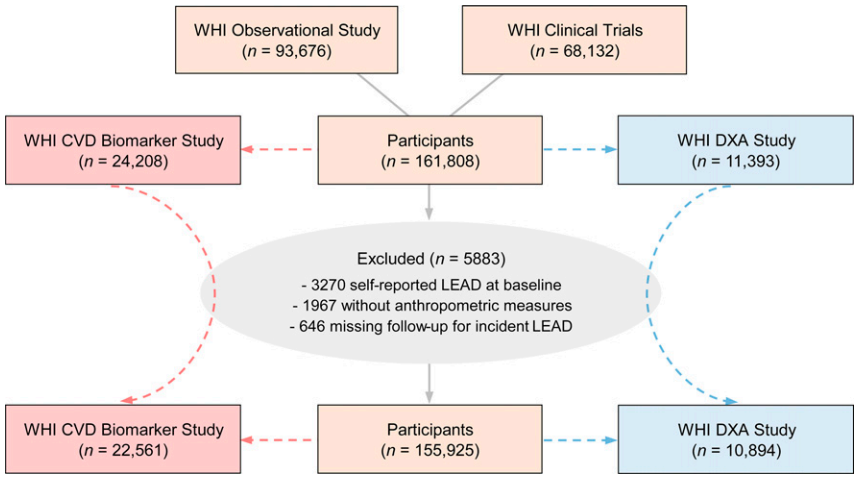

Figure 1—Flow diagram of participant selection.

For the current analysis, we excluded 3,270 participants with self-reported LEAD at baseline, 1,967 participants without anthropometric measures, and 646 participants missing follow-up information for incident LEAD. The final analytic sample comprised 155,925 participants (Fig. 1).

Assessments of Anthropometric Measures and Body Composition

Weight and height were measured without shoes on a beam scale to the nearest 0.1 kg and a wall-mounted stadiometer to the nearest 0.1 cm, respectively (20). Waist and hip circumferences were measured at the umbilicus and at the maximum circumference, respectively, to the nearest 0.1 cm (20). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2), and WHR was the ratio of the circumference of the waist to that of the hips.

At enrollment, a subset of 11,393 participants (10,894 were in the present analysis) (Fig. 1) underwent whole-body DXA scans at three designated WHI clinical centers (Birmingham, AL; Tucson/Phoenix, AZ; and Pittsburgh, PA), where participants' body compositions, including whole-body and regional fat mass, bone mass, and lean mass, were determined using the fan-beam mode of QDR 2000, 2000+, or 4500 scanners (Hologic, Waltham, MA). Standard WHI protocols were used for the positioning and analysis of the DXA scans by trained and certified radiology technicians. More details regarding the procedures and quality control of the DXA scans have been presented elsewhere (21). Participants in the DXA study had a lower socioeconomic status but similar anthropometric measures compared with participants of the whole sample (Supplementary Table 1).

Outcome Ascertainment

The outcome of interest in our analysis was incident symptomatic LEAD. Participants reported overnight hospitalizations and emergency department visits on medical update forms collected semiannually, and corresponding medical records were scrutinized for the potential outcome of interest (22). Locally and/or centrally trained physician adjudicators classified outcomes

from medical record review. Potential cases were confirmed by multiple procedures (Supplementary Table 2). Most (94.0%) of the incident cases of LEAD were confirmed by one or both of the following: *1*) surgery, angioplasty, or thrombolysis for LEAD and *2*) obstruction or ulcerated plaque (i.e., ≥50% of the diameter or ≥75% of the cross-sectional area) demonstrated on ultrasound or angiogram of the iliac arteries or below.

Assessments of Covariates and Biomarkers

Information on demographic and socioeconomic characteristics; reproductive, medical, and family histories; cigarette smoking; and alcohol drinking was collected at baseline through self-report. Dietary intake was assessed from a self-administered, validated, food frequency questionnaire (23). Recreational physical activity was quantified using the WHI physical activity questionnaire, and the data were summarized in MET-h/week (24). Systolic and diastolic blood pressure were measured through auscultation using a conventional sphygmomanometer after participants rested quietly for 5 min in a clinic room without excessive noise, and the average of two measures taken at least 30 s apart was recorded (25). Previous diagnosis and treatment of hypertension, hyperlipidemia, or diabetes were reported through a questionnaire. Participants were also instructed to bring prescription medication containers during the baseline screening interview. Dyslipidemia was defined as a report of a physician's diagnosis of hyperlipidemia or recorded statin use.

A subset of 24,208 participants (22,561 were in the present analysis) (Fig. 1) constituted the WHI CVD Biomarker Study, where White women were randomly drawn from the hormone therapy trial, and non-White women were selected from all parts of the WHI to maximize ethnic diversity. As a result, 35.6% and 16.5% of the participants in this subcohort were African American and Hispanic/Latina, respectively. Along with the diverse ethnic backgrounds, participants in the WHI CVD Biomarker Study had a lower socioeconomic status, higher rates of hypertension and diabetes, and slightly higher levels of anthropometric measures than participants of the whole sample (Supplementary Table 1). Using fasting blood samples collected at baseline, serum glucose and insulin, major lipids, and high-sensitivity C-reactive protein (hs-CRP) were quantified. HOMA of insulin resistance (HOMA-IR) was derived from glucose and insulin measurements (21). Other biomarkers, including serum/plasma fatty acids, apolipoproteins, LDL and HDL (with information on both concentration and size of lipoproteins), sex hormone–binding globulin, and adiponectin were quantified in a number of case-control studies nested within the WHI. These measurements of biomarkers have been found to be reproducible and have acceptable coefficients of variation in quality control studies (Supplementary Table 3).

Statistical Analysis

Baseline characteristics of study participants were described by quartiles of waist and hip circumference, respectively. Measures of waist and hip circumference were substantially correlated (Pearson $r = 0.79$). Thus, participant characteristics according to quartile of waist circumference were standardized to the levels of hip circumference (5-cm intervals), and data by quartile of hip circumference were standardized to the levels of waist circumference (5-cm intervals). Pearson partial correlations between anthropometric measures and body fat mass were calculated, with adjustment for age, race/ethnicity, and study group.

Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs of LEAD for each anthropometric measure. Person-time of follow-up was calculated from the date of enrollment to the date of diagnosis of LEAD, death, withdrawal from the study, or end of the most recent follow-up (March 2019), whichever came first. The first model was adjusted for age, race/ethnicity, education, annual family income, and study group. The second (full) model was additionally adjusted for smoking status, pack-years of smoking, alcohol consumption, recreational physical activity, diet-quality score (Alternate Healthy Eating Index-2010, excluding alcohol), hormone therapy, aspirin use, use of nonsteroidal anti-inflammatory drug, history of CHD or stroke, and height (not for BMI). We used height as an indicator of total body size because of the high correlations among BMI and waist and hip circumference (Supplementary Fig. 1). An additional exploratory analysis further adjusted for potential intermediate factors, including dyslipidemia, antihypertensive drugs, systolic blood pressure, and reported diabetes. For all models, waist and hip circumferences were mutually adjusted for each other by adding both measures in the same Cox model.

Potential nonlinearity for the examined associations was evaluated using restricted cubic spline models with three knots at the 10th, 50th, and 90th percentiles of the distributions. The main analyses (model 2) for waist and hip circumference were further stratified and tested for potential interactions with age, race/ethnicity, smoking status, BMI, recreational physical activity, hormone use at baseline, years since menopause, and study group. Several sensitivity analyses were performed by excluding *1*) incident cases of LEAD that were identified within the first 5 or 10 years of follow-up, *2*) participants who were not diagnosed with LEAD and died as a result of CVD during the follow-up period because CVD deaths may have occurred competitively with LEAD, and *3*) participants with self-reported CHD or stroke at baseline. Given the high correlation between waist and hip circumference, we also derived (relative) measures of predicted waist circumference and predicted hip circumference and assessed their associations with risk of LEAD. The measure of predicted waist circumference was the residuals from a multivariable linear regression model in which waist circumference was regressed against hip circumference and age, study group, race, smoking status, and hormone use at baseline, and the measure was not associated with hip circumference ($r < 0.0001$). The measure of predicted hip circumference was likewise derived and was not associated with waist circumference ($r < 0.0001$).

Next, we examined associations of waist and hip circumference with the multiple cardiometabolic biomarkers described above. Biomarker concentrations were transformed using a rank-based inverse normal transformation to approximate a normal distribution. The associations were examined using

Pearson partial correlations after multivariable adjustment. Then, we examined the associations of waist and hip circumference with risk of LEAD among 22,561 participants from the WHI CVD Biomarker Study and adjusted the associations for various metabolic factors (i.e., hs-CRP, antihypertensive drugs and systolic blood pressure, reported diabetes and HOMA-IR, dyslipidemia and serum major lipids) both individually and concordantly.

Finally, we analyzed body composition data available from a subset of 10,894 participants. Whole-body and regional (trunk and leg) fat mass as well as the ratio of trunk-to-leg fat mass were examined for association with risk of LEAD. Because of the positive correlations between body fat mass and lean mass (e.g., $r = 0.45$ between trunk fat mass and trunk lean mass), the multivariable models for these analyses further included whole-body or regional lean mass (e.g., the analysis for leg fat mass was further adjusted for leg lean mass) to address the possibility of residual confounding by body lean mass. Statistical analyses were performed using Stata 15.1 software (StataCorp).

RESULTS

Participant Characteristics

Participants with higher waist circumference were older, had lower levels of education and family income, were more likely to be current smokers, and were less likely to be using hormone therapy at baseline (Table 1). Those with higher waist circumference were also more likely to have hypertension, dyslipidemia, diabetes, and CHD/stroke. Conversely, after adjusting for waist circumference, distributions of these participant characteristics by hip circumference were in directions opposite to the distributions by waist circumference. Higher waist circumference and higher hip circumference were both associated with a lower level of recreational physical activity and a lower diet-quality score.

BMI, waist circumference, and hip circumference were highly correlated with one another ($r = 0.79$ to $\sim$0.85) (Supplementary Fig. 1). Correlations between BMI and whole-body fat mass ($r = 0.90$), waist circumference and trunk fat mass ($r = 0.87$), and hip circumference and leg fat mass ($r = 0.71$) were also substantial. WHR was moderately correlated with the ratio of trunk-to-leg fat mass ($r = 0.56$).

Anthropometric Measures and Risk of LEAD

During up to 25.1 years of follow-up (median 18.8 years), 1,152 incident cases of LEAD were identified. After multivariable adjustment for demographic and socioeconomic factors, lifestyle behaviors, and height in addition to mutual adjustment for one another, waist and hip circumferences exhibited opposite (i.e., positive vs. inverse) associations with risk of LEAD (model 2 in Table 2). The multivariable-adjusted HRs comparing the highest with the lowest quartiles were 2.62 (95% CI 2.04–3.36) for waist circumference (P-trend $<$ 0.0001) and 0.41 (95% CI 0.32–0.51) for hip circumference (P-trend $<$0.0001). After further adjustment for reported diabetes, dyslipidemia, and blood pressure measures, the association between waist circumference and LEAD was substantially attenuated ($HR_{Q4\ vs.\ Q1}$ 1.57 [95% CI 1.21–2.03]; P-trend = 0.0009), but the association between hip circumference and LEAD did not change materially ($HR_{Q4\ vs.\ Q1}$ 0.46 [95% CI 0.36–0.58]; P-trend $<$ 0.0001). There was no clear evidence for a nonlinear association between waist or hip circumference and risk of LEAD (Supplementary Fig. 2).

WHR remained associated with a moderately higher risk of LEAD after multivariable adjustment and further adjustment for reported diabetes, dyslipidemia, and blood pressure measures (Table 2). There was no association between BMI and risk of LEAD after the multivariable adjustment (P-trend = 0.47). However, BMI was inversely associated with risk of LEAD after further adjustment for reported diabetes, dyslipidemia, and blood pressure ($HR_{Q4\ vs.\ Q1}$ 0.67 [95% CI 0.55–0.80]; P-trend $<$ 0.0001).

The positive association of waist circumference and the inverse association of hip circumference with risk of LEAD were observed across various population subgroups defined by baseline participant characteristics as well as in a number of sensitivity analyses (Fig. 2). Both associations appeared to vary by smoking status. The association for waist circumference was stronger in never smokers than in former or current smokers (P-interaction = 0.0001), while the association for hip circumference was most pronounced in current smokers (P-interaction = 0.0005). The measures of predicted waist circumference and predicted hip circumference were also oppositely (i.e., positively and inversely) associated with risk of LEAD (Supplementary Table 4).

Waist circumference was moderately associated with various biomarkers (especially HOMA-IR, $r = 0.40$) in directions that may increase cardiometabolic risk (Supplementary Fig. 3). Conversely, hip circumference was associated with these biomarkers, although modestly, in risk-decreasing directions. There were 334 incident cases of LEAD among the 22,561 participants of the WHI CVD Biomarker Study. In this subset, similar to the results in the whole study sample, waist and hip circumferences were positively and inversely associated with risk of LEAD, respectively, after multivariable adjustment (model 2 in Table 3). The association of waist circumference with risk of LEAD was attenuated or eliminated after further adjustment for metabolic factors, especially reported diabetes and HOMA-IR ($HR_{Q4\ vs.\ Q1}$ 1.01 [95% CI 0.62–1.64]; P-trend = 0.89). For hip circumference, the association was not substantially altered after adjustment for all known risk factors ($HR_{Q4\ vs.\ Q1}$ 0.47 [95% CI 0.29–0.75]; P-trend = 0.0031).

Body Fat Mass and Risk of LEAD

There were 119 incident cases of LEAD among the 10,894 participants with body composition data. After adjustment for multiple potential confounders (model 2, including trunk or leg lean mass) in addition to mutual adjustment, higher trunk fat mass was associated with an increased risk of LEAD ($HR_{Q4\ vs.\ Q1}$ 2.56 [95% CI 1.28–5.12]; P-trend = 0.0081), while higher leg fat mass was associated with a 75% reduction in the risk of LEAD when comparing extreme quartiles ($HR_{Q4\ vs.\ Q1}$ 0.25 [95% CI 0.13–0.49]; P-trend $<$0.0001) (Table 4). In stratified analyses with a small number of cases in each group, for both trunk and leg fat, the associations with risk of LEAD were stronger in current

Table 1—Baseline participant characteristics according to quartile of waist or hip circumference in the WHI (n = 155,925)

	Waist circumference				Hip circumference			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Age, years	60.8	62.8	64.1	64.9	65.7	63.8	62.4	61.1
Race/ethnicity								
White	84.8	82.5	78.8	81.1	80.4	84.2	84.3	80.1
Black/African American	8.4	8.9	11.3	11.0	7.0	8.2	9.4	14.6
Hispanic/Latina	3.2	4.1	4.6	4.0	4.3	4.1	3.7	3.4
Other/unknown	3.6	4.5	5.2	3.9	8.4	3.5	2.6	1.9
Education ≥ college degree	47.2	43.0	36.7	32.0	39.1	40.2	40.1	41.3
Annual family income ≥$50,000	49.1	43.8	35.8	31.2	38.1	40.0	42.0	42.0
Smoking status								
Never	56.9	52.0	51.0	47.3	49.3	50.4	52.2	55.1
Former	37.0	41.3	41.1	44.3	41.1	42.0	41.7	39.8
Current	6.1	6.7	7.8	8.4	9.5	7.6	6.1	5.1
Moderate alcohol consumption*	19.9	18.6	15.4	12.5	17.4	17.0	17.4	15.6
Recreational PA, MET-h/week	15.0	13.1	11.3	9.9	13.6	12.8	12.0	10.9
AHEI-2010 (excluding alcohol)	49.1	47.9	46.7	45.7	47.8	47.4	47.2	46.8
Hormone replacement therapy								
Never	36.1	40.8	45.8	50.9	44.7	42.9	41.8	44.5
Former	14.0	15.8	17.3	17.8	17.5	16.5	16.2	14.5
Current	50.0	43.4	37.0	31.3	37.8	40.5	42.1	40.9
Hypertension	27.0	33.2	44.8	52.2	41.3	38.8	36.8	37.7
Dyslipidemia	11.3	13.1	18.2	21.8	18.6	17.0	13.9	12.8
Reported diabetes	3.0	2.7	6.9	15.8	10.6	7.7	6.1	5.5
Reported CHD or stroke	1.6	3.4	5.3	6.9	5.8	4.7	3.8	3.3
Study group								
WHI observational study	61.3	59.4	55.2	51.7	63.3	59.1	54.9	51.7
Control of WHI clinical trials	15.1	16.0	17.6	18.5	14.5	16.0	17.3	17.9
Active arms of WHI clinical trials	23.6	24.6	27.1	29.8	22.2	24.9	27.8	30.5
Anthropometric measures								
BMI, kg/m^2	22.4	25.5	28.7	34.8	22.5	25.4	28.5	34.9
Waist circumference, cm	72.6	81.1	89.5	101.6	73.8	81.1	88.2	101.6
Hip circumference, cm	95.5	101.9	107.8	119.8	94.9	102.1	108.5	119.2
WHR	0.74	0.79	0.83	0.88	0.80	0.80	0.82	0.83
Height, cm	161.0	161.8	161.9	162.5	159.7	161.9	162.6	162.8

Data are mean for continuous variables and % for categorical variables. All results (except for anthropometric measures) by quartile of waist circumference were standardized to hip circumference (5-cm interval) and vice versa. AHEI, Alternate Healthy Eating Index; NA, not applicable; PA, physical activity. *Alcohol consumption of 5–15 g/day.

smokers than in former or never smokers (Supplementary Table 5). The positive association of trunk fat with risk of LEAD was eliminated after further adjustment for reported diabetes, dyslipidemia, and blood pressure measures ($HR_{Q4\ vs.\ Q1}$ 1.33 [95% CI 0.65–2.73]; P-trend = 0.49). The inverse association between leg fat and risk of LEAD remained significant after such an additional adjustment ($HR_{Q4\ vs.\ Q1}$ 0.41 [95% CI 0.21–0.82]; P-trend = 0.0082). Whole-body fat mass and the ratio of trunk-to-leg fat mass were not associated with risk of LEAD after additional adjustment for the metabolic factors (Supplementary Table 6).

Associations of trunk and leg fat mass with cardiovascular biomarkers were similar but stronger compared with those for waist and hip circumference, respectively (e.g., Pearson correlation coefficients with HOMA-IR were r = 0.54 for trunk fat mass and r = −0.25 for leg fat mass) (Supplementary Fig. 3).

CONCLUSIONS

In a large prospective study of U.S. postmenopausal women, we found that higher waist circumference was associated with a higher risk of LEAD, whereas higher hip circumference was associated with a lower risk of LEAD. In a subset of participants with additional measures of key cardiometabolic biomarkers, the positive association between waist circumference and LEAD was completely eliminated by further adjustment for diabetes and HOMA-IR, yet the inverse association between hip circumference and LEAD seemed to be not fully explained by traditional cardiometabolic risk factors. These findings were further supported by our analyses using data

Table 2—Anthropometric measures and risk of LEAD in the WHI (n = 155,925)

	Quartile					
	Q1	Q2	Q3	Q4	*P*-trend	Continuous*
Waist circumference						
Median (range), cm	71.0 (<76.0)	80.0 (76.0–84.4)	89.0 (84.5–94.7)	102.5 (≥94.8)		
Cases, *n*	185	276	318	373		
Person-years	603,801	672,968	614,014	579,174		
Model 1†	1.00 (Referent)	1.53 (1.25–1.86)	2.25 (1.81–2.79)	3.54 (2.77–4.52)	<0.0001	1.32 (1.25–1.38)
Model 2†	1.00 (Referent)	1.37 (1.12–1.67)	1.81 (1.46–2.25)	2.62 (2.04–3.36)	<0.0001	1.24 (1.17–1.31)
Model 2 + metabolic factors†‡	1.00 (Referent)	1.19 (0.97–1.45)	1.33 (1.07–1.66)	1.57 (1.21–2.03)	0.0009	1.09 (1.02–1.16)
Hip circumference						
Median (range), cm	94.0 (<97.9)	101.0 (98.0–104.5)	108.0 (104.5–112.4)	120.0 (≥112.5)		
Cases, *n*	302	296	269	285		
Person-years	578,405	666,418	616,119	609,014		
Model 1†	1.00 (Referent)	0.62 (0.52–0.74)	0.44 (0.36–0.54)	0.32 (0.26–0.41)	<0.0001	0.73 (0.68–0.78)
Model 2†	1.00 (Referent)	0.69 (0.58–0.83)	0.53 (0.43–0.65)	0.41 (0.32–0.51)	<0.0001	0.77 (0.71–0.82)
Model 2 + metabolic factors†‡	1.00 (Referent)	0.73 (0.61–0.88)	0.60 (0.49–0.73)	0.46 (0.36–0.58)	<0.0001	0.79 (0.73–0.86)
WHR						
Median (range)	0.73 (<0.76)	0.78 (0.76–0.80)	0.83 (0.81–0.85)	0.90 (≥0.86)		
Cases, *n*	150	246	310	446		
Person-years	662,181	632,842	606,787	568,146		
Model 1	1.00 (Referent)	1.47 (1.20–1.80)	1.72 (1.42–2.10)	2.41 (2.00–2.91)	<0.0001	1.25 (1.20–1.31)
Model 2	1.00 (Referent)	1.30 (1.06–1.59)	1.45 (1.19–1.76)	1.88 (1.55–2.27)	<0.0001	1.21 (1.14–1.27)
Model 2 + metabolic factors‡	1.00 (Referent)	1.20 (0.97–1.47)	1.20 (0.98–1.46)	1.31 (1.08–1.60)	0.0090	1.09 (1.02–1.16)
BMI						
Median (range), kg/m^2	22.0 (<23.7)	25.3 (23.7–26.8)	28.7 (26.9–31.0)	34.6 (≥31.1)		
Cases, *n*	254	303	295	300		
Person-years	636,857	632,391	613,767	586,941		
Model 1	1.00 (Referent)	1.09 (0.92–1.28)	0.97 (0.82–1.15)	0.98 (0.83–1.17)	0.53	0.95 (0.90–1.01)
Model 2	1.00 (Referent)	1.10 (0.93–1.31)	0.98 (0.83–1.16)	0.98 (0.82–1.17)	0.47	0.95 (0.90–1.00)
Model 2 + metabolic factors‡	1.00 (Referent)	0.98 (0.83–1.16)	0.79 (0.67–0.94)	0.67 (0.55–0.80)	<0.0001	0.84 (0.79–0.89)

Data are HR (95% CI) unless otherwise indicated. Model 1 was adjusted for age (years), race/ethnicity (White, Black/African American, Hispanic/Latina, other/unknown), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and study group (three variables with each being classified as observational, control, and intervention). Model 2 was adjusted for covariates in model 1 plus smoking status (never, former, current), pack-years of smoking (for current smokers), alcohol consumption (0, 0 to <5, 5 to <15, 15 to <25, ≥25 g/day), recreational physical activity (MET-h/week), diet-quality score (Alternate Healthy Eating Index-2010, excluding alcohol), hormone replacement therapy (never, former, current [<5, 5 to <10, 10 to <15, ≥15 years]), aspirin use (never, ever), use of nonsteroidal anti-inflammatory drug (never, ever), history of CHD or stroke (yes, no), and height (cm; not for BMI). *Scales are 10 cm for waist and hip circumference, 0.1 for WHR, and 5 kg/m^2 for BMI. †Waist and hip circumferences were mutually adjusted for each other. ‡Including reported diabetes (yes, no), dyslipidemia (yes, no), use of antihypertensive drugs (yes, no), and systolic blood pressure (mmHg).

on DXA-assessed body fat mass in which trunk fat was positively and leg fat inversely associated with risk of LEAD.

Multiple lines of evidence support the notion that regional fat depots are functionally distinct (15–17). Such differences are even found for apparently similar abdominal subcutaneous and gluteofemoral subcutaneous adipose tissue, with the latter being associated with reduced severity of inflammation and favorable patterns of glycemic and lipid metabolism and adipokine release (15–18). Expression of a set of genes that may shape the functional characteristics of adipose tissue also appears to be depot specific (26–28). In a recent large analysis of a U.K. population, a genetic score of 22 single nucleotide polymorphisms specific to lower hip circumference (and independent of waist circumference) was associated with lower gluteofemoral and leg fat (29). A higher level of this genetic score was further associated with poorer profiles of various cardiometabolic traits and higher risks of diabetes and CHD. A genetically determined favorable adiposity phenotype (identified by genome-wide association studies using body fat percentage and metabolic biomarkers) has been repeatedly associated with higher subcutaneous but lower visceral adipose tissue as well as with lower risks of various cardiometabolic diseases (30–32). Among obese individuals, measures of waist and hip circumference were oppositely (i.e., positively and inversely) associated with postprandial lipemia after a high-fat meal (33).

Only a few studies have examined the associations between measures of general or central adiposity and incident LEAD, and the findings are mixed. In the U.S. Atherosclerosis Risk in Communities study (6), higher BMI, waist circumference, and WHR all were associated with a higher risk of hospitalizations related to LEAD. After further adjustment for a number of clinical risk factors, including diabetes, the associations were attenuated substantially. Likewise, in a cohort of 15,737 Scottish men and women (7), these three adiposity measures were associated with a higher risk

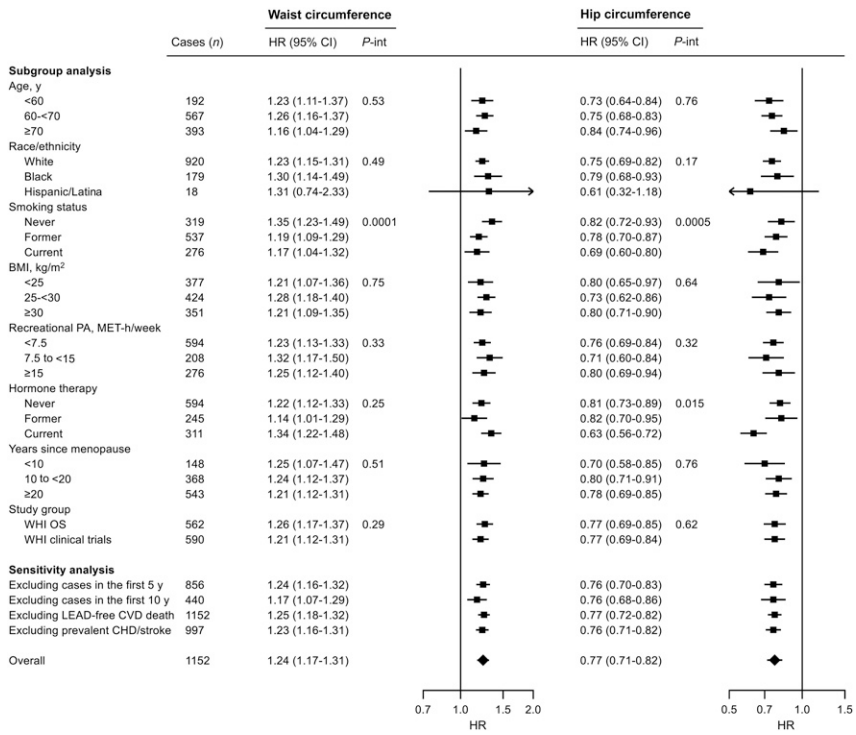

Figure 2—Subgroup and sensitivity analyses for the association of waist or hip circumference with risk of LEAD. Results are for each additional 10-cm increment in waist or hip circumference, with adjustment for covariates listed for model 2 of Table 2 (where appropriate). OS, Observational Study; PA, physical activity; P-int, *P* value for interaction.

of LEAD in age-adjusted models (only for women) but not after adjusting for lifestyle and clinical risk factors. A positive association between waist circumference and risk of LEAD was also found in the U.S. Multi-Ethnic Study of Atherosclerosis (8) in which adjustment for clinical risk factors was not performed. Other studies have found no significant association with BMI (9,12–14) or waist circumference (12,13) or a positive association with BMI only in specific subgroups of the study population (10,11) (e.g., never smokers [10]).

In line with previous findings (6,7), we found that the associations between waist circumference or WHR and risk of LEAD were largely attenuated (but remained significant) after adjustment for reported diabetes, dyslipidemia, and blood pressure measures. The higher risk of LEAD associated with a larger waist size was consistent across BMI categories, supporting the notion that being centrally obese is detrimental regardless of total body size (21,34,35). The positive association between waist circumference and risk of LEAD was completely eliminated by further

Table 3—Waist and hip circumference and risk of LEAD in the WHI CVD Biomarker Study (*n* = 22,561)

	Quartile					
	Q1	Q2	Q3	Q4	*P*-trend	Per 10-cm increment
Waist circumference						
Median (range), cm	74.5 (<79.5)	84.0 (79.6–88.4)	93.0 (88.5–98.3)	106.0 (≥98.4)		
Cases, *n*	82	77	83	92		
Person-years	95,452	94,128	91,690	87,873		
Model 2	1.00 (Referent)	1.12 (0.80–1.58)	1.40 (0.96–2.03)	1.94 (1.25–3.01)	0.0020	1.17 (1.05–1.30)
Model 2 + hs-CRP	1.00 (Referent)	1.03 (0.74–1.45)	1.22 (0.83–1.78)	1.63 (1.04–2.55)	0.026	1.12 (1.00–1.25)
Model 2 + BP measures*	1.00 (Referent)	1.03 (0.74–1.44)	1.22 (0.84–1.77)	1.60 (1.03–2.49)	0.027	1.12 (0.99–1.25)
Model 2 + reported diabetes + HOMA-IR	1.00 (Referent)	0.89 (0.63–1.26)	0.92 (0.62–1.36)	1.01 (0.62–1.64)	0.89	0.99 (0.87–1.13)
Model 2 + dyslipidemia + major lipids†	1.00 (Referent)	0.94 (0.66–1.32)	1.05 (0.70–1.54)	1.37 (0.86–2.18)	0.14	1.07 (0.95–1.21)
Model 2 + all above	1.00 (Referent)	0.76 (0.54–1.09)	0.73 (0.49–1.10)	0.78 (0.47–1.27)	0.42	0.89 (0.77–1.04)
Hip circumference						
Median (range), cm	95.5 (<99.9)	103.0 (100.0–106.9)	110.5 (107.0–115.9)	123.0 (≥116.0)		
Cases, *n*	102	76	88	68		
Person-years	87,935	92,923	97,620	90,665		
Model 2	1.00 (Referent)	0.67 (0.48–0.93)	0.60 (0.42–0.87)	0.38 (0.24–0.59)	0.0001	0.80 (0.70–0.91)
Model 2 + hs-CRP	1.00 (Referent)	0.65 (0.47–0.91)	0.58 (0.40–0.84)	0.35 (0.22–0.55)	<0.0001	0.78 (0.68–0.89)
Model 2 + BP measures*	1.00 (Referent)	0.69 (0.50–0.95)	0.63 (0.44–0.91)	0.40 (0.25–0.62)	0.0001	0.81 (0.71–0.93)
Model 2 + reported diabetes + HOMA-IR	1.00 (Referent)	0.72 (0.52–0.99)	0.68 (0.47–0.98)	0.44 (0.28–0.70)	0.0007	0.84 (0.73–0.95)
Model 2 + dyslipidemia + major lipids†	1.00 (Referent)	0.69 (0.50–0.96)	0.68 (0.47–0.98)	0.45 (0.28–0.71)	0.0011	0.84 (0.73–0.96)
Model 2 + all above	1.00 (Referent)	0.73 (0.52–1.01)	0.71 (0.49–1.03)	0.47 (0.29–0.75)	0.0031	0.85 (0.75–0.97)

Data are HR (95% CI) unless otherwise indicated. BP, blood pressure. *Including use of antihypertensive drugs and systolic BP. †Including triglycerides and HDL and LDL cholesterol.

Table 4—Trunk and leg fat mass and risk of LEAD in the WHI (*n* = 10,894)

	Quartile					
	Q1	Q2	Q3	Q4	*P*-trend	Per 5-kg increment
Trunk fat mass						
Median (range), kg	8.3 (<10.6)	12.6 (10.6–14.4)	16.4 (14.5–18.7)	22.3 (≥18.8)		
Cases, *n*	25	33	31	30		
Person-years	43,969	43,303	42,258	40,835		
Model 1*	1.00 (Referent)	1.64 (0.96–2.81)	1.85 (1.04–3.31)	2.73 (1.41–5.31)	0.0034	1.39 (1.13–1.70)
Model 2*	1.00 (Referent)	1.60 (0.93–2.75)	1.91 (1.05–3.47)	2.56 (1.28–5.12)	0.0081	1.28 (1.04–1.57)
Model 2 + metabolic factors*†	1.00 (Referent)	1.35 (0.78–2.34)	1.31 (0.71–2.41)	1.33 (0.65–2.73)	0.49	1.06 (0.85–1.33)
Leg fat mass						
Median (range), kg	7.9 (<9.2)	10.4 (9.2–11.4)	12.8 (11.5–14.3)	16.9 (≥14.4)		
Cases, *n*	41	33	26	19		
Person-years	41,850	43,069	43,239	42,207		
Model 1*	1.00 (Referent)	0.61 (0.38–0.99)	0.39 (0.23–0.68)	0.21 (0.11–0.41)	<0.0001	0.44 (0.31–0.62)
Model 2*	1.00 (Referent)	0.62 (0.38–1.01)	0.40 (0.23–0.70)	0.25 (0.13–0.49)	<0.0001	0.52 (0.37–0.72)
Model 2 + metabolic factors*†	1.00 (Referent)	0.75 (0.46–1.23)	0.57 (0.33–1.00)	0.41 (0.21–0.82)	0.0082	0.66 (0.46–0.93)

Data are HR (95% CI) unless otherwise indicated. Model 1 was adjusted for age (years), race/ethnicity (White, Black/African American, Hispanic/Latina, other/unknown), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and study group (three variables with each being classified as observational, control, and intervention). Model 2 was adjusted for covariates in model 1 plus smoking status (never, former, current), pack-years of smoking (for current smokers), alcohol consumption (0, 0 to <5, 5 to <15, 15 to <25, ≥25 g/day), recreational physical activity (MET-h/week), diet-quality score (Alternate Healthy Eating Index-2010, excluding alcohol), hormone replacement therapy (never, former, current [<5, 5 to <10, 10 to <15, ≥15 years]), aspirin use (never, ever), use of nonsteroidal anti-inflammatory drug (never, ever), history of CHD or stroke (yes, no), height, and body lean mass at the trunk (for trunk fat mass) or leg region (for leg fat mass). *Trunk and leg fat were mutually adjusted for each other. †Including reported diabetes (yes, no), dyslipidemia (yes, no), use of antihypertensive drugs (yes, no), and systolic blood pressure (mmHg).

adjusting for reported diabetes and HOMA-IR in the WHI CVD Biomarker Study. Perhaps more importantly, we also found, for the first time, that higher trunk fat mass was associated with a higher risk of LEAD and that such an association disappeared after adjustment for reported diabetes, dyslipidemia, and blood pressure measures. Collectively, these findings support the possibility that an accumulation of upper-body fat may increase the risk of LEAD through increases of traditional cardiometabolic risk factors, especially insulin resistance.

A novel finding of our study is that larger hip size and higher leg fat mass both were associated with a lower risk of LEAD. To our knowledge, no previous studies have examined either hip circumference or leg fat measures in relation to incident LEAD. There are some previous studies in which hip circumference was inversely associated with risks of CHD and all-cause mortality (36,37), especially after adjustment for waist circumference (37). A few prospective studies also reported that higher leg fat was associated with lower risk of CVD (21,38). Of note, recent population studies have identified specific genetic loci (39) and metabolomic biomarkers (40) for LEAD that are different from those for CHD, suggesting a potential unique pathogenesis of this vascular disease.

There was no association between BMI and risk of LEAD after multivariable adjustment but an inverse association after further adjustment for metabolic factors. BMI reflects total body mass, and this inverse association may have been driven by the inverse association of lower-body fat with LEAD given that the association between upper-body (but not lower-body) fat and risk of LEAD was largely attenuated after adjustment for metabolic factors.

Strengths of our study include its prospective design, long-term follow-up, objective assessments of anthropometric measures, DXA-assessed body fat mass, and adjudication of major LEAD events. The observed association of waist or hip circumference with risk of LEAD was, respectively, consistent with the association with DXA-assessed trunk and leg fat mass after adjustment for trunk or leg lean mass. Additional analyses conducted by using data on multiple blood biomarkers may further provide some mechanistic insights into the observed associations between body fat and risk of LEAD.

Several limitations to our study need to be acknowledged. Our study only included symptomatic LEAD for which the incidence is lower than that of asymptomatic LEAD (2). Follow-up of asymptomatic LEAD requires periodic reexamination of study participants, which involves substantial time, expense, and resources. As such, it is more practical for large population studies to focus on clinically symptomatic LEAD (4). Given that some at-risk individuals (e.g., those with severe diabetes) who have reduced body fat are more likely to develop LEAD, the possibility that the inverse association between lower-body fat and risk of LEAD may have partially resulted from reverse causation merits attention. However, the inverse association between hip circumference and risk of LEAD was largely similar after excluding incident cases of LEAD that were diagnosed within the first 10 years of follow-up. Finally, our analyses included only postmenopausal women who are predominantly White. Although our findings are reproducible in the CVD Biomarker Study, a more ethnically diverse subsample, additional studies conducted

in men and in other racial/ethnic groups or age-groups are still needed.

In a broad sample of U.S. postmenopausal women, our findings suggest that an accumulation of upper-body fat, as reflected by larger waist circumference or higher trunk fat mass, was associated with an elevated risk of LEAD and that the association may be attributable to the established clinical risk factors, especially insulin resistance. A greater amount of lower-body fat as measured by hip circumference or leg fat mass was associated with a lower risk of LEAD, independently of known risk factors. Additional research is required to confirm our findings and to better understand the mechanisms underlying the beneficial relationship between lower-body fat accumulation and risk of LEAD.

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A full list of all the investigators who have contributed to the WHI science appears at https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf.

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