ORIGINAL RESEARCH

Associations of Obesity With Incident Hospitalization Related to Peripheral Artery Disease and Critical Limb Ischemia in the ARIC Study

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***Background*—**We conducted an analysis of data from the ARIC (Atherosclerosis Risk in Communities) study to assess the independent association of obesity with peripheral artery disease (PAD) and critical limb ischemia (CLI).

***Methods and Results*—**All black and white ARIC participants without prevalent PAD at baseline (1987–1989) were included. We used Cox proportional hazards models adjusting for potential confounders and then potential mediators to quantify the association between body mass index (BMI) and incident hospitalizations related to PAD without CLI and with CLI through 2013. Our analysis included 13 988 men and women followed for a median of 24 years. Incident PAD without CLI and PAD with CLI occurred in 373 and 201 participants, respectively. After adjusting for potential confounders, higher BMI at baseline was associated with increased risk of PAD without CLI when BMI was modeled continuously (hazard ratio per 1-SD increment in BMI: 1.23; 95% confidence interval, 1.11–1.37) and with PAD with CLI regardless of whether BMI was modeled categorically ($P<0.05$) or continuously (hazard ratio per 1-SD increment in BMI: 1.51; 95% confidence interval, 1.34–1.69). The associations of BMI with PAD without CLI and with CLI were attenuated after further accounting for potential mediators but remained significant for PAD with CLI when BMI was linearly modeled (hazard ratio per 1-SD increment in BMI: 1.19; 95% confidence interval, 1.04–1.36). The positive association between BMI and PAD with CLI was stronger than the association between BMI and PAD without CLI for all models ($P<0.001$).

***Conclusions*—**In the general population, BMI is positively associated with incident hospitalized PAD after adjusting for potential confounders, particularly its most severe form of CLI. Maintaining an optimal weight, in addition to controlling other cardiovascular risk factors, may play a role in reducing risk of PAD with CLI. **(*J Am Heart Assoc*. 2018;7:e008644. DOI: 10.1161/JAHA.118.008644.)**

Key Words: ARIC (Atherosclerosis Risk in Communities) • critical limb ischemia • obesity • peripheral artery disease • peripheral vascular disease

Peripheral artery disease (PAD) affects 8 million to 10 million individuals in the United States and >200 million individuals worldwide.[1] The most severe form of PAD is critical limb ischemia (CLI), which is characterized by rest pain, ulcers, or gangrene. Even with surgical intervention, as many as 40% of patients with CLI will require major amputation at 1 year.[2] Individuals with PAD also have twice the risk of overall mortality, cardiovascular mortality, and major coronary events over 10 years compared with the general population.[3]

Prospective data from the Framingham Heart Study have shown that age, sex, serum cholesterol, hypertension, cigarette smoking, diabetes mellitus, and coronary heart disease (CHD) are associated with an increased risk of incident intermittent claudication.[4] Similarly, a recent report from the Health Professionals Follow-up Study also identified smoking, hypertension, hypercholesterolemia, and type 2 diabetes mellitus as major risk factors for clinically significant PAD.[5] Although each of these risk factors is associated with obesity, there is a paucity of data describing the association between obesity itself and the future development of PAD or CLI.

Obesity has been shown to be a predictor of cardiovascular disease (CVD), including CHD, stroke, and heart failure, in a

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/7/16/e008644/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Using data from the ARIC (Atherosclerosis Risk in Communities) study, we found that body mass index is positively associated with incident hospitalized peripheral artery disease, particularly its most severe form of critical limb ischemia.

What Are the Clinical Implications?

- Our findings suggest that obesity may play a role in the development and progression of peripheral artery disease and support the notion that both weight loss and medical management of obesity-related cardiovascular risk factors are essential for decreasing the risk of atherosclerotic disease.

large number of previous cohort studies.[6–8] Ndumele et al have also recently shown that the adjustment for obesity-related risk factors such as diabetes mellitus, hypertension, and dyslipidemia considerably attenuates the association between obesity and CHD and stroke but not heart failure.[7] This relationship, however, has not been investigated for PAD. Not all patients with CHD have PAD, so risk factors associated with lower extremity atherosclerosis may be different than for those of CHD.[9] Furthermore, the association between obesity and CLI has not been reported previously. Given that CLI has some pathophysiological aspects that are unique from PAD, such as higher levels of inflammation and potential nonvascular contributions from nonhealing ulcers,[10,11] we hypothesized that any association between obesity and PAD would be magnified in CLI.

To address this knowledge gap, we undertook an analysis of data from the ARIC (Atherosclerosis Risk in Communities) study to assess the independent associations of a range of obesity measures with PAD and CLI.

Methods

Study Cohort

The ARIC study is a prospective, predominantly biracial, community-based cohort comprising participants from 4 US communities (Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and the suburbs of Minneapolis, Minnesota). Participants were recruited and examined at a baseline visit between 1987 and 1989 and then followed longitudinally to describe and assess the risk of atherosclerotic disease in the general population. All ARIC participants signed informed consent for longitudinal data collection and reporting at all study visits, and the institutional review boards for all participating institutions and field centers approved the study protocol. Availability of data and material detailed policies for accessing ARIC data can be found online.[12] It is also possible to obtain the study's data from the National Heart, Lung, and Blood Institute BioLINCC repository.[13]

Of 15 792 ARIC participants, we included all black and white participants without a history of PAD at the baseline visit (visit 1). Participants who were of a race other than black or white were excluded, given the small number (n=48). Participants were also excluded if they were missing data on the variables of interest (n=1010) or if they had a history of PAD at their baseline visit (defined as leg pain that started during walking and went away within 10 minutes after rest, an ankle-brachial index <0.9, or self-reported leg artery revascularization at visit 1; n=746). The ankle-brachial index results were not reported to participants.

Covariates

Baseline (visit 1) data included sociodemographics (age, race, sex, education level, insurance), lifestyle (smoking status, alcohol habit), and cardiovascular risk factors or diseases (diabetes mellitus, dyslipidemia, hypertension, kidney function [based on estimated glomerular filtration rate], CHD, stroke, and heart failure). Plasma total and HDL (high-density lipoprotein) cholesterol, systolic blood pressure, and use of medications were also assessed. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, use of antidiabetic medications, or self-reported physician diagnosis of diabetes mellitus. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications.

Exposures

Our primary exposure of interest was obesity at visit 1 assessed by body mass index (BMI). Secondarily, we also investigated waist circumference (WC) and waist-to-hip ratio (WHR). BMI was calculated based on measured weight (in kilograms) divided by height (in square meters; m^2) and analyzed both as a continuous variable and based on standard BMI categories (underweight: <18.5; normal: 18.5–24.9; overweight: 25.0–29.9; obese: 30.0–34.9; severely obese: ≥35.0). WC was measured in centimeters and analyzed both as a continuous variable and based on quartiles. Sex-specific quartiles were assembled for WC due to sex-based differences in absolute measurements. WHR was calculated as WC divided by hip circumference and analyzed both as a continuous variable and based on quartiles.

Outcomes

The outcomes of interest in our study were incident hospitalizations with a discharge diagnosis of PAD and CLI through December 31, 2013. PAD-related hospitalizations were identified according to the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes based on the previous literature[6,7]: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); and leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 were considered CLI. In addition, any PAD cases with coexisting codes of leg amputation (84.1x), lower extremity ulcer (707.1x), or gangrene (785.4) were considered to be CLI. Ankle-brachial indexes were measured at some follow-up visits in the ARIC study but not systematically or regularly (eg, only in a single leg and sometimes different legs between visits). Therefore, clinical PAD based on discharge diagnosis was the only way to identify PAD cases consistently over the study follow-up and across study participants. Because of the difference in the manifestation of PAD without CLI versus PAD with CLI, we analyzed the 2 outcomes separately. Cases with PAD with CLI as the first PAD event were censored in the analysis of PAD without CLI. Conversely, those who first developed PAD without CLI and then PAD with CLI were included in the analyses for each outcome accounting for an appropriate follow-up time. All participants were followed up until the date of PAD, death, loss to follow-up, or the end of follow-up.

Statistical Analysis

Baseline data for all patients across BMI categories were described as mean (SD), median (interquartile interval), or count (percentage), as appropriate. Cox proportional hazards models were then used to quantify the association between obesity and incident hospitalizations related to PAD without and with CLI, with adjustment for covariates. Analyses were performed using BMI (both as categorical and continuous variables), WC (by sex-specific quartile, as a continuous variable, and as a binary outcome based on the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] guidelines,[14] which defines abdominal obesity as WC >102 cm for male participants and >88 cm for female participants), and WHR (by quartile and as a continuous variable) as the exposure variables.

We constructed 3 different models to account for the impact of potential confounders and mediators for any obesity–PAD relationship. Model 1 was a crude (unadjusted) model. Model 2 was adjusted for potential confounding variables, including age; sex; race; education level; smoking; and history of stroke, CHD, or heart failure. Model 3 included all covariates from model 2 as well as potential mediators, including diabetes mellitus, total and HDL cholesterol, systolic blood pressure, antihypertensive medications, and estimated glomerular filtration rate. The covariates in both models 2 and 3 were chosen based on previously published work describing obesity-related confounding variables and CVD mediators.[7] To evaluate whether obesity measures have uniquely strong associations with PAD with CLI, we then compared the hazard ratios (HRs) for PAD without CLI from each model versus those for PAD with CLI using seemingly unrelated estimation that computes a simultaneous sandwich/robust covariance matrix for the 2 models.[15] In addition, sensitivity analyses were conducted by stratifying the study sample into key clinical subgroups (median age, sex, race, smoking status, diabetes mellitus, hypertension, prevalent CVD) to define the interaction between those subgroups and obesity on incident PAD without or with CLI using model 2 (adjusting for potential confounders). Interactions were tested using a likelihood ratio test with each of the obesity measures modeled as a continuous variable (per 1-SD increment).

Stata version 14.2 (StataCorp LP) was used for all analyses. All *P* values were 2-sided, and the significance level was set at $P<0.05$.

Results

Baseline Characteristics

Among the 13 988 ARIC participants analyzed, the mean age was 54±6 years, 45.2% (n=6329) were male, and 26.4% (n=3691) were black. When stratified by baseline BMI, 118 participants (0.8%) were underweight (BMI <18.5), 4528 (32.4%) were normal weight (BMI 18–24.9), 5529 (39.5%) were overweight (BMI 25.0–29.9), 2574 (18.4%) were obese (BMI 30.0–34.9), and 1239 (8.9%) were severely obese (BMI ≥35).

Participant sociodemographics, comorbidities, blood pressure, renal function, and plasma cholesterol levels differed significantly across BMI categories (Table 1). Participants with higher BMI were more frequently black and had lower prevalence of advanced education compared with those with normal BMI. Higher BMI was associated with lower prevalence of smoking and lower weekly activity levels but higher

Table 1. Baseline Characteristics of ARIC Participants by BMI Category, 1987–1989

	BMI Category*				
	Underweight	Normal	Overweight	Obese	Severely Obese
Participants, n (%)	118 (0.8)	4528 (32.4)	5529 (39.5)	2574 (18.4)	1239 (8.9)
Age, y, mean (SD)	54.5 (6.1)	53.9 (5.8)	54.2 (5.7)	54.2 (5.7)	53.4 (5.6)
Male, n (%)	28 (23.7)	1710 (37.8)	3116 (56.4)	1179 (45.8)	296 (23.9)
Black, n (%)	35 (29.7)	775 (17.1)	1377 (24.9)	907 (35.2)	597 (48.2)
Education level,† n (%)					
Basic	28 (23.7)	764 (16.9)	1223 (22.1)	742 (28.8)	417 (33.7)
Intermediate	50 (42.4)	1955 (43.2)	2220 (40.2)	1011 (39.3)	490 (39.5)
Advanced	40 (33.9)	1809 (40.0)	2086 (37.7)	821 (31.9)	332 (26.8)
Smoking status, n (%)					
Current	78 (66.1)	1429 (31.6)	1304 (23.6)	551 (21.4)	189 (15.3)
Former	15 (12.7)	1292 (28.5)	1996 (36.1)	880 (34.2)	385 (31.1)
Never	25 (21.2)	1807 (39.9)	2229 (40.3)	1143 (44.4)	665 (53.7)
Diabetes mellitus, n (%)	4 (3.4)	198 (4.4)	559 (10.1)	483 (18.8)	353 (28.5)
Prevalent stroke, n (%)	1 (0.8)	83 (1.8)	92 (1.7)	47 (1.8)	23 (1.9)
Prevalent coronary heart disease, n (%)	6 (5.1)	149 (3.3)	275 (5.0)	133 (5.2)	68 (5.5)
Prevalent heart failure, n (%)	3 (2.5)	95 (2.1)	207 (3.7)	171 (6.6)	138 (11.1)
Antihypertensive medication, n (%)	25 (21.2)	831 (18.4)	1571 (28.4)	1037 (40.3)	668 (53.9)
Systolic blood pressure, mm Hg, mean (SD)	116.4 (20.4)	116.1 (18.2)	121.2 (18.0)	125.1 (18.0)	130.1 (18.8)
Diastolic blood pressure, mm Hg, mean (SD)	71.4 (11.4)	70.6 (11.1)	74.1 (10.9)	76.2 (10.9)	78.3 (11.1)
Total cholesterol, mmol/L, mean (SD)	5.2 (1.0)	5.4 (1.0)	5.6 (1.1)	5.6 (1.1)	5.5 (1.1)
HDL cholesterol, mmol/L, mean (SD)	1.8 (0.6)	1.5 (0.5)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)
LDL cholesterol, mmol/L, mean (SD)	3.0 (1.0)	3.4 (1.0)	3.6 (1.0)	3.7 (1.0)	3.5 (1.0)
eGFR, mL/min/1.73 m^2, mean (SD)	106.7 (16.1)	103.3 (13.7)	101.3 (15.7)	102.2 (17.1)	106.4 (17.8)
Ankle brachial index, mean (SD)	1.1 (0.1)	1.1 (0.1)	1.2 (0.1)	1.1 (0.1)	1.1 (0.1)
Total sports MET, min/wk, mean (SD)	510.0 (686.6)	718.6 (839.0)	663.5 (771.5)	510.8 (692.6)	367.9 (581.4)
BMI, kg/m^2, mean (SD)	17.5 (0.9)	22.7 (1.6)	27.3 (1.4)	32.0 (1.4)	39.4 (4.3)
WC, cm (SD)	71.5 (5.8)	84.6 (7.6)	96.9 (7.0)	107.3 (7.6)	122.4 (11.8)
WHR, (SD)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)
Incident PAD without CLI, n (%)	4 (3.4)	101 (2.2)	149 (2.7)	87 (3.4)	32 (2.6)
Incident PAD with CLI, n (%)	1 (0.8)	37 (0.8)	60 (1.1)	59 (2.3)	44 (3.6)

ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; CLI, critical limb ischemia; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent; PAD, peripheral artery disease; WC, waist circumference; WHR, waist-to-hip ratio.
*BMI range for each category: underweight: <18.5; normal: 18.5–24.9; overweight: 25.0–29.9; obese: 30.0–34.9; severely obese: ≥35.0.
†Basic education: some high school or less; intermediate education: high school graduate or vocational school; advanced education: some college or graduate school.

prevalence of diabetes mellitus, CHD, heart failure, and use of antihypertensive medications. Accordingly, participants with higher BMI had higher systolic and diastolic blood pressure, higher total cholesterol, and lower HDL cholesterol. As anticipated, WC and WHR increased with increasing BMI. There was a strong correlation between BMI and WC (r=0.88) and a somewhat weaker correlation between BMI and WHR (r=0.43).

Association Between Baseline BMI and Incident Hospitalized PAD Without and With CLI

During a median follow-up of 24.4 years (interquartile interval: 18.4–25.4 years), 373 participants (2.7%) developed PAD without CLI and 201 participants developed PAD with CLI (1.4%). The crude incidence rate of hospitalized PAD without CLI per 1000 person-years was 1.26 (95% confidence interval

Table 2. HRs (95% CIs) for the Association of Baseline BMI With Incident PAD Without and With CLI, ARIC, 1987–2013

Outcome	Model	BMI Category					Per 1 SD of BMI
		Underweight	Normal	Overweight	Obese	Severe Obese	
PAD without CLI	1	1.88 (0.69–5.10)	Ref	1.23 (0.96–1.58)	1.61 (1.21–2.14)	1.26 (0.85–1.87)	1.11 (1.01–1.23)
	2	1.35 (0.50–3.68)	Ref	1.16 (0.90–1.50)	1.69 (1.26–2.27)	1.82 (1.20–2.76)	1.23 (1.11–1.37)
	3	1.74 (0.63–4.75)	Ref	0.88 (0.68–1.15)	1.05 (0.77–1.42)	0.95 (0.62–1.46)	0.98 (0.87–1.11)
PAD with CLI	1	1.30 (0.18–9.49)	Ref	1.35 (0.90–2.03)	2.97 (1.97–4.49)	4.75 (3.07–7.35)	1.61 (1.46–1.79)
	2	1.07 (0.15–7.83)	Ref	1.14 (0.76–1.73)	2.28 (1.50–3.47)	3.64 (2.28–5.80)	1.51 (1.34–1.69)
	3	1.62 (0.22–11.90)	Ref	0.75 (0.50–1.15)	1.15 (0.74–1.77)	1.34 (0.83–2.17)	1.19 (1.04–1.36)

Model 1: unadjusted. Model 2: adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure. Model 3: additionally adjusted for total and HDL (high-density lipoprotein) cholesterol, systolic blood pressure, antihypertensive medications, diabetes mellitus, and glomerular filtration rate. ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; CI, confidence interval; CLI, critical limb ischemia; HR, hazard ratio; PAD, peripheral artery disease; Ref, reference.

[CI], 1.14–1.40), and the crude incidence rate of hospitalized PAD with CLI was 0.67 (95% CI, 0.59–0.77).

Incident PAD without CLI occurred in 3.4% (n=4) underweight, 2.2% (n=101) normal-weight, 2.7% (n=149) overweight, 3.4% (n=87) obese, and 2.6% (n=32) severely obese participants (P=0.07, χ^2 test). Incident PAD with CLI occurred in 0.8% (n=1) underweight, 0.8% (n=37) normal-weight, 1.1% (n=60) overweight, 2.3% (n=59) obese, and 3.6% (n=44) severely obese participants (P<0.001).

The risk of PAD without CLI was significantly higher in participants with obese BMI in an unadjusted Cox proportional hazards model (HR: 1.61; 95% CI, 1.21–2.14), and there was a significant association between PAD without CLI and increasing baseline BMI when BMI was modeled continuously (HR per 1-SD increment: 1.11; 95% CI, 1.01–1.23; Table 2). The risk of PAD with CLI also increased significantly with increasing baseline BMI in an unadjusted Cox proportional hazards model regardless of whether BMI was modeled continuously or categorically (Table 2). Specifically, obese and severely obese participants demonstrated ≈3 to 5 times higher risk of PAD with CLI compared with normal weight. The HR for PAD with CLI was significantly greater than the HR for PAD without CLI (P<0.001 in seemingly unrelated estimation; Table S1).

After adjusting for potential confounding variables (ie, age, sex, race, education, smoking, history of stroke, heart disease, and heart failure), increasing BMI was more strongly associated with PAD without CLI (HR per 1-SD increment: 1.23; 95% CI, 1.11–1.37), whereas the association between BMI and PAD with CLI was somewhat attenuated (Table 2). Nonetheless, the association was consistently stronger for PAD with CLI than for PAD without CLI (P<0.001 in seemingly unrelated estimation; Table S1).

The associations of BMI with PAD without and with CLI were considerably attenuated after further accounting for potential mediators (ie, diabetes mellitus, plasma total and HDL cholesterol, systolic blood pressure, antihypertensive medications, kidney function; Table 2). Although there was no longer a significant association between BMI and PAD without CLI after adjusting for potential mediators, the association remained significant for PAD with CLI when BMI was linearly modeled (HR per 1-SD increment:1.19; 95% CI, 1.04–1.36). Again, the association with BMI was stronger for PAD with CLI than for PAD without CLI in this model (P<0.001 in seemingly unrelated estimation; Table S1).

Association Between Alternative Measures of Obesity and Risk of Incident Hospitalized PAD Without and With CLI

The risk of both PAD without CLI and PAD with CLI increased significantly with increasing WC and WHR in unadjusted Cox proportional hazards models, regardless of whether those obesity measures were modeled continuously and categorically (model 1 in Table 3), and persisted after adjusting for potential confounding variables (model 2 in Table 3). The associations between WC quartiles and incident PAD without and with CLI were attenuated in model 3 (adjusting for potential mediators) with WC as a categorical variable but remained significant for PAD with CLI when WC was linearly modeled (HR per 1-SD increment:1.27; 95% CI, 1.10–1.46). The association between WC and PAD with CLI was stronger than the association between WC and PAD without CLI for all models (all, P<0.001 in seemingly unrelated estimation; Table S1).

When WC was modeled as a binary outcome based on NCEP ATP III criteria, the association between abdominal obesity and incident PAD without CLI was significant for model 2 (adjusted for confounders) but not for model 1 (unadjusted) or model 3 (adjusted for mediators; Table S2). In contrast, the association between abdominal obesity and incident PAD with CLI was significant for model 1 (unadjusted) and model 2 (adjusted for confounders) but attenuated for model 3 (adjusted for mediators; Table S2).

Table 3. HRs (95% CIs) for the Associations of Baseline WC and WHR With Incident PAD and CLI, ARIC, 1987–2013

Measure	Outcome	Model	Quartile				Per 1 SD
			Q1	Q2	Q3	Q4	
WC*	PAD without CLI	1	Ref	1.13 (0.83–1.55)	1.61 (1.20–2.15)	1.71 (1.27–2.28)	1.30 (1.18–1.43)
		2	Ref	1.15 (0.84–1.58)	1.55 (1.15–2.07)	1.67 (1.24–2.25)	1.29 (1.16–1.44)
		3	Ref	0.89 (0.64–1.22)	1.06 (0.78–1.44)	0.92 (0.67–1.27)	1.03 (0.92–1.17)
	PAD with CLI	1	Ref	0.94 (0.56–1.58)	1.63 (1.03–2.57)	3.90 (2.60–5.84)	1.81 (1.61–2.02)
		2	Ref	0.94 (0.56–1.59)	1.42 (0.89–2.25)	3.10 (2.05–4.69)	1.66 (1.47–1.88)
		3	Ref	0.66 (0.39–1.11)	0.76 (0.47–1.22)	1.19 (0.76–1.85)	1.27 (1.10–1.46)
WHR	PAD without CLI	1	Ref	2.06 (1.39–3.04)	3.23 (2.24–4.67)	4.81 (3.36–6.86)	1.74 (1.56–1.94)
		2	Ref	1.60 (1.07–2.39)	2.18 (1.47–3.22)	2.83 (1.92–4.18)	1.46 (1.29–1.66)
		3	Ref	1.24 (0.83–1.87)	1.49 (0.99–2.23)	1.56 (1.03–2.35)	1.17 (1.01–1.34)
	PAD with CLI	1	Ref	2.50 (1.46–4.28)	3.05 (1.81–5.16)	5.41 (3.29–8.91)	1.84 (1.59–2.13)
		2	Ref	2.10 (1.22–3.62)	2.55 (1.48–4.38)	4.10 (2.42–6.92)	1.74 (1.47–2.06)
		3	Ref	1.47 (0.84–2.55)	1.37 (0.79–2.39)	1.47 (0.85–2.54)	1.16 (0.96–1.39)

Model 1: unadjusted. Model 2: adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure. Model 3: additionally adjusted for total and HDL (high-density lipoprotein) cholesterol, systolic blood pressure, antihypertensive medications, diabetes mellitus, and glomerular filtration rate. Range for each sex-specific quartile of WC (cm): Q1: 52–92; Q2: 85–98; Q3: 94–105; Q4: 105–178. Range for each quartile of WHR: Q1: 0.49–0.88; Q2: 0.88–0.93; Q3: 0.93–0.98; Q4: 0.98–1.39. WC, 1 SD=13.87 cm. WHR, 1 SD=0.08. ARIC indicates Atherosclerosis Risk in Communities; CI, confidence interval; CLI, critical limb ischemia; HR, hazard ratio; PAD, peripheral artery disease; Ref, reference; WC, waist circumference; WHR, waist-to-hip ratio.
*WC quartile variable in the regression model was assembled from separate quartile variables for men and women.

The association between WHR ratio and PAD without CLI persisted for both continuous (HR per 1-SD increment:1.17; 95% CI, 1.01–1.34) and categorical models after adjusting for mediators (Table 3). The estimates were similar for PAD with CLI but were not statistically significant after adjusting for both potential confounding and mediator variables (Table 3). There were no significant differences in the associations between baseline WHR and PAD with CLI versus PAD without CLI after adjusting for mediators (P=0.86 in seemingly unrelated estimation; Table S1).

Sensitivity Analysis

We performed a sensitivity analysis of the study cohort stratified by median age, sex, race, smoking status, diabetes mellitus, hypertension, and prevalent CVD (Table 4). After adjusting for confounders (Model 2), there was a weaker association between continuous BMI and PAD without CLI for patients with prevalent CVD (P=0.001 for interaction). A similar trend was observed for continuous WC and PAD without CLI; the association was weaker for patients with prevalent CVD (P=0.006 for interaction). The association between continuous WHR and incident PAD without CLI was stronger for female versus male participants (P=0.02 for interaction; Table 4).

For PAD with CLI, the associations of BMI (P=0.02 for interaction) and WC (P=0.04 for interaction) were stronger for white versus black patients. The association of WHR with PAD with CLI was somewhat stronger for age <54 versus ≥54 years (P=0.07 for interaction), but this was not statistically significant. There were no significant interactions for the associations of BMI, WC, or WHR with PAD with CLI for any of the other subgroups studied (all P≥0.13; Table 4).

Discussion

The 2013 American Heart Association (AHA) scientific statement on obesity describes obesity as an independent risk factor for CVD, including CHD and stroke.[16] However, there is a paucity of data describing the association between obesity and PAD and CLI—important and severe subtypes of atherosclerotic CVD. In the current study, we sought to assess the independent association between a range of obesity measures and PAD without and with CLI. We found that BMI was significantly and positively associated with both PAD with CLI and PAD without CLI after adjusting for potential confounding variables. We also found that, the association of BMI with PAD without CLI, but not necessarily with PAD with CLI, was mitigated after adjusting for mediators like diabetes mellitus, hypertension, cholesterol, and renal function. WC was also associated with both PAD with CLI and PAD without CLI after accounting for confounders, but again the association was stronger for PAD with CLI. For WHR, the positive associations were similar between PAD with and without CLI regardless of the model studied. Overall, our data suggest that there is a positive association of obesity with PAD and CLI

Table 4. Sensitivity Analysis Assessing the Associations of BMI, WC, and WHR With Incident PAD Without and With CLI for Different Demographic and Clinical Subgroups, ARIC, 1987–2013

		PAD Without CLI		PAD With CLI	
Measure	Subgroup	HR (95% CI)	*P* Value for Interaction	HR (95% CI)	*P* Value for Interaction
BMI*	Age		0.33		0.99
	≥54 y	1.16 (1.01–1.34)		1.48 (1.29–1.71)	
	<54 y	1.29 (1.10–1.50)		1.48 (1.24–1.76)	
	Sex		0.25		0.95
	Male	1.15 (0.97–1.35)		1.50 (1.21–1.86)	
	Female	1.30 (1.13–1.48)		1.51 (1.32–1.73)	
	Race		0.88		0.02
	Black	1.25 (1.04–1.50)		1.36 (1.17–1.58)	
	White	1.23 (1.08–1.40)		1.78 (1.50–2.11)	
	Diabetes mellitus		0.30		0.36
	Yes	1.23 (1.02–1.49)		1.34 (1.15–1.57)	
	No	1.09 (0.95–1.25)		1.19 (0.97–1.46)	
	Hypertension		0.54		0.46
	Yes	1.14 (0.99–1.32)		1.43 (1.26–1.63)	
	No	1.22 (1.04–1.43)		1.29 (0.99–1.67)	
	Prevalent CVD		0.001		0.37
	Yes	0.88 (0.70–1.11)		1.38 (1.10–1.72)	
	No	1.33 (1.18–1.50)		1.54 (1.35–1.76)	
	Smoking		0.47		0.99
	Current	1.16 (0.99–1.37)		1.49 (1.20–1.85)	
	Former	1.23 (1.02–1.48)		1.52 (1.25–1.85)	
	Never	1.36 (1.12–1.66)		1.51 (1.27–1.78)	
WC*	Age		0.13		0.87
	≥54 y	1.20 (1.04–1.38)		1.66 (1.42–1.93)	
	<54 y	1.41 (1.20–1.65)		1.63 (1.35–1.96)	
	Sex		0.09		0.79
	Male	1.16 (0.98–1.37)		1.62 (1.31–2.01)	
	Female	1.39 (1.22–1.60)		1.68 (1.45–1.94)	
	Race		0.72		0.04
	Black	1.25 (1.03–1.53)		1.50 (1.27–1.76)	
	White	1.31 (1.15–1.48)		1.92 (1.60–2.31)	
	Diabetes mellitus		0.52		0.13
	Yes	1.26 (1.02–1.56)		1.50 (1.26–1.79)	
	No	1.16 (1.02–1.32)		1.21 (0.98–1.50)	
	Hypertension		0.51		0.35
	Yes	1.19 (1.02–1.38)		1.59 (1.38–1.84)	
	No	1.28 (1.09–1.49)		1.39 (1.07–1.79)	
	Prevalent CVD		0.006		0.94
	Yes	0.97 (0.77–1.21)		1.66 (1.29–2.14)	
	No	1.37 (1.21–1.54)		1.65 (1.43–1.89)	

Continued

Table 4. Continued

Measure	Subgroup	PAD Without CLI		PAD With CLI	
		HR (95% CI)	*P* Value for Interaction	HR (95% CI)	*P* Value for Interaction
	Smoking		0.45		0.79
	Current	1.21 (1.03–1.42)		1.57 (1.25–1.98)	
	Former	1.31 (1.08–1.58)		1.64 (1.32–2.03)	
	Never	1.44 (1.16–1.78)		1.74 (1.45–2.08)	
WHR*	Age		0.07		0.07
	≥54 y	1.35 (1.15–1.58)		1.55 (1.26–1.91)	
	<54 y	1.69 (1.39–2.04)		2.09 (1.62–2.70)	
	Sex		0.02		0.23
	Male	1.23 (1.01–1.49)		1.51 (1.13–2.02)	
	Female	1.66 (1.41–1.97)		1.87 (1.52–2.30)	
	Race		0.87		0.16
	Black	1.44 (1.12–1.85)		1.56 (1.25–1.95)	
	White	1.47 (1.27–1.70)		1.96 (1.56–2.48)	
	Diabetes mellitus		0.42		0.58
	Yes	1.20 (0.91–1.59)		1.37 (1.07–1.75)	
	No	1.36 (1.18–1.58)		1.24 (0.98–1.58)	
	Hypertension		0.32		0.43
	Yes	1.30 (1.07–1.57)		1.68 (1.37–2.06)	
	No	1.47 (1.24–1.74)		1.46 (1.10–1.94)	
	Prevalent CVD		0.28		0.52
	Yes	1.26 (0.97–1.64)		1.94 (1.30–2.88)	
	No	1.48 (1.29–1.71)		1.68 (1.40–2.02)	
	Smoking		0.18		0.24
	Current	1.31 (1.10–1.56)		1.48 (1.11–1.96)	
	Former	1.69 (1.35–2.13)		1.66 (1.22–2.27)	
	Never	1.53 (1.19–1.96)		2.03 (1.59–2.59)	

Adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure. ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; CI, confidence interval; CLI, critical limb ischemia; CVD, cardiovascular disease; HR, hazard ratio; PAD, peripheral artery disease; WC, waist circumference; WHR, waist-to-hip ratio.

*Per 1-SD increment.

independent of potential confounders, but that this relationship tends to be stronger for PAD with CLI.

Obesity, and specifically BMI, has been associated with increased risk of cardiovascular morbidity and mortality in prior studies.[7,17,18] The strength of association, however, is not consistent across CVD phenotypes. Ndumele et al demonstrated, for example, that BMI was independently associated with heart failure but not with CHD and stroke after accounting for traditional mediators like blood pressure and diabetes mellitus.[7] In our study, there was a significant association of BMI with PAD with and without CLI. Furthermore, these associations demonstrated a similar pattern to that of CHD and stroke,[7] with considerably attenuated results once we accounted for obesity-related mediators. Given that PAD is a subtype of atherosclerotic disease and thus has shared pathophysiology with CHD and stroke, these findings were not unexpected.

Importantly, our data suggest that obesity measures (specifically, BMI and WC) tend to be more strongly associated with PAD with CLI than with PAD without CLI. Although the exact mechanism of this observation is not clear, several potential explanations exist. First, the pathophysiology of the findings that we report may relate to a proinflammatory state caused by obesity. Adipose tissue has been associated with elevated levels of circulating IL-6 (interleukin 6), TNF-α (tumor necrosis factor α), and other proinflammatory cytokines.[19]

Although PAD without CLI and PAD with CLI likely share some of the proinflammatory profiles engendered by obesity, CLI may be the result of an accelerated or dose-dependent inflammatory pathway that occurs to a higher burden of obesity.[20,21] Indeed, compared to patients with PAD without CLI, patients with PAD with CLI have been found to have higher circulating levels of inflammatory markers, including C-reactive protein, several cytokines, and α-defensin.[10] Consequently, the association of obesity with PAD with CLI may be stronger than the association of obesity with PAD without CLI simply because CLI is a more severe form of PAD. Second, adipose tissue alters coagulation and fibrinolysis cascades, and this leads to microcirculation obstruction.[22] The prothrombotic diathesis associated with obesity may result in a dose-dependent increase in platelet hyperaggregability, hypercoagulability, and hypofibrinolysis that could contribute to the development of CLI.[21] Finally, systemic obesity is also associated with poor wound healing,[11,23] which may exacerbate the association between obesity and PAD with CLI that we report.

The associations of WHR with PAD with and without CLI were not significantly different in our study. Some, but not all, studies report that WHR is more strongly associated with CVD than BMI.[24,25] A number of different explanations have been offered as to why certain measures of obesity outperform others in predicting CVD risk. Some data suggest that the association of BMI, WHR, and WC with CVD are confounded by sex, ethnicity, and age group and that different measures may be more appropriate for different populations.[26] Alternatively, some investigators suggest that WHR is a better predictor of CVD and CVD-related events because it specifically captures body fat mass, whereas BMI also includes fat free mass.[25] In our study, WC, the other measure of central obesity, was more strongly associated with PAD with CLI than PAD without CLI, especially when WC was modeled based on the NCEP ATP III definition of abdominal obesity. Notably, there was a strong correlation between BMI and WC in our study. Given these disparate findings, future investigations in other demographic and regional settings would be warranted to compare BMI, WC, and WHR for their associations with PAD with and without CLI.

Our findings may have important clinical implications. Because there is a significant association between obesity and PAD with CLI that persists even after adjusting for potential confounders and mediators, weight loss may play an important role in reducing individuals' risk of the disease. The AHA guidelines on the management of overweight and obese adults recommends that primary care physicians assess and treat risk factors for CVD among individuals with BMI $\geq$25.[16] The results of our study support this concept and suggest that aggressive management of obesity may not only reduce individuals' risk of CHD and stroke but also limb-threatening PAD. Weight loss would theoretically be effective to reduce obesity effects on PAD and CLI, not just by BMI-independent pathways but also by BMI risk factor–mediated pathways. Consistent with this notion, intensive weight loss programs have been shown to reduce cardiometabolic risk profiles in overweight patients while improving lower extremity functional scale scores.[27] Intensive medical management of other cardiovascular risk factors, including hypertension, diabetes mellitus, and dyslipidemia, would likely augment this benefit because the adjustment for these factors considerably attenuated the associations of obesity with the risk of PAD with and without CLI in our study.

The limitations of our study deserve discussion. First, use of hospital discharge codes for defining PAD with and without CLI may have resulted in some misclassification. We based all diagnoses of incident PAD and CLI on clinical diagnosis codes; the ARIC database does not have angiographic or duplex imaging or ankle-brachial indexes from the data of diagnosis to review. Second, our analysis was limited to only white and black participants, and thus future investigations are warranted for other racial/ethnic groups. Finally, it is possible that some residual confounding is present. Despite these limitations, to our knowledge, our study represents one of the first characterizations of the prospective association between multiple measures of obesity and incident PAD with and without CLI.

Conclusions

Obesity is positively associated with incident hospitalized PAD independent of potential confounders, and particularly its most severe form of CLI, in the general population. Of note, all observed associations were attenuated after adjusting for potential mediators such as blood pressure, diabetes mellitus, and dyslipidemia. These data suggest that obesity may play a role in the development and progression of PAD and support the notion that both weight loss and medical management of obesity-related CVD risk factors are essential for decreasing the risk of limb-threatening ischemia.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Difference in log hazard ratio (95% CI) comparing PAD-with-CLI vs. PAD-without-CLI for each obesity measurement.

Obesity measure*	Model	CLI vs. PAD Difference in log HR (95% CI)	P-value
BMI	1	0.37 (0.33-0.41)	<0.001
	2	0.20 (0.16-0.25)	<0.001
	3	0.18 (0.13-0.23)	<0.001
Waist circumference	1	0.32 (0.28-0.37)	<0.001
	2	0.25 (0.20-0.30)	<0.001
	3	0.20 (0.14-0.25)	<0.001
Waist-to-hip ratio	1	0.05 (-0.02-0.12)	0.14
	2	0.17 (0.09-0.25)	<0.001
	3	-0.01 (-0.10-0.08)	0.86

*All log HRs were for per 1 SD increment of each obesity measure, and were obtained from a parametric survival-time model assuming an exponential survival distribution

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure

Model 3: Additionally adjusted for total & HDL cholesterol, systolic blood pressure, antihypertensive medications, diabetes, and GFR

BMI: body mass index; PAD: peripheral arterial disease (without CLI); CLI: critical limb ischemia

Table S2. Hazard ratios (95% CI) for the association of abdominal obesity (based on the NCEP ATP III definition) with incident PAD-without-CLI and PAD-with-CLI, ARIC, 1987-2013.

Measure	Outcome	Model	HR (95% CI)
Abdominal obesity*	PAD-without-CLI	1	1.03 (0.84-1.27)
	PAD-without-CLI	2	1.28 (1.03-1.58)
	PAD-without-CLI	3	0.90 (0.72-1.13)
	PAD-with-CLI	1	1.93 (1.44-2.57)
	PAD-with-CLI	2	1.85 (1.35-2.53)
	PAD-with-CLI	3	1.04 (0.75-1.46)

** NCEP ATP III abdominal obesity was defined as waist circumference cutoff >102 cm for men, and >88 cm for women.*

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure

Model 3: Additionally adjusted for total & HDL cholesterol, systolic blood pressure, antihypertensive medications, diabetes, and GFR

BMI: body mass index; PAD: peripheral arterial disease (without CLI); CLI: critical limb ischemia

SUPPLEMENTAL MATERIAL

Table S1. Difference in log hazard ratio (95% CI) comparing PAD-with-CLI vs. PAD-without-CLI for each obesity measurement.

Obesity measure*	Model	CLI vs. PAD Difference in log HR (95% CI)	P-value
BMI	1	0.37 (0.33-0.41)	<0.001
	2	0.20 (0.16-0.25)	<0.001
	3	0.18 (0.13-0.23)	<0.001
Waist circumference	1	0.32 (0.28-0.37)	<0.001
	2	0.25 (0.20-0.30)	<0.001
	3	0.20 (0.14-0.25)	<0.001
Waist-to-hip ratio	1	0.05 (-0.02-0.12)	0.14
	2	0.17 (0.09-0.25)	<0.001
	3	-0.01 (-0.10-0.08)	0.86

*All log HRs were for per 1 SD increment of each obesity measure, and were obtained from a parametric survival-time model assuming an exponential survival distribution

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure

Model 3: Additionally adjusted for total & HDL cholesterol, systolic blood pressure, antihypertensive medications, diabetes, and GFR

BMI: body mass index; PAD: peripheral arterial disease (without CLI); CLI: critical limb ischemia

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Measure	Outcome	Model	HR (95% CI)
Abdominal obesity*	PAD-without-CLI	1	1.03 (0.84-1.27)
	PAD-without-CLI	2	1.28 (1.03-1.58)
	PAD-without-CLI	3	0.90 (0.72-1.13)
	PAD-with-CLI	1	1.93 (1.44-2.57)
	PAD-with-CLI	2	1.85 (1.35-2.53)
	PAD-with-CLI	3	1.04 (0.75-1.46)

** NCEP ATP III abdominal obesity was defined as waist circumference cutoff >102 cm for men, and >88 cm for women.*

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race, education, smoking, history of stroke, coronary heart disease, and congestive heart failure

Model 3: Additionally adjusted for total & HDL cholesterol, systolic blood pressure, antihypertensive medications, diabetes, and GFR

BMI: body mass index; PAD: peripheral arterial disease (without CLI); CLI: critical limb ischemia