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Association of Chronic Kidney Disease with the Spectrum of Ankle Brachial Index: The Cardiovascular Health Study

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Abstract

Background—Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (CVD) events. A high ankle brachial index (ABI) - a marker of lower extremity arterial stiffness – is associated with CVD events and mortality. The association between CKD and high ABI is unknown.

Methods—The Cardiovascular Health Study enrolled community-living persons > 65 years, and measured kidney function and ABI. Glomerular filtration rate (GFR) was estimated using equations that incorporated either cystatin C or creatinine, and CKD was defined by estimated GFR < 60 ml/min/1.73m^2. The ABI was categorized as low (< 0.90), low-normal (0.90 – 1.09), normal (1.10 –

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1.40), and high (> 1.40 or incompressible). Multinomial logistic regression was used to evaluate the associations of CKD with the ABI categories.

Results—Among 4,513 participants, 23% had CKD, 13% had low ABI, and 3% had high ABI. In models adjusted for age, sex, race, hypertension, diabetes, smoking, BMI, LDL cholesterol, HDL cholesterol, and CRP, cystatin C based CKD was associated with both low ABI (relative risk [RR] 2.0; 95% confidence interval [CI] 1.6 – 2.5; P value < 0.001) and high ABI (RR 1.6; 95% CI 1.0 – 2.3; P = 0.03). Results were similar when CKD was defined by creatinine.

Conclusions—CKD is associated with both the high and low extremes of ABI in community-living older persons. Future studies should evaluate whether arterial stiffness is an important mechanism leading to CVD in persons with CKD.

Keywords

kidney disease; chronic; atherosclerosis; calcium; cardiovascular disease; arterial stiffness

INTRODUCTION

Chronic kidney disease (CKD) affects approximately 13% of adults in the United States,[1] and is strongly associated with cardiovascular disease (CVD) events and all-cause mortality.2 These associations are not fully explained by traditional CVD risk factors, and are detected even with modest decrements in kidney function.2, [3] At each stage of CKD, the risk of CVD mortality is several fold higher than the risk of progression to end-stage renal disease (ESRD). [4] Despite intense investigation,5 the mechanisms responsible remain largely unknown.

Arterial calcification is one potential mechanism linking CKD and CVD. Arterial calcification is highly prevalent in maintenance dialysis patients,[6–8] and its presence and severity predict all-cause mortality.[9, 10] However, vascular calcification may be due to either intimal, or medial arterial calcification.[11, 12] As part of the atherosclerotic process, calcium is deposited within the tunica intima with lipid-rich plaque and focal arterial narrowing. Alternatively, medial arterial calcification is limited to the tunica media, has a uniform character resembling a ring in vessel cross-section and tram-tracks in longitudinal view, is not inflammatory or flow limiting,[12] and directly contributes to arterial stiffness in animal models.[13, 14] Medial arterial calcification is particularly prevalent in the distal arteries of the lower extremities and is correlated with higher pulse-wave velocity, left ventricular hypertrophy, and mortality in maintenance dialysis populations.[9, 11]

The ankle-brachial index (ABI) is a non-invasive measure of subclinical CVD which may allow for determination of the predominant pattern of arterial disease in the lower limbs. A low ABI is sensitive and specific for angiographically determined atherosclerosis of the lower extremeties,[15, 16] and is strongly associated with CVD events and mortality in a variety of populations.[17–23] Alternatively, a high ABI reflects generalized stiffening of the lower limb arteries,[24, 25] and an elevated ankle systolic blood pressure has high specificity for medial arterial calcification.[26] Recent studies demonstrate U-shaped relationships between ABI and mortality, wherein subjects with a high ABI had nearly equal mortality risk to subjects with a low ABI, and both groups were at approximately 2-fold mortality risk compared to subjects with intermediate ABI scores.[27–29]

While prior studies have demonstrated that CKD is associated with low ABI,[30–33] the association of CKD with high ABI has not been studied. Such an association would suggest that medial arterial calcification may begin early in the process of kidney dysfunction. Here, we evaluate the association of CKD with high ABI, and compare the strength of association to that with low ABI in the Cardiovascular Health Study (CHS); a community-based cohort of

older adults. We hypothesized that CKD would be associated with both low and high ABI, independent of traditional CVD risk factors.

METHODS

Participants

The CHS is a community-based study of older adults, designed to evaluate risk factors for development and progression of CVD. Its tudy design has been described previously.[34, 35] In brief, eligibility required age ≥ 65 years, expectation to remain in the area for 3 years after recruitment, no active cancer treatment, and the ability to provide consent. Between 1989 and 1990, 5201 participants were recruited from 4 communities (Sacramento, CA; Forsyth County, NC; Washington County, MD; and Allegheny County, PN). An additional 687 African-Americans were recruited in 1992 to 1993. Participants were sampled from Medicare eligibility lists in each area. The present study represents a cross-sectional analysis using data from the 1992 to 1993 study visit, where ABI and kidney function were measured concurrently. Among the 5,265 subjects who participated at that visit, 488 (9%) were excluded due to missing ABI measurements, and 246 (5%) were excluded due to missing kidney function measurement, resulting in a study sample of 4,531 subjects for this analysis.

All participants provided written informed consent, and the study was approved by the investigational review boards of the 4 clinical sites and the Data Coordinating Center at the University of Washington.

Measurements

Kidney Function—Fasting (8 hour) blood specimens were collected at the 1992–93 study visit, and were stored at −70º Celsius. Cystatin C concentrations were measured using a BNII nephelometer (Dade Behring Inc., Deerfield, IL) as described elsewhere.[36] The intra-assay and inter-assay coefficients of variation (CV) were < 2.9 and < 3.2%, respectively. Cystatin C based estimated GFR was calculated using the equation $eGFR_{cys}$=76.7*cystatin C [mg/L]$^{-1.19}$.[37]

Serum creatinine concentrations were measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY), a colorimetric method. The intra-assay CV was < 2%. Creatinine measurements were indirectly calibrated to the reference standard at the Cleveland Clinical laboratory – the core lab of the Modification of Diet and Renal Disease (MDRD) study – as previously described.[38] The abbreviated (4 variable) MDRD study formula to estimate GFR,39 ($eGFR_{Cr}$). CKD was defined by an eGFR < 60 ml/min/1.73m^2 by either equation.[40]

Ankle Brachial Index—The ABI protocol has been described previously.[20] Briefly, after at least 5 minutes of rest and with the subject in supine position, standard mercury sphygmomanometers and a Doppler stethoscope (8 MHz, Huntleigh Technology, Inc., PLC, Luton, UK) determined the right brachial artery and right and left leg posterior tibial artery systolic blood pressures. Duplicate measurements were obtained and averaged. When a blood pressure could not be taken in the right arm, the left arm was used. The ratio of the systolic blood pressure in the leg to the arm defined the leg-specific ABI. The lower of the leg-specific ABIs was used as the patient specific ABI for this analysis. When arterial flow was not abolished with the leg blood pressure cuff inflated to > 300mmHg, the artery was deemed incompressible.

Secondary Predictors—Age, sex, and race/ethnicity were determined by self report. After 5 minutes of rest, seated blood pressure was determined in duplicate using standard mercury sphygmomanometers (Hawksley & Sons Ltd, Sussex, UK).[41] Results were averaged. Prevalent hypertension was defined by a seated systolic blood pressure ≥ 140 mmHg, diastolic blood

pressure ≥ 90mmHg, or treatment for hypertension. Prevalent diabetes was defined by history of physician's diagnosis, use of hypoglycemic agents or insulin, or fasting glucose level ≥ 126 mg/dL. Smoking history was determined by questionnaire and categorized as former, past, or never. Height (cm) and weight (kg) were recorded without shoes and with the patient wearing light clothes, and body mass index (BMI) was calculated (kg/m^2). The Olympus Demand System (Olympus, Lake Success, NY) determined serum total and HDL cholesterol and triglyceride concentrations; LDL cholesterol concentrations were calculated by the Friedewald equation.[42] C-reactive protein (CRP) was determined by an ultra-sensitive enzyme linked immunosorbent assay as described previously.[43, 44]

Statistical Analysis—We developed natural piecewise-cubic spline functions to evaluate parametric nonlinear functions for $eGFR_{cys}$ and ABI measurements. Pre-specified interior knots were placed at the quartiles of the distribution of $eGFR_{cys}$. Subjects with the 2.5% highest and lowest extreme $eGFR_{cys}$ measurements were excluded from spline functions to avoid clinically implausible extrapolation by extreme values. Because prior studies consistently demonstrated higher risk for all-cause mortality and CVD events among persons with ABI < 0.9 or > 1.4,[27–29] we developed mutually exclusive categories that simultaneously captured the functional form of the spline analysis and also utilized these cut-points (< 0.90, 0.90 – 1.09, 1.10 – 1.40, and > 1.40/incompressible). Subjects with ABI measurements of 1.10 – 1.40 served as the reference group for subsequent analyses.

We compared the distribution of demographic characteristics and traditional CVD risk factors across ABI groups by analysis of variance (ANOVA) for continuous variables and Chi-Square for categorical variables. When statistically significant difference were observed across groups, pair-wise comparisons between groups were evaluated by the T-test or Wilcoxon rank sum test for continuous variables, and by the Chi-Square test or Fisher's Exact test for categorical variables. We adjusted for multiple comparisons using the Holm-Sidak test.[45]

Multinomial logistic regression evaluated the associations of CKD with low and high ABI simultaneously. It utilizes a log-, rather than logit-link, and therefore provides estimates of the relative risk (RR). The initial model was unadjusted, and a subsequent model was adjusted for age, sex, and race. The final model evaluated these variables and all other variables that were significantly different across ABI categories, providing a parsimonious list of covariates to facilitate comparison of the relative strength of associations of CKD with high and low ABI. We performed a sensitivity analyses evaluating ankle systolic blood pressure as the outcome, adjusting for the identical covariates and brachial blood pressure, because previous studies provide test characteristics of ankle blood pressure for medial arterial calcification, rather than the high ABI.[26] Results were similar, so data are presented for ABI only. Last, we created multiplicative interaction terms to evaluate whether the observed relationships differed by diabetes status, selected *a priori* due to prior published research.[46, 47]

S-Plus (version 8.0) and SPSS statistical software (version 15.0.1.1, SPSS, Inc., Chicago, IL) were used for the analyses.

RESULTS

Among the 4,513 study participants, the mean age was 75 years, 58% were female, and 83% were Caucasian. The mean $eGFR_{cys}$ was 73 ± 19 and mean $eGFR_{MDRD}$ was 76 ± 20 ml/min/$1.73m^2$, respectively. CKD was detected among 23% (N=1,042) by $eGFR_{cys}$, and 21% (N=939) by $eGFR_{MDRD}$. Thirteen percent of participants (N=579) had ABI measurements < 0.90, 33% (N=1,478) had ABI between 0.90 and 1.09, 51% (N=2,304) had ABI between 1.10 and 1.40, and 3% (N=152) had ABI > 1.40 or incompressible. Fifty-seven participants were categorized in this latter group on the basis of incompressible lower limb arteries.

Compared to participants with ABI 1.10–1.40, lower ABI participants were older, more frequently male and African-American, had higher prevalence of hypertension, diabetes, and tobacco use, and wre more likely to have an atherogenic lipid profile and higher CRP levels (Table 1). In contrast, participants with higher ABI measurements did not differ significantly by age or race. With the exception of male sex, diabetes, and lower HDL cholesterol, high ABI was not associated with traditional CVD risk factors. Participants with ABI > 1.40 had similar tobacco use and BMI, and had lower prevalence of hypertension, lower total and LDL cholesterol, triglycerides, and CRP levels compared to the reference group.

We evaluated the association of kidney function as a continuous variable with ABI measurements. Adjusted spline functions demonstrated a U-shaped relationship, wherein persons with either high or low ABI had lower eGFR, compared to persons with intermediate ABI measurements (Figure 1). Subjects with the most preserved kidney function (highest eGFR) were centered at an ABI measurement of 1.20.

When defined by $eGFR_{cys}$, CKD was associated with an approximate 3-fold greater risk of ABI < 0.90, and an approximate 1.5 fold risk of high ABI compared to subjects with ABI measurements of 1.10 to 1.40 in unadjusted analyses (Table 2). The association of CKD with ABI < 0.90 was moderately attenuated in the fully adjusted model, but CKD remained significantly associated with a 2 fold risk for low ABI. In contrast, statistical adjustment for traditional CVD risk factors had minimal effect on the association of CKD with ABI > 1.40. Results were similar when CKD was defined by creatinine, as well as in companion analyses that evaluated ankle systolic blood pressure as the dependent variable, rather than ABI (Data not shown).

To determine the severity of CKD at which these associations became evident, we evaluated the association of kidney function as a continuous measure with low and high ABI. For each outcome, there was a modest linear association at early decrements in kidney function that became generally steeper among subjects with estimated GFR values < 80 ml/min/1.73m^2 (Figure 2).

Next, we evaluated the association of each kidney function measure with the ABI categories, stratified by diabetes status. The associations of CKD with low ABI appeared similar in persons with or without diabetes (Table 3). The association of CKD with high ABI, however, was qualitatively stronger among persons with diabetes, and the interaction was of borderline significance for cystatin, though less so for creatinine (Interaction P-values 0.07 and 0.24, respectively). Due to the small numbers in the high ABI group, the power to detect such an interaction was low.

DISCUSSION

The primary finding of this study is that moderate CKD is associated with high ABI in community-living older persons. Participants with CKD had an approximately 50% greater risk of high ABI in adjusted models; an association of approximately equal strength to the association of CKD with low ABI. High ABI has predicted all-cause[27–29] and CVD mortality, [28, 29] stroke, and heart failure[29] in prior studies. Therefore, this association may provide novel insights to the underlying mechanisms of arterial disease among persons with CKD.

The association of kidney function with high ABI was evident at an eGFR of approximately 80 ml/min/1.73m^2 or lower in this study. This observation may be important to elucidating mechanisms linking early decrements in kidney function with CVD risk. A prior study from our group demonstrated that subjects with early decrements in kidney function not sufficiently severe to result in elevated serum creatinine levels are strongly associated with future CVD events in the CHS cohort.[3] The mechanisms responsible for this relatively strong association,

despite only modest decrements in kidney function, remain uncertain. Therefore, if the association of mild kidney dysfunction and high ABI is confirmed, future studies elucidating the responsible mechanisms may provide novel insights to the link between CKD and CVD events.

Medial arterial calcification is thought to lead to high ABI measurements in the majority of cases.[24, 25] Indeed, Young and colleagues demonstrated that high ABI scores were directly correlated to medial arterial calcification severity as determined by lower limb plain x-ray, and that an ankle systolic blood pressure ≥ 190 mmHg had greater than 90% specificity for x-ray determined medial arterial calcification.[26] Medial arterial calcification is characterized by a diffuse distribution that may directly contribute to arterial stiffness.[13, 14, 48, 49] Among maintenance dialysis patients, medial arterial calcification has been associated with increased left ventricular mass and aortic pulse-wave velocity,[13] which may lead to cardiac fibrosis and increased arrhythmia risk. If similar relations extend to persons without severe kidney disease, high ABI might indicate elevated risk for CVD events and mortality by mechanisms entirely distinct from atherosclerosis. These hypotheses require future study, but may be particularly relevant in persons with CKD, where the prevalence of arterial calcification is high,[50, 51] and where traditional CVD risk factors only partially account for CVD risk.[2, 52]

Although a high ABI may identify individuals at higher risk for CVD events, it is uncertain whether or not this association is entirely independent of atherosclerosis. Atherosclerotic peripheral arterial disease (PAD) and medial arterial calcification may co-exist within individuals.[53, 54] When this occurs, the stiff lower limb arteries may increase the ABI measurements, thus precluding the detection of atherosclerotic disease via a low ABI. Therefore, the associations of high ABI with CKD in this analyses, and with CVD events and all-cause mortality in prior reports. may in part reflect residual confounding by undetected peripheral atherosclerosis. Future studies with confirmatory tests for atherosclerotic PAD that are less effected by concomitant medial arterial calcification such as toe brachial index measurement[25] are required to evaluate the contributions of medial arterial calcification to CVD events, independent of atherosclerosis.

With the exception of age, diabetes, and lower HDL, traditional CVD risk factors were not associated with high ABI in this study. Similar findings have been observed in other community-based studies.[28, 29] Future research should evaluate risk factors for high ABI and, by extension, risk factors for arterial stiffness. Small studies among persons with advanced CKD have suggested that alterations in mineral metabolism may be associated with medial arterial calcification or high ABI.[13, 55] Whether or not such associations extend to populations with normal to moderate decrements in kidney function is unknown. In addition, future studies should evaluate the associations of high ABI with cardiac structure and function, both at rest and with stress, as prior studies suggest that subjects with high ABI may have a more pronounced vasoreactive response to exercise.[56]

Strengths of this study include its community-based setting, large sample size, and uniform measurement of creatinine, cystatin C, ABI, and multiple potential confounding variables. The simultaneous availability of creatinine and cystatin C has specific advantages. eGFR by creatinine is commonly available in clinical practice and many observational studies, improving generalizability of our study and allowing comparison of strengths of association across studies if these associations are evaluated in other settings in the future. Alternatively, cystatin C provides a more accurate measure of kidney function among persons with normal or near-normal kidney function;[57–60] the range of kidney function observed in the majority of CHS study participants. Its availability in this study allows us to evaluate more accurately whether or not early decrements in kidney function were associated with high and low ABI.

This study also has important limitations. First, the cross-sectional study design does not allow evaluation of temporality. Next, we lacked measurements of urine albumin excretion. A prior study demonstrated that albuminuria was associated with high ABI in bivariate analysis, but this was not subjected to multivariable models; an area that requires further investigation.[61] ABI was defined by right arm blood pressures and without dorsalis pedis blood pressures. This may have introduced some misclassification in ABI categories. Future studies should include both ABI and toe brachial index measurements to evaluate more completely the respective associations of atherosclerotic PAD and arterial stiffness to CVD events. Next, because the prevalence of high ABI was only 3% (N=152) in our study sample, we had imprecise estimates of strengths of association, as demonstrated by relatively wide confidence intervals (Table 2). This was particularly true when analyses were stratified by diabetes status. While the association of CKD with high ABI was qualitatively stronger in persons with diabetes, future studies are required to determine if this observation is reproducible or may have been observed by chance. Last, participants in this study were older, community-living, and few had advanced CKD. Results may not generalize to younger persons or those with late stage CKD.

In conclusion, we demonstrate that diminished kidney function is associated with high ABI measurements. The relationship of kidney function with high ABI was not explained by traditional CVD risk factors. While much is known about risk factors and consequences of atherosclerotic PAD, future studies are needed to elucidate mechanisms leading to high ABI and medial arterial calcification, and to understand mechanisms linking them to CVD events. Such studies may ultimately provide novel insights to mechanisms of CVD in subjects with kidney disease.

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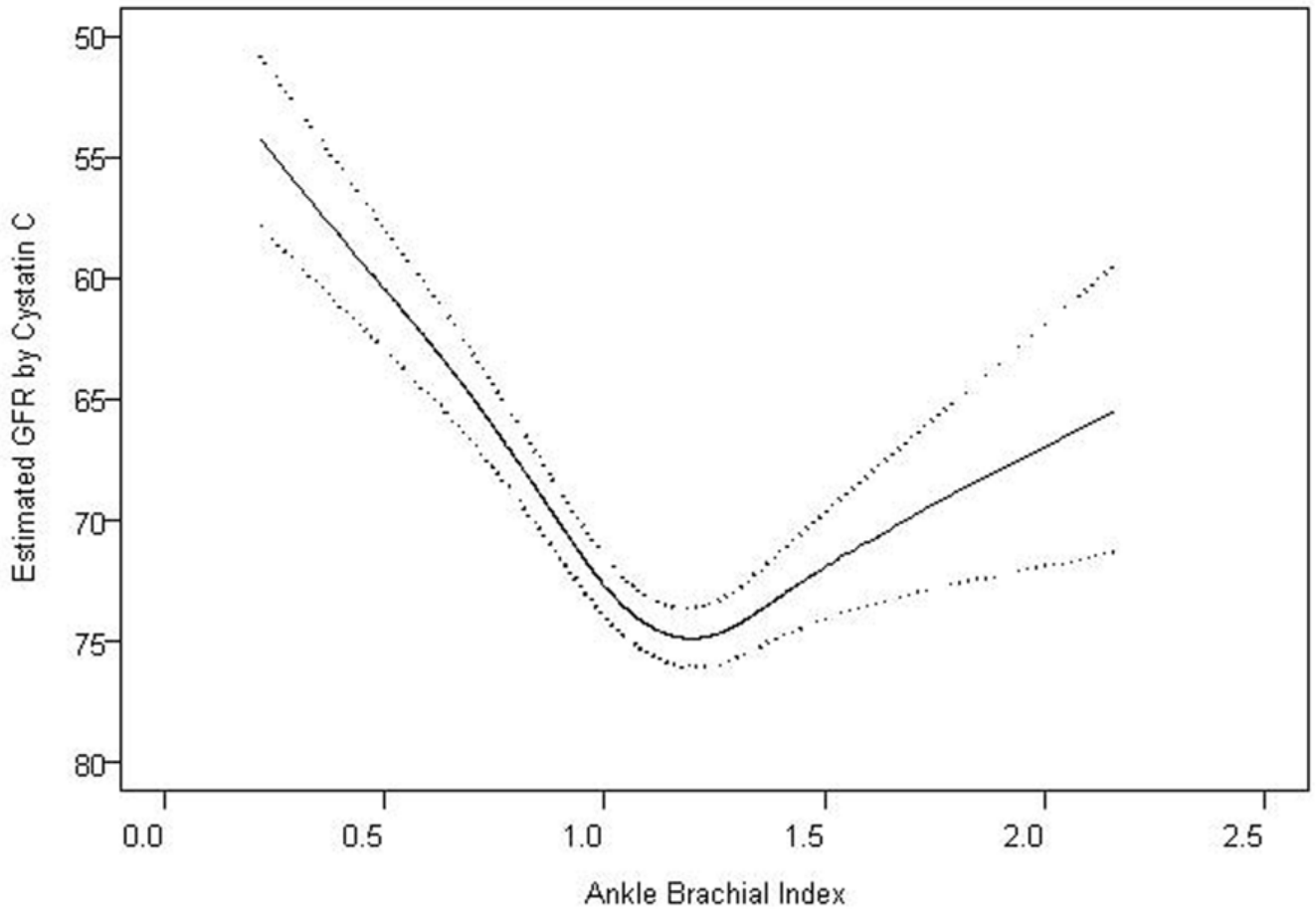

Figure 1. Estimated Glomerular Filtration Rate by Ankle-Brachial Index

Figure depicts a natural cubic spline function. The solid line represents mean adjusted GFR, and dotted lines represent 95% confidence intervals. The spline function was adjusted for age, sex, race, hypertension, diabetes, smoking, BMI, LDL, HDL, and CRP.

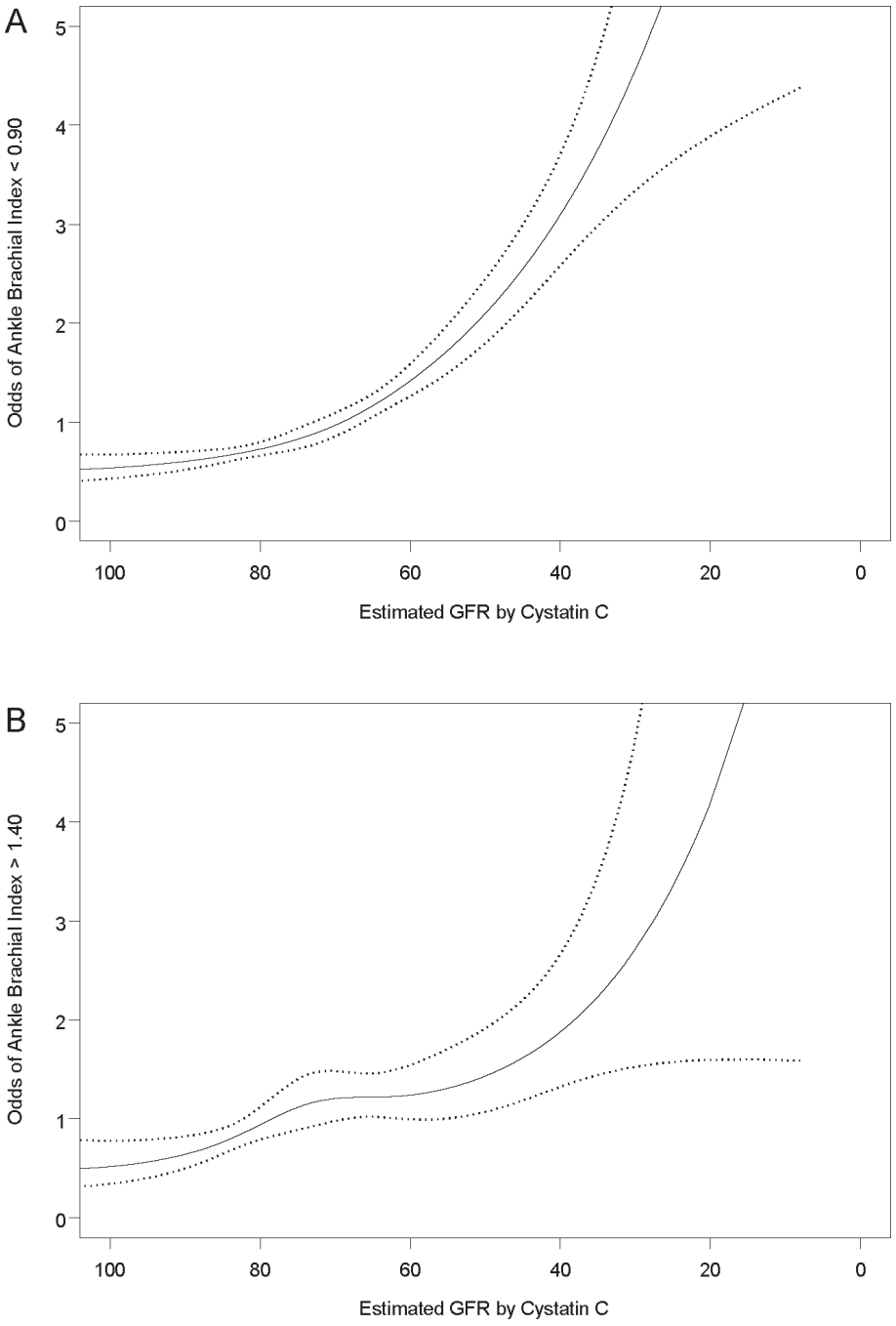

Figure 2. The Association of the Spectrum of Glomerular Filtration Rate with High and Low Ankle Brachial Index

Natural cubic spline function. The solid line represents relative risk, and dotted lines represent 95% confidence intervals. The spline function was adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, LDL, HDL, and CRP.

Table 1

Participants Categorized by Ankle Brachial Index*

	Ankle Brachial Index			
	< 0.90	0.90 – 1.10	1.10 – 1.40	> 1.40/Incompressible
Number (%)	**579 (13%)**	**1478 (33%)**	**2,304 (51%)**	**152 (3%)**
Demographics				
Age (years) ± SD	77 ± 6‡	75 ± 5‡	74 ± 5	75 ± 6
Female (%)	292 (50%)‡	1004 (68%)‡	1266 (55%)	54 (36%)‡
Race/ethnicity (%)				
White	410 (71%)‡	1182 (80%)‡	1980 (86%)	135 (89%)
Black	163 (28%)‡	289 (20%)‡	312 (14%)	17 (11%)
Other	6 (1%)‡	7 (1%)‡	12 (1%)	0 (0%)
Medical History				
Hypertension (%)	428 (74%)‡	919 (62%)‡	1155 (50%)	63 (41%)†
Diabetes (%)	140 (24%)‡	216 (15%)	300 (13%)	34 (22%)‡
Smoking (%)				
Current	96 (17%)‡	179 (12%)‡	151 (7%)	12 (8%)
Past	284 (50%)‡	619 (43%)‡	1007 (45%)	74 (49%)
Never	189 (33%)‡	645 (45%)‡	151 (7%)	65 (43%)
Measurements				
Body mass index (kg/m^2) ± SD	26.2 ± 4.7	26.4 ± 4.6‡	27.2 ± 4.7	27.1 ± 5.2
Systolic blood pressure (mmHg) ± SD	144 ± 24‡	140 ± 22‡	133 ± 19	126 ± 25‡
Diastolic blood pressure (mmHg) ± SD	70 ± 13‡	72 ± 12	71 ± 11	68 ± 11‡
Total cholesterol (mg/dL) ± SD	215 ± 43	211 ± 37‡	207 ± 37	195 ± 38‡
LDL cholesterol (mg/dL) ± SD	134 ± 38‡	128 ± 33	126 ± 33	119 ± 34
HDL cholesterol (mg/dL) ± SD	50 ± 14‡	55 ± 15‡	53 ± 14	51 ± 13
Triglycerides (mg/dL)§	133 [94, 194]‡	123 [90, 174]	122 [88, 169]	117 [86, 153]
C-reactive protein (mg/dL)§	3.9 [1.8, 8.4]‡	2.8 [1.3, 6.4]‡	2.4 [1.1, 5.3]	1.9 [0.9, 4.7]
Kidney Function				
eGFR MDRD (ml/min/ 1.73m^2) ± SD	71 ± 24‡	77 ± 21	77 ± 19	75 ± 21
eGFR cysC (ml/min/ 1.73m^2) ± SD	64 ± 20‡	74 ± 19	75 ± 18	68 ± 19‡
Cystatin C (mg/L) ± SD	1.27 ± 0.47‡	1.09 ± 0.28	1.08 ± 0.30	1.21 ± 0.55‡

*Across-groups P-values were < 0.001 for all comparisons.

§Median [Interquartile Range]

† P < 0.05 compared to the ABI 1.10 to 1.40 category (Sidak adjusted)

‡ P < 0.01 compared to the ABI 1.10 to 1.40 category (Sidak adjusted)

Table 2

Associations of Chronic Kidney Disease* with High and Low Ankle Brachial Index

	ABI Groups			
	< 0.90	**0.90–1.10**	**1.10–1.40**	**> 1.40/Incompressible**
	RR (95% CI)	**RR (95% CI)**	**Reference**	**RR (95% CI)**
Number	579 (13%)	1478 (33%)	2304 (51%)	152 (3%)
Moderate CKD by Cystatin based eGFR (N=1042, 23%)				
Unadjusted	3.07 (2.53, 3.74)	1.22 (1.03, 1.43)	--	1.65 (1.14, 2.38)
Age, sex, race adjusted	2.55 (2.06, 3.15)	1.18 (1.00, 1.40)	--	1.57 (1.06, 2.32)
Fully adjusted†	2.00 (1.60, 2.51)	1.11 (0.93, 1.33)	--	1.55 (1.04, 2.33)
Moderate CKD by MDRD based eGFR (N=936, 21%)				
Unadjusted	2.12 (1.73, 2.61)	1.19 (1.01, 1.41)	--	1.43 (0.97, 2.10)
Age, sex, race adjusted	1.83 (1.48, 2.28)	1.13 (0.96, 1.34)	--	1.45 (0.97, 2.16)
Fully adjusted†	1.59 (1.26, 2.01)	1.07 (0.90, 1.28)	--	1.50 (1.00, 2.24)

*Defined as eGFR < 60 ml/min/1.73m^2.

†Adjusted for age, gender, race, hypertension, diabetes, smoking, BMI, LDL, HDL and CRP.

Table 3

Association of Chronic Kidney Disease with High and Low ABI, Stratified by Diabetes Status

	ABI Groups			
	< 0.90	**0.90–1.10**	**1.10–1.40**	**> 1.40/Incompressible**
Moderate CKD by Cystatin* (N=1042, 23%)				
Diabetes, N (%)	56 (40%)	56 (26%)	65 (22%)	14 (41%)
Adjusted Association†	1.78 (1.04, 3.05)	1.03 (0.63, 1.68)	--	3.94 (1.71, 9.09)
No Diabetes, N (%)	185 (42%)	269 (21%)	369 (18%)	28 (24%)
Adjusted Association†	2.08 (1.62, 2.68)	1.12 (0.92, 1.36)	--	1.15 (0.71, 1.85)
Interaction P-Values (cystatin[continuous]* DM)	0.60	0.65	--	0.07
Moderate CKD by MDRD* (N=936, 21%)				
Diabetes, N (%)	38 (27%)	44 (20%)	50 (17%)	10 (29%)
Adjusted Association†	1.43 (0.82, 2.49)	1.07 (0.64, 1.77)	--	2.56 (1.11, 5.90)
No Diabetes, N (%)	145 (33%)	261 (21%)	362 (18%)	26 (22%)
Adjusted Association†	1.63 (1.27, 2.11)	1.06 (0.88, 1.28)	--	1.26 (0.79, 2.00)
Interaction P-Values (MDRD [continuous]* DM)	0.84	0.61	--	0.27

*Defined as eGFR < 60 ml/min/1.73m^2.

†Adjusted for age, gender, race, hypertension, smoking, BMI, LDL, HDL and CRP.