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ORIGINAL ARTICLE

Impact of Body Mass Index on the Association of Ankle-Brachial Index With All-Cause and Cardiovascular Mortality: Results from the National Health and Nutrition Examination Survey

Mohammad-Ali Jazayeri, MD; Salman Waheed, MD, MPH, MHS; Zubair Shah, MD; Deepak Parashara, MD; and Kamal Gupta, MD

Abstract

Objective: To assess the influence of body-mass index (BMI) on the association of ankle-brachial index (ABI) with mortality.

Patients and Methods: We conducted a prospective study of National Health and Nutrition Examination Survey participants enrolled from January 1, 1999 to December 31, 2002 with BMI and ABI data available. ABI categories were <0.9 (low), 0.9 to 1.3 (reference), and >1.3 (high). BMI categories were <30 kg/m^2 (nonobese) and ≥30 kg/m^2 (obese). Cardiovascular (CV) and all-cause mortality were assessed by National Death Index records. Cox proportional-hazards models and Kaplan-Meier survival estimates were used to compare groups.

Results: In total, 4614 subjects were included, with mean age 56±12 years and BMI 28±6 kg/m^2. Median follow-up was 10.3 years (interquartile range [IQR]: 9.3 to 11.4 years). Low and high ABI were present in 7% and 8%, respectively. After adjustment, low ABI was associated with increased all-cause and CV mortality in nonobese (hazard ratio [HR] 1.5, 95% CI, 1.1-2.1 for all-cause and 3.0 [1.8-5.1] for CV mortality) and obese individuals (1.8 [1.2-2.7] and 2.5 [1.2-5.6], respectively) compared with reference. High ABI was associated with increased CV mortality in nonobese (2.2 [1.1-4.5]) but not obese patients; it was not associated with all-cause mortality overall or when stratified by BMI.

Conclusion: In a US cohort, weight influenced the prognostic significance of high ABI. This may be related to technical factors reducing compressibility of the calf arteries in obese persons compared with those who are nonobese.

Low ankle brachial index (ABI) has been consistently associated with increased cardiovascular (CV) and all-cause mortality in several epidemiologic studies in a wide variety of populations.[1–6] However, the prognostic significance of a high ABI is less clear. Various studies have yielded conflicting results, with some showing a strong association with CV and all-cause mortality, others showing no association, and still others showing an association with CV events but not mortality.[4,7–10] The reasons for these discrepant findings are not well understood. One hypothesis is that obesity may itself contribute to a high ABI measurement and thus influence the prognostic significance of ABI in obese individuals.[11,12] However, the impact of BMI on the association between abnormal ABI (either low or high ABI) and both all-cause and CV mortality has not been previously examined. We hypothesized that the prognostic significance of an abnormal ABI (especially high ABI) is significantly affected by BMI. The objective of this study was to examine the association of ABI with CV and all-cause mortality according to BMI

Department of Cardiovascular Medicine, University of Kansas Medical Center, Kansas City, KS (M.-A.J., Z.S. K.G.); Division of Cardiovascular Disease, University of Alabama Birmingham, AL (S.W.); Division of Cardiovascular Disease, Kansas City Veterans Affairs Medical Center, MO (D.P.).

(in both obese and nonobese individuals) in the general US population using the National Health and Nutrition Examination Survey (NHANES) sample from 1999 to 2002.

PATIENTS AND METHODS

Study Population

We used data from NHANES, which is a cross-sectional study of US residents.[13] The NHANES design consisted of a multistage, stratified, clustered probability dataset providing a representative sample of the noninstitutionalized civilian population of the United States. The study protocol was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention institutional review board. All participants gave written informed consent for the study. We queried the NHANES population database between January 1, 1999, and December 31, 2002. All subjects with available BMI and ABI data were included. We excluded those with missing data on any of the key variables outlined herein. The final sample size for the study was 4614 subjects.

Data Collection

The methodology used for data collection by NHANES has been described in detail elsewhere.[13] In brief, data including past medical history, medication use, demographics, education level, alcohol consumption, and smoking status were collected using a standardized questionnaire. Using a mobile examination center, a detailed physical examination was completed for each participant. Blood pressure was measured 3 times during the visit. For the purpose of the study, hypertension was defined as a systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg, or receipt of antihypertensive therapies. Diabetes mellitus was defined as a fasting plasma glucose level $\geq$126 mg/dL, a nonfasting plasma glucose $\geq$200 mg/dL, or ongoing use of oral hypoglycemic agents for diabetes treatment.

The NHANES ABI measurement protocol is detailed elsewhere.[14] In brief, the right arm blood pressure (BP) and the posterior tibial artery BP were used to calculate the ABI. For patients whose right arm BP could not be recorded (for various reasons listed in the NHANES protocol), left arm BP was used. The size of the arm cuff was based on the arm circumference, with a larger cuff used for larger circumference. The lower extremity cuff used for each patient was the same size as that used for his or her upper arm. Thus, the study accounted for patient size in choosing the cuff. Categories for ABI were defined as $<$0.9 (low), 0.9 to 1.3 (normal, reference range), and $>$1.3 (high). Height and weight were measured, and BMI was calculated as weight in kilograms divided by height in meters squared. BMI categories were $<$30 kg/m^2 (nonobese) and $\geq$30 kg/m^2 (obese).

For the purposes of our investigation, a single measurement of ABI, as obtained in the NHANES cohort, was thought to be adequate for analysis, given that several previous epidemiologic studies have used single ABI measurements to predict CV outcomes with consistent results.[15–17] The inter- and intraobserver variability of ABI measurements has been shown to be quite small, especially in relatively healthy populations such as the NHANES cohort.[18–23] The factor that may most significantly affect the accuracy of ABI measurements is use of an appropriately sized cuff, which was well standardized in the NHANES protocol.

Outcomes

All participants were followed up from their entry into the NHANES study (baseline) to December 31, 2011. Outcomes assessed for this study were all-cause and CV mortality. Vital status and assignment of cause of death were based upon probabilistic matching of NHANES data with National Death Index records. CV mortality was defined based on reported cause of death on death certificate records. For deaths between 1988 through 1998, International Classification of Diseases, 10th Revision (ICD-10) was used (ICD-10 codes I00-I99), as has been used in previous studies from NHANES.[13]

Statistical Analysis

Sampling weights were used to account for the complex survey design. Descriptive statistics were reported as mean and standard deviation for continuous variables and percentages for categorical variables. Baseline characteristics were compared using analysis of variance (ANOVA) and χ^2 tests in pairwise analyses when appropriate. We presented 10-year

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predicted incidence rates, adjusted for demographic characteristics and CV risk factors, for all-cause and CV mortality for each ABI category in both obese and nonobese participants. Kaplan-Meier survival curves were presented for the outcome of interest for each category of ABI according to BMI. Cox proportional hazards models were used to estimate hazards ratios (HRs) for mortality. We used 2 different models with Model 1 adjusting for age, race, gender, income (<$20,000 vs ≥$20,000), and education (<12 years vs >12 years) and Model 2 further adjusting for history of diabetes, systolic blood pressure, total cholesterol, HDL cholesterol, history of CV disease, and current smoking. Interaction between ABI and BMI for all-cause and CV mortality was examined from the fully adjusted model using the Wald test. We used continuous net reclassification index to test if risk stratification for all-cause and CV mortality improved with the addition of ABI to conventional CV risk factors for both obese and nonobese individuals. *P* values <.05 were considered statistically significant. All statistical analyses were done using STATA 12 (StataCorp, College Station, TX).

RESULTS

The study cohort was composed of 4614 subjects, among whom 52% were female. Mean age was 56±12 years. Subjects were followed up for a median period of 10.3 years (IQR: 9.3 to 11.4 years) from enrollment. Baseline characteristics of the study population by ABI and BMI are displayed in Table 1. Seven percent (n=325) had low ABI (<0.9), whereas 8% (n=358) had high ABI (>1.3). The population was predominantly white (n=3583, 78%), and 52% were women. In the nonobese group, there were significant differences in age (*P*<.001), female sex (*P*<.001), and the percentage of white subjects (*P*=.03). Similar findings were seen in nonobese patients with respect to education, household income, smoking status, systolic blood pressure, and prevalent CV disease (*P*<.001 for all). In obese subjects, significant differences in baseline characteristics were also observed for age, female sex, percentage of white subjects, education, income, and prevalent CV disease. Obese subjects demonstrated differences in prevalence of diabetes (*P*=.01), as well as total cholesterol and HDL cholesterol concentrations (*P*<.001), which were not observed in the nonobese subjects. Finally, in contrast to the nonobese group, obese subjects did not have significant differences in smoking status (*P*=.4) or systolic blood pressure (*P*=.1) between ABI groups. Other factors—such as level of education, household income, blood pressure, diabetes, and incident CV disease—were not significantly different at baseline among the ABI groups, regardless of obesity status.

To assess the outcomes of all-cause and CV mortality in subjects stratified by ABI and BMI, survival curves were constructed using the Kaplan-Meier method, as depicted in the Figure (A and B, respectively). A significantly lower probability of survival from all-cause mortality was observed for low ABI subjects with both normal and high BMI, compared with all other groups (log rank test *P*<.001). This survival difference was detectable at 2 years, and its magnitude continued to increase throughout the duration of follow-up. Similar trends were seen for survival from cardiovascular mortality (Figure [B]), with worse survival in the low ABI groups for both normal and high BMI (*P*<.001).

The association of ABI with risk of all-cause and cardiovascular mortality stratified by BMI is presented in Table 2. After adjustment for demographic variables and traditional cardiovascular risk factors, low ABI was associated with increased risk of all-cause and cardiovascular mortality in both normal BMI (HR 1.5, 95% confidence interval [CI], 1.1-2.1 for all cause and 3.0 (1.8-5.1) for cardiovascular mortality) and high BMI 1.8 (1.2-2.7) for all-cause and 2.5 (1.2-5.6) for cardiovascular mortality) compared with those with ABI 0.9-1.3. We also observed that those with high ABI had a higher risk of cardiovascular mortality compared with ABI 0.9-1.3 in the nonobese individuals (2.2 [1.1-4.5]) but not in the obese group (0.6 [0.2-1.7]). High ABI was not associated with all-cause mortality when stratified by body mass. Adjusted incidence rates for all-cause and cardiovascular mortality according to ABI and BMI are shown in Table 3 to convey absolute risk.

We found no significant multiplicative interaction between ABI and BMI for either all-cause or cardiovascular mortality (*P*=.8 and *P*=.09 for all-cause and cardiovascular mortality, respectively). In our risk

TABLE 1. Baseline Characteristics of the Study Population

		BMI <30 kg/m^2				BMI ≥ 30 kg/m^2			
	Overall sample	ABI <0.9	ABI 0.9 to 1.3	ABI >1.3	*P*	ABI <0.9	ABI 0.9 to 1.3	ABI >1.3	*P*
n	4,614	232	2653	227	NA	93	1278	131	NA
Age	56 (12)	69 (14)	55 (12)	55 (12)	<.001	64 (14)	55 (11)	55 (11)	<.001
Female %	2380 (52)	52	54	33	<.001	55	64	40	.01
White %	3583 (78)	80	77	85	.03	77	76	77	.01
African Americans %	404 (9)	11	8	3		18	11	5	
Mexican Americans %	208 (5)	3	4	6		3	5	2	
Hispanics %	240 (5)	5	6	3		2	5	2	
Education ≥12 years %	3641 (79)	64	80	84	<.001	63	78	80	.02
Income ≥$20,000 %	3829 (83)	67	84	90	<.001	70	81	88	.02
Current smoker %	962 (21)	34	23	9	<.001	21	17	12	.4
Diabetes %	692 (15)	18	12	10	.08	42	21	20	.01
Systolic BP mm Hg	127 (19)	141 (28)	126 (19)	121 (17)	<.001	137 (27)	130 (18)	125 (15)	.1
Prevalent cardiovascular disease %	508 (11)	28	9	9	<.001	30	12	16	.006
Cholesterol mg/dL	212 (41)	216 (51)	212 (41)	205 (35)	.08	198 (41)	214 (41)	202 (34)	<.001
HDL cholesterol mg/dL	52 (16)	54 (21)	55 (17)	53 (14)	.26	49 (16)	47 (13)	47 (11)	<.001
BMI (kg/m^2)	28 (6)	25 (4)	25 (3)	25 (3)	.07	35 (6)	35 (4)	35 (5)	.8

Continuous variables reported as mean (standard deviation), whereas categorical variables are reported as n (%) in the overall sample column and percentages in subsequent columns with corresponding n values included in the first row.

P values were computed using ANOVA or χ^2 tests where indicated. Values <.05 were considered statistically significant.

ABI = ankle-brachial index; BMI = body mass index; HDL = high density lipoprotein; BP = blood pressure.

prediction analysis, we found that risk prediction for both all-cause and cardiovascular mortality improved significantly when BMI was added to the fully adjusted model with ABI for both obese and nonobese individuals ($P<.05$).

DISCUSSION

This study provides a comprehensive examination of the influence of BMI on the association of ABI and both all-cause and cardiovascular mortality in a nationally representative sample of United States residents. A key finding of the study is that high ABI (>1.3) was not associated with an increased risk of all-cause mortality irrespective of BMI, although a high ABI was associated with increased risk of cardiovascular mortality in nonobese but not obese individuals (there was no association in the overall group, however). The study also found that low ABI is associated with a significantly increased risk of both all-cause and cardiovascular mortality in both obese and nonobese individuals.

A number of large-scale epidemiologic studies have previously associated low ABI with adverse cardiovascular outcomes and mortality.[4,7,16,17,24] In a meta-analysis including 44,590 patients from 11 epidemiologic studies representing 6 national populations, Heald et al.[1] found that ABI <0.9 conferred a higher risk of both all-cause mortality (pooled risk ratio [RR] 1.60, 95% CI, 1.32-1.95) and CV mortality (pooled RR 1.96, 95% CI, 1.46-2.64) after adjustment for conventional cardiovascular risk factors.

Although many of the cited studies adjusted for BMI when estimating the association between ABI and their outcomes of interest, the risk conferred by abnormal ABI stratified by BMI has not been previously examined, to our knowledge. Despite the well-known association of obesity with all-cause mortality,[25,26] the validity of ABI-based risk assessment in an obese population is less clear. We found that low ABI was associated with a similarly elevated risk of all-cause and CV mortality in both obese and nonobese patients.

Beyond the associations between abnormal ABI and all-cause and CV mortality, our study sought to examine the impact of ABI on CV risk prediction in this population. Fowkes

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et al. found significant associations between low ABI and cardiovascular mortality after adjusting for the Framingham Risk Score (FRS).[2] In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, Criqui et al. found the association between abnormal ABI and CV disease events remained significant following adjustment for other known measures of subclinical atherosclerosis.[4] In the NHANES cohort, we also found that there was a significant improvement in risk prediction for both all-cause and CV mortality when ABI was added to the model while adjusting for most conventional CV risk factors. This relationship remained true for both obese and nonobese patients, a finding that has not been clearly demonstrated previously.

The association of high ABI and CV outcomes is less well established. Most—although not all—studies showing an association of high ABI with adverse outcomes have been in populations with a high underlying cardiovascular risk. The Strong Heart Study (SHS) was among the first to show an association between high ABI (>1.4) and CV outcomes.[7] In that study, Resnick et al. examined 4393 American Indian patients over an 8-year follow-up period.[7] In patients with high ABI, the relative risk ratio was 1.77 (95% CI, 1.48-2.13) for all-cause mortality and 2.09 (95% CI, 1.49-2.94) for CV mortality.[7] SHS featured a high-risk population with diabetes present in more than half the subjects and a relatively high prevalence of high ABI at 9.2%. Similarly, in another study of high-risk patients on hemodialysis in Japan, Ono et al. noted a higher risk of all-cause and CV mortality with ABI >1.3.[27] A Dutch study of 7538 patients with prevalent CV disease or risk factors found that an ABI ≥1.4 was associated with an increased risk of myocardial infarction.[10] High ABI has traditionally been thought to result from noncompressibility of lower extremity (LE) arteries related to medial arterial calcification (MAC). MAC does portend a poor prognosis in diabetic patients and in at least 1 study in patients with type 1 diabetes, subjects with ABI >1.3 had a higher likelihood of having MAC on x-ray.[28–30]

It is likely that the association of high ABI with adverse CV outcomes in high-risk populations is related to MAC being an etiologic factor in causing high ABI readings. In these high-risk populations, the relationship of high ABI and adverse CV outcomes is quite consistent across studies. However, in more general populations, the findings have been discrepant. The Atherosclerosis Risk in Communities (ARIC) investigators assessed the clinical significance of high ABI in their general population cohort from 4 US communities,[9,31] They found high ABI was not associated with an increased CV event rate, compared with normal ABI. In this general population, in which the incidence of diabetes and MAC is expected to be lower than SHS, for example, there may be other factors that result in high ABI. The MESA investigators showed an independent, positive, and graded

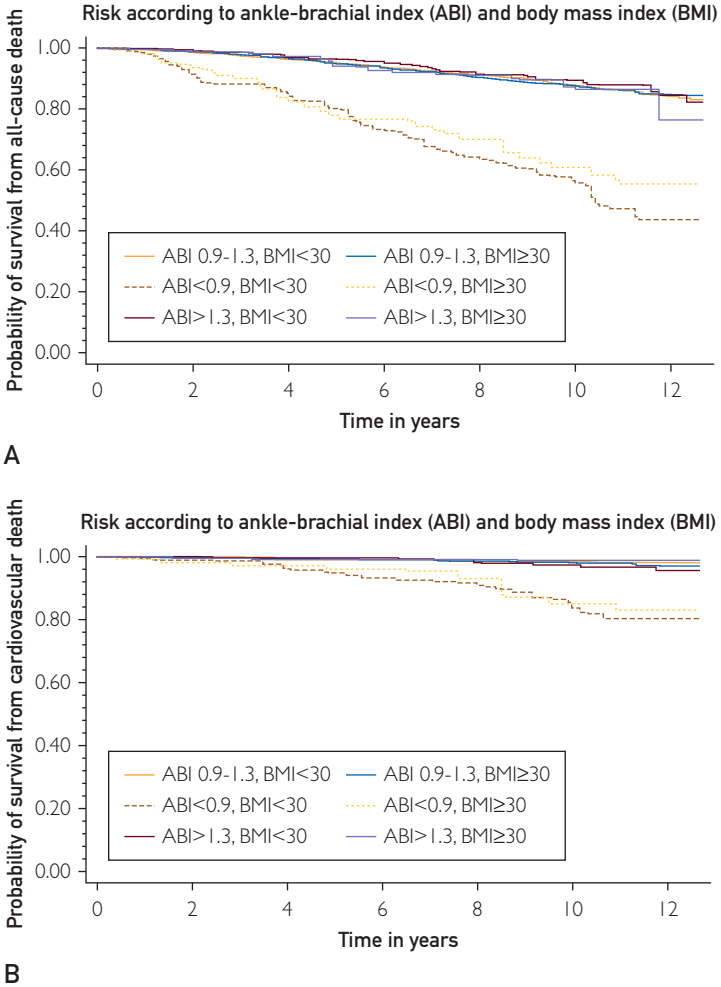

FIGURE. (A) Survival estimates for all-cause mortality using Kaplan-Meier analysis. **(B)** Survival estimates for cardiovascular mortality using Kaplan-Meier analysis.

TABLE 2. Association of Ankle-Brachial Index With All-Cause and Cardiovascular Mortality According to Body Mass Index

	BMI <30 kg/m^2		BMI ≥30 kg/m^2		Overall	
ABI	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
All-Cause Mortality						
0.9-1.3	Reference	Reference	Reference	Reference	Reference	Reference
<0.9	1.8 (1.3-2.5)	1.5 (1.1-2.1)	2.0 (1.3-3.1)	1.8 (1.2-2.7)	1.8 (1.4-2.5)	1.6 (1.2-2.1)
>1.3	0.9 (0.6-1.4)	1.1 (0.8-1.6)	1.0 (0.5-2.0)	1.1 (0.6-2.3)	1.0 (0.7-1.4)	1.1 (0.8-1.6)
Cardiovascular Mortality						
0.9-1.3	Reference	Reference	Reference	Reference	Reference	Reference
<0.9	3.4 (2.0-5.8)	3.0 (1.8-5.1)	3.2 (1.3-7.9)	2.5 (1.2-5.6)	3.2 (2.0-5.5)	2.9 (1.8-4.7)
>1.3	1.9 (0.9-4.1)	2.2 (1.1-4.5)	0.5 (0.2-1.4)	0.6 (0.2-1.7)	1.3 (0.7-2.6)	1.5 (0.8-2.8)

[a]Model 1 adjusted for age, race, gender, income (< $20,000 vs ≥ $20,000), and education (<12 years vs ≥12 years).
[b]Model 2 further adjusted for history of diabetes, systolic blood pressure, total cholesterol, HDL cholesterol, history of cardiovascular disease, and current smoking.
Interaction P=.8 for all-cause and 0.09 for cardiovascular mortality.
Net reclassification index P<.05 for both all-cause and cardiovascular mortality with addition of ankle-brachial index to conventional cardiovascular risk factors for both obese and nonobese individuals.
ABI = ankle-brachial index; BMI = body mass index.

association with increasing obesity and prevalent high ABI.[12] Furthermore, they found that indicators of general obesity, such as BMI, were a stronger predictor of high ABI than measures of visceral adiposity. This observation is supported by previous work assessing the relationship between LE soft tissue composition and ABI. Tabara et al. used computed tomography to measure trunk and LE soft tissue composition in relation to ABI.[11] After adjustment for CV risk factors, the study found LE muscle mass and not visceral or femoral fat or femoral circumference was independently associated with high ABI. The authors hypothesized that increased LE muscle mass confers resistance to compression in LE arteries, leading to higher ABI. This could explain the lack of association of high ABI and CV events seen in the general risk populations such as the ARIC cohort, in which BMI was significantly higher in the high ABI group.

Furthermore, it has been shown that for the same BMI, racial and ethnic differences exist in body fat and muscle content. This has been observed in comparisons of several ethnicities including European, African, and Asian populations.[32–34] These differences in BMI and body fat/mass content and distribution may—to some degree—explain differences in various population-based studies examining outcomes with high ABI. The MESA study showed high ABI was associated with elevated CV risk in persons free of known CV disease.[4] The high ABI group was significantly different from the normal ABI group in terms of BMI (30.1 vs 28.3 kg/m^2) and ethnic distribution (Caucasians 48.2% vs 38.2%, Chinese 2.7% vs 12.7%). It is possible that these factors also exert influence on the prognostic significance of high ABI.

TABLE 3. Incidence Rates for All-Cause and Cardiovascular Mortality by Ankle-Brachial Index and Body Mass Index Categories

ABI	Total (n)	Total deaths	Cardiovascular deaths	Mortality rate[a]	Cardiovascular mortality rate[a]
BMI <30 kg/m^2					
0.9-1.3	2653	508	67	16.7 (14.8-18.5)	2.1 (1.5-2.8)
<0.9	232	129	38	24.7 (18.8-30.6)	6.2 (3.6-8.7)
>1.3	227	48	10	19.4 (12.8-26.0)	4.8 (1.9-7.6)
BMI ≥30 kg/m^2					
0.9-1.3	1278	215	37	16.1 (14.0-18.2)	2.9 (1.2-4.6)
<0.9	93	42	11	26.2 (17.3-35.0)	6.2 (1.6-10.7)
>1.3	131	22	3	18.2 (6.5-29.8)	1.7 (0.4-3.7)

[a]10-year predicted incidence rates per 100 person-years. All rates adjusted for age, race, gender, income (< $20,000 vs ≥ $20,000) and education (<12 years vs ≥12 years), history of diabetes, systolic blood pressure, total cholesterol, HDL cholesterol, history of cardiovascular disease, and current smoking.
ABI = ankle-brachial index; BMI = body mass index

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Similar to the ARIC study, in the NHANES cohort we found—looking at the overall study population—high ABI (>1.3) was not associated with an increased risk of all-cause or CV mortality. However, when stratified according to BMI, in those with BMI < 30, a high ABI was associated with increased CV mortality, although not all-cause mortality. In those with BMI ≥ 30, high ABI was not associated with increased CV or all-cause mortality. It is likely that, in a population with a low prevalence of diabetes, CV disease and, by extension, a low likelihood of MAC, high ABI measured in obese individuals is related to poor compressibility of the LE arteries due to such factors as LE muscle mass, rather than arterial disease. Another issue is that of accurate cuff sizing when measuring ABI. Unlike the upper extremity, where there are recommendations for appropriate cuff sizing, no recommendations or guidelines are available for adequate cuff sizing based on calf circumference for the LE.[6,35] In the NHANES protocol, there is a detailed description of cuff-sizing methodology based on BMI, and thus cuff sizing is likely not a significant factor to be considered when interpreting the findings of the current study.[14]

Limitations

The main limitations of our study include the potential for residual confounding not accounted for in our analyses, particularly with regard to associations between high ABI and mortality for which there is a need for further investigation to better elucidate the underlying mechanisms leading to high ABI. The NHANES data set does not include peripheral arterial disease symptoms for consideration with ABI measurements, a potentially useful discriminator in determining whether high ABI is reflective of noncompressible vessels or artifact related to body habitus. A cutoff value of 1.3 was used to define high ABI, based on previous studies of the ARIC and MESA populations,[9,36] although a more recent societal guideline suggests using a value of 1.4.[37] A sensitivity analysis to assess for changes in outcome using an ABI cutoff of 1.4 for high ABI in our study population was not possible because of low numbers of subjects and events in this higher ABI group. For the ankle pressure, only the *posterior tibialis* (PT) measurement was obtained in the NHANES protocol, without an assessment of the *dorsalis pedis* site for comparison and potential incorporation into ABI calculation. Although the latter approach is preferable, previous studies have established the relationship between the ABI calculated with a PT measurement only and CV outcomes.[6,17] Only a single measure of ABI and BMI was obtained at baseline, which may have affected the accuracy of our findings, although considering the large cohort and multiple patient sites in NHANES, a significant impact on the outcomes measured seems unlikely. Furthermore, there was no serial assessment of BMI in the NHANES data set, which would have provided additional valuable insights regarding the relationship between BMI, ABI, and CV outcomes.

CONCLUSIONS

In a nationally representative US cohort, obesity significantly influenced the prognostic significance of high ABI. High ABI is associated with an increased risk of CV mortality in nonobese but not in obese patients. Low ABI is associated with an increased risk of all-cause and CV mortality in both nonobese and obese patients.

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Abbreviations and Acronyms: **ABI** = ankle-brachial index; **BMI** = body mass index; **BP** = blood pressure; **CV** = cardiovascular; **LE** = lower extremity; **MAC** = medial arterial calcification; **NHANES** = National Health and Nutrition Examination Survey

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Correspondence: Address to Kamal Gupta, MD, Department of Cardiovascular Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd., MS 3006 Kansas City, KS 66160 (kgupta@kumc.edu).

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