ORIGINAL ARTICLE

Prediabetes and Diabetes Are Associated With Arterial Stiffness in Older Adults: The ARIC Study

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BACKGROUND
To determine whether prediabetes and diabetes in older adults are associated with arterial stiffness measured in central and peripheral arteries and to examine characteristics that modify these associations.

METHODS
Cohort members attending the 5th exam (2011–2013) of the Atherosclerosis Risk in Communities (ARIC) study had pulse wave velocity (PWV) measures performed at the carotid-femoral (cfPWV), brachial-ankle (baPWV), and femoral-ankle (faPWV) segments. Fasting glucose ≥126 mg/dl, glycated hemoglobin (HbA1c) ≥6.5%, or currently taking diabetes medication defined diabetes. Fasting glucose 100–125 mg/dl or HbA1c 5.7%–6.4% among those without diabetes defined prediabetes. Cross-sectional associations were modeled using multivariable linear regression.

RESULTS
Among 4,279 eligible participants with cfPWV measures (mean age 75 years), 22% were African–American, 25.5% had diabetes, and 54.7% had prediabetes. Compared to those with normal glucose, cfPWV was 95.8 cm/s higher (stiffer) on average for those with diabetes (for reference: being 1 year older was associated with 14.4 cm/s higher cfPWV). Similar findings were seen for diabetes and baPWV, although attenuated. Interestingly, faPWV was 17.6 cm/s lower for those with diabetes compared to normal glucose. There was a significant positive association between baPWV and prediabetes. Among those with diabetes, cfPWV was higher for those with albuminuria, reduced kidney function, duration of diabetes ≥10 years, and elevated HbA1c (HbA1c ≥7).

CONCLUSION
Among older adults, diabetes is associated with higher central arterial stiffness and lower peripheral arterial stiffness, and prediabetes is associated with higher baPWV. Cross-sectionally, the magnitude of the effect of diabetes on central stiffness is equivalent to 6 years of arterial aging.

Keywords: arterial stiffness; blood pressure; diabetes; hypertension; peripheral arterial stiffness; prediabetes; pulse wave velocity; race.

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Accelerated arterial stiffness occurs in those with diabetes.[1] Arterial stiffness may be a result of or a cause of diabetic vascular complications such as diabetic nephropathy and retinopathy.[2] Pulse wave velocity (PWV) is a noninvasive measure of arterial stiffness that predicts mortality and cardiovascular events, and also among individuals with diabetes.[3–5] Given the differences in the predominant components of the arterial wall between central and peripheral arteries, and the small vessel involvement among those with diabetes, we would expect the effect of diabetes on arterial stiffness to differ across arterial territories. Carotid-femoral PWV (cfPWV) is often considered the reference standard measurement for central (aortic) stiffness.[6,7] Although not used clinically in the United States, a recent European expert consensus statement suggests that cfPWV >10 m/s (1,000 cm/s) be considered among cardiovascular risk factors and other measures such as electrocardiography, carotid intimal media thickness, and albuminuria in classifying cardiovascular risk for middle-aged adults with hypertension.[8] Higher cfPWV thresholds have been suggested as a reference for those aged 70+ years.[9] At present, there are no guideline recommendations for measurement of PWV among those with diabetes.[10]

As a precursor state to diabetes, prediabetes is associated with higher burden of prevalent cardiac disease in the elderly.[11] In a Chinese middle-aged population (N = 4,938), an increasingly significant difference in brachial-ankle PWV (baPWV) was seen as glucose tolerance worsened from

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impaired glucose tolerance to newly diagnosed diabetes in comparison to those with normal glucose, although no association was seen for prediabetes.[12] Further understanding of the association of prediabetes with arterial stiffness is needed.

Prior studies of the association of prediabetes and diabetes with PWV have been primarily performed in selected clinical populations, Asian populations, and subsets from community cohorts, with results shown only for single PWV segments.[13–15] No prior studies have measured PWV in a population-based US cohort of older adults with detailed measures of diabetes. We set out to study central (cfPWV), peripheral (femoral-ankle PWV (faPWV)), and composite central and peripheral (baPWV) measures of arterial stiffness and their cross-sectional association with diabetes and prediabetes in a population-based bi-ethnic cohort of older adults (mean age 75 years) from the Atherosclerosis Risk in Communities (ARIC) study.

METHODS

The ARIC study is an ongoing community-based observational cohort study of cardiovascular disease and its risk factors. The original cohort of 15,792 was recruited in 1987–1989 from the following 4 US communities: Forsyth County, North Carolina (both African–Americans and Whites); 8 suburbs of Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi (African–Americans only).[16] We conducted a cross-sectional analysis of data collected at the 5th study visit (2011–2013) when the age range was 66–90 years. There were 10,036 participants alive and eligible for the 5th study visit, of which 6,538 participated in the study visit (65% response rate for eligible participants), and 5,918 completed the full exam in the clinic, of which 5,683 had PWV measurements. After the exclusions (see Supplementary Material for details) , a total of 4,682 (82%) participants remained. Depending on the PWV measurement analyzed, the final analytic sample excluded those with missing and outlying values, as defined by values greater than 3 SDs above the mean. The ARIC study was approved by Institutional Review Boards (IRBs) at all centers, and all procedures were in accordance with the ethical standards of these IRBs. Participants provided informed consent.

Participants were asked to bring in all of their medications, fast for 8 hours, and avoid tobacco, caffeinated beverages, and vigorous physical activity the day of the study visit. All measures were performed by trained staff and using standardized methodology (protocols are available at https://www2.cscc.unc.edu/aric/cohort-manuals).

PWV was measured using the VP-1000 Plus system (Omron, Kyoto, Japan). With the participant supine, the following were applied: blood pressure cuffs on the arm and ankle, a phonocardiogram sensor, left carotid and femoral arterial sensors, and electrocardiography clips on both wrists. After 5–10 minutes of rest, a minimum of 2 measures were performed, and the last 2 nonzero measures were averaged. Carotid and femoral arterial pressure waveforms were acquired for 30 seconds by applanation tonometry sensors, and a segmometer (Rosscraft, Surray, Canada) was used to measure the carotid femoral distance. The carotid femoral path length (cm) was calculated as the distance from the carotid to femoral arteries minus the distance from the suprasternal notch to carotid artery. Bilateral brachial and posterior-tibial arterial pressure waveforms were detected over 10 seconds by extremity cuffs connected to plethysmographic and oscillometric pressure sensors. Using height-based formulas, distances for baPWV and faPWV were automatically calculated.[17] In this analysis, right-sided measures were used for baPWV and faPWV. See Supplementary Material for details regarding the quality assurance protocol for PWV measures.

Behavioral and lifestyle factors were assessed with interviewer-administered questionnaires. Participant's brought in medications, and names and dosages were documented and classified. A standard resting 12-lead electrocardiogram was read at the Epidemiological Cardiology Research Center located at Wake Forest University School of Medicine, and abnormalities were coded with Minnesota codes.[18] Body weight and height were measured in scrub suits. Seated blood pressure was measured 3 times, and the average of the last 2 measures was used. Hypertension was defined as blood pressure ≥140 mm Hg systolic, or ≥90 mm Hg diastolic, or taking antihypertensive medication. Albuminuria was defined as albumin-to-creatinine ratio > 30 mg/g from a urine test, and includes those with macroalbuminuria. A standard venipuncture protocol was followed to obtain blood samples, processed within 90 minutes, and shipped weekly to the Atherosclerosis Clinical Research Laboratory (ACRL) at the Baylor College of Medicine and the Advanced Research and Diagnostic Laboratory (ARDL) at the University of Minnesota (see Supplementary Material for details).

Diabetes mellitus was defined as fasting glucose ≥126 mg/dl, or glycated hemoglobin (HbA1c) ≥6.5%, or currently taking diabetes medication including insulin or oral hypoglycemic agents. Prediabetes was defined among those without diabetes, as fasting glucose of 100–125 mg/dl or HbA1c 5.7%–6.4%. Normal glucose was defined as fasting glucose <100 mg/dl and HbA1c <5.7% among those without diabetes. Duration of diabetes of 10 or more years was based on self-report, fasting glucose, and use of diabetes medications from the 5 study visits and from the annual phone calls.

Statistical analysis

The associations between diabetes status and continuous PWV measures were examined using multivariable linear regression analysis adjusting for race-center, age, gender, heart rate, hypertension, current smoking status, and body mass index. Models included those with nonmissing values for all covariates. From these models, the cross-sectional effect of age on PWV was estimated (among nonsmokers without diabetes) as a measure of the effect of aging on PWV. Effect modification by gender or race was tested by including interaction terms in the model along with the main effects ($P < 0.1$ threshold for significance of interaction). Results were presented stratified for significant interactions. Among those with diabetes, cross-sectional associations with PWV were stratified into to those with and without the following: (i) albuminuria, (ii) reduced kidney function as defined by glomerular filtration rate <60 ml/min/1.73 m^2, (iii) elevated

HbA1c as defined by HbA1c ≥7%, and (iv) greater than or equal to 10 years duration of diabetes.

RESULTS

There were 1,090 participants with diabetes, 2,340 with prediabetes, and 849 without diabetes and with normal glucose (Table 1 shows numbers for cfPWV measures only, as numbers vary by PWV measure). Mean age was 75 (range of 66–90 years), with 22% African–Americans and 60% women. The mean age across diabetes status was similar. There were a higher percentage of women (69%) among those with normal glucose compared to those with diabetes (53%). Hypertension was more prevalent in those with diabetes at 84%, compared to 70% of those with prediabetes, and 61% among those with normal glucose. Albuminuria, defined as albumin-to-creatinine ratio >30 mg/g, was more prevalent among those with diabetes (22%) compared to those without diabetes (10%).

Multivariable-adjusted cfPWV (aortic PWV) and baPWV were higher on average for those with diabetes compared with those free of diabetes or prediabetes (Table 2, 95.8 cm/s for cfPWV and 51.6 cm/s for baPWV). For comparison, the average difference in cfPWV by year of age among non-smokers without diabetes is 14.4 cm/s. Peripheral PWV measured by faPWV was negatively associated with diabetes compared with those with normal glucose (−17.6 cm/s for faPWV). There was a significant association of prediabetes with baPWV (difference = 23.4 cm/s, 95% CI: 1.1–45.7), but there was no statistically significant association with cfPWV or faPWV.

Race and gender were evaluated as effect modifiers of the association of diabetes and prediabetes with PWV. There was no significant effect modification by gender (*P* values range from 0.17–0.97, results not shown). There was effect modification of diabetes by race for cfPWV only ($P = 0.06$; Table 3). The association of diabetes and cfPWV was stronger among White participants compared to African-American participants. cfPWV was 69.3 cm/s higher, on average, for

Table 1. Characteristics of participants (*N* = 4,279) with cfPWV at ARIC visit 5 (2011–2013)[a], stratified by diabetes status

	Normal glucose (*n* = 849)	Prediabetes (*n* = 2,340)	Diabetes mellitus (*n* = 1,090)
Age (years), mean (SE)	75.2 (0.2)	75.3 (0.1)	75.0 (0.1)
BMI (kg/m^2), mean (SE)	26 (0.1)	27.7 (0.1)	29.6 (0.1)
Women, *n* (%)	590 (69)	1,385 (59)	574 (53)
African–American, *n* (%)	144 (17)	443 (19)	344 (32)
ARIC study center, *n* (%)			
Jackson, MS	140 (16)	409 (17)	324 (30)
Forsyth, NC	160 (19)	525 (22)	191 (18)
Washington County, MD	234 (28)	620 (26)	318 (29)
Minneapolis, MN	315 (37)	786 (34)	257 (24)
Current smoker, *n* (%)	52 (6)	138 (6)	56 (5)
Hypertension[b], *n* (%)	518 (61)	1,640 (70)	916 (84)
Prevalent CHD[c], *n* (%)	70 (8)	287 (12)	189 (18)
Heart rate (beats/min), mean (SE)	63.3 (0.3)	64.1 (0.2)	66.5 (0.3)
Fasting glucose (mg/dl), mean (SE)	92.7 (0.2)	106.1 (0.2)	139.5 (1.2)
Hemoglobin A1c (%), mean (SE)	5.3 (0.01)	5.7 (0.01)	6.7 (0.03)
Cholesterol-lowering medication, *n* (%)	338 (40)	1,245 (54)	770 (71)
Antihypertensive medication, *n* (%)	491 (58)	1,620 (69)	966 (89)
eGFR < 60 ml/min/1.73m^2, *n* (%)	191 (22)	584 (25)	326 (30)
Albumin-to-creatinine ratio >30 mg/g, *n* (%)	71 (10)	223 (11)	221 (22)
cfPWV (cm/s), mean (SE)	1,107 (10)	1,140 (6)	1,239 (10)
baPWV (cm/s), mean (SE)	1,710 (11)	1,733 (7)	1,750 (10)
faPWV (cm/s), mean (SE)	1,112 (6)	1,101 (4)	1,075 (6)

Abreviations: ARIC, Atherosclerosis Risk in Communities; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; cfPWV, carotid-femoral pulse wave velocity; CHD, coronary heart disease; eGFR, glomerular filtration rate; faPWV, femoral-ankle pulse wave velocity.

[a]There were differing numbers with PWV measures by segment. This table shows the numbers for those with cfPWV.

[b]Hypertension was defined as blood pressure ≥140 mm Hg systolic, or ≥90 mm Hg diastolic, or taking antihypertensive medication.

[c]Prevalent CHD was defined as a history of myocardial infarction, coronary revascularization procedure, coronary artery bypass surgery, or the development of any of these during the years of the study prior to visit 5.

Table 2. Multivariable-adjusted[a] differences in PWV measurements (cm/s) by diabetes status[b], ARIC visit 5 (2011–2013)

	Carotid-femoral PWV		Brachial-ankle PWV		Femoral-ankle PWV	
	N	Difference[a] (cm/s), (95% CI); *P* value	*N*	Difference[a] (cm/s), (95% CI); *P* value	*N*	Difference[a] (cm/s), (95% CI); *P* value
Diabetes	1,090	95.8 (69.4, 122.1); $P < 0.0001$	1,197	51.6 (25.1, 78.1); $P = 0.0001$	1,075	−17.6 (−34.1, −1); $P = 0.04$
Prediabetes	2,340	21.3 (−0.8, 43.4); $P = 0.06$	2,489	23.4 (1.1, 45.7); $P = 0.04$	2,306	−3.2 (−17.1, 10.6); $P = 0.65$
Normal glucose	849	0 (ref.)	904	0 (ref.)	837	0 (ref.)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; PWV, pulse wave velocity.
[a]Models adjusted for age, gender, race-center, heart rate, hypertension, smoking, and body mass index.
[b]Fasting glucose (FG) and glycated hemoglobin (HbA1c) criteria: (i) diabetes if FG ≥126 mg/dl, or currently taking diabetes medication, or HbA1c ≥6.5%; among those without diabetes, then (ii) prediabetes if fasting glucose 100–125 mg/dl or HbA1c 5.7%–6.4%; and (iii) normal glucose if FG <100 mg/dl and HbA1c <5.7%.

African–Americans with diabetes compared to those with normal glucose and free of diabetes, whereas among White participants, cfPWV was 106 cm/s higher among those with diabetes compared to those with normal glucose and free of diabetes. There was no significant effect modification by race of the association between prediabetes and cfPWV.

Albuminuria, duration of diabetes ≥10 years, and elevated HbA1c were associated with higher cfPWV among those with diabetes (Table 4). Among those with diabetes, the presence of albuminuria as compared to absence of albuminuria was strongly associated with higher cfPWV and baPWV, with a difference of 114.4 cm/s for cfPWV and 58.6 cm/s for baPWV. A similar association was observed for reduced kidney function as estimated by reduced glomerular filtration rate and cfPWV, although not significant. Among those with diabetes, presence of reduced kidney function compared to normal kidney function was not significantly different for cfPWV but was associated with significantly lower baPWV and faPWV. Duration of diabetes ≥10 years was also associated with a higher cfPWV (84.2 cm/s, 95% CI: 48, 120.3) and a lower faPWV (−34.3 cm/s, 95% CI: −55.5, −13.1). Duration of diabetes ≥10 years was not statistically significantly associated with baPWV.

DISCUSSION

In this large cohort of older adults, we found that diabetes mellitus is associated with aortic stiffness measured by cfPWV. We estimate the magnitude of this association to be comparable to over 6 years of chronologic age among nonsmokers without diabetes, on average. Interestingly, the association of diabetes with peripheral stiffness measured by faPWV was in the opposite direction from that of aortic stiffness measured by cfPWV such that diabetes was associated with lower peripheral stiffness. There was an interaction by race that indicated a stronger association between diabetes and cfPWV among Whites. Prediabetes was only associated with higher baPWV, a composite of central and peripheral arterial stiffness.

Several smaller studies reported on the association of diabetes with aortic stiffness as measured by cfPWV.[15,19–23] In our study of elderly adults, we found a significant association between aortic stiffness and diabetes, but did not with prediabetes. We add to the literature that the association of diabetes with aortic stiffness (cfPWV) did not vary by gender but was significantly stronger in Whites compared to African–Americans.

We did not find an association of prediabetes with cfPWV or faPWV, but we did find an association with baPWV in older adults. This was similarly found in a healthy Chinese population.[12] Studies in younger populations have shown an association with aortic stiffness and insulin resistance (and/or hyperglycemia) among those without known diabetes.[24,25]

Diabetes was associated with lower peripheral arterial stiffness, opposite from the associations seen for cfPWV and baPWV. This was unexpected, and to our knowledge has not been shown previously. We hypothesize that the arterial wall tissue remodeling that occurs with diabetes may differ pathophysiologically in muscular versus elastic large arteries, and that loss of elasticity and recoil does not necessarily

Table 3. Multivariable-adjusted[a] differences in PWV measurements (cm/s) by diabetes status[b] and race, ARIC (2011–2013)

	African–American			Whites			
	Diabetes	Prediabetes	Normal glucose	Diabetes	Prediabetes	Normal glucose	*P* value
Carotid-femoral PWV							
N	344	443	144	746	1,897	705	
Difference[a] (cm/s)	69.3	13.6	0	106	22.3	0	
95% CI	4.1, 134.6	−47.3, 74.4	ref.	77.2, 134.7	−0.9, 45.6	ref.	
P value, diabetes by race interaction							0.06
P value, prediabetes by race interaction							0.52
Brachial-ankle PWV							
N	357	459	151	840	2,030	753	
Difference[a] (cm/s)	45.4	4.3	0	51.3	24.6	0	
95% CI	−13.2, 104.1	−50.6, 59.3	ref.	21.3, 81.2	0.2, 49.1	ref.	
P value, diabetes by race interaction							0.37
P value, prediabetes by race interaction							0.37
Femoral-ankle PWV							
N	340	438	143	735	1,868	694	
Difference[a] (cm/s)	−8.8	5.1	0	−21.2	−6.4	0	
95% CI	−45, 27.3	−28.6, 38.9	ref.	−40, −2.5	−21.5, 8.8	ref.	
P value, diabetes by race interaction							0.35
P value, prediabetes by race interaction							0.35

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; PWV, pulse wave velocity.

[a]Models adjusted for age, gender, race-center, heart rate, hypertension, smoking, and body mass index. The indicator variables for center varied by race group given the varying representation at each of the 4 centers.

[b]Fasting glucose (FG) and glycated hemoglobin (HbA1c) criteria: (i) diabetes if FG ≥126 mg/dl, or currently taking diabetes medication, or HbA1c ≥6.5%. Among those without diabetes, then (ii) prediabetes if fasting glucose 100–125 mg/dl or HbA1c 5.7%–6.4%, and (iii) normal glucose if FG <100 mg/dl and HbA1c <5.7%.

Table 4. Multivariable-adjusted differences[a] in PWV (cm/s) among persons with diabetes by diabetes complications

	Carotid-femoral PWV		Brachial-ankle PWV		Femoral-ankle PWV	
		Difference[a] (cm/s), (95% CI);		Difference[a] (cm/s), (95% CI);		Difference[a] (cm/s), (95% CI);
	N[b]	*P* value	*N*[b]	*P* value	*N*[b]	*P* value
Albuminuria						
Present, albumin-to-creatinine ratio > 30 mg/g	221	114.4 (68.8, 160.1); $P < 0.0001$	257	58.6 (17, 100.2); $P = 0.01$	221	16.8 (−10, 43.7); $P = 0.22$
Absent, albumin-to-creatinine ratio ≤ 30 mg/g	784	ref.	841	ref.	770	ref.
Reduced kidney function						
Present (eGFR < 60 ml/min/1.73 m^2)	324	39.9 (−0.5, 80.4); $P = 0.05$	365	−75.8 (−112.7, −38.8); $P < 0.0001$	319	−60.9 (−84.2, −37.5); $P < 0.0001$
Absent (eGFR ≥ 60 ml/min/1.73 m^2)	760	ref.	824	ref.	750	ref.
Duration of diabetes						
≥10 years	544	84.2 (48, 120.3); $P < 0.0001$	586	−4.4 (−38.2, 29.4); $P = 0.80$	534	−34.3 (−55.5, −13.1); $P = 0.0015$
<10 years	540	ref.	603	ref.	535	ref.
Diabetes control						
HbA1c ≥ 7	354	83.3 (44.3, 122.3); $P < 0.0001$	381	34.6 (−1.8, 71.0); $P = 0.06$	351	−11.5 (−34.4, 11.4); $P = 0.33$
HbA1c < 7	730	ref.	808	ref.	718	ref.

Abbreviations: CI, confidence interval; eGFR, glomerular filtration rate; HbA1c, glycated hemoglobin; PWV, pulse wave velocity.

[a]Models adjusted for age, gender, race-center, heart rate, hypertension, smoking, and body mass index. The indicator variables for center varied by race group given the varying representation at each of the 4 centers.

[b]Note that numbers vary slightly by the stratifying variables due to variability in missingness of albumin-to-creatinine ratio, eGFR, HbA1c, and estimated duration of diabetes.

translate into stiffening of the muscular arteries. Tsuchikura *et al.* found opposing directions of effect for the association of peripheral and central stiffness with coronary artery disease,[26] including in a subset of participants with type 2 diabetes. Similarly, a recent publication from the ARIC study reported that cfPWV and baPWV were positively associated with age and with HbA1c, whereas faPWV was not.[27] These studies support the observation that peripheral stiffness does not have the same associations with coronary heart disease, or its risk factors, that are observed for central arterial stiffness.

baPWV is being used in the clinical setting primarily in East Asian countries, presumably because its cuff-based measurement is considerably easier to implement compared to cfPWV or faPWV, which require tonometry of the carotid and femoral arteries.[28] baPWV is not widely used elsewhere, however, possibly due to uncertainty of interpretation of this composite measure since it spans from the central elastic arteries to the peripheral arteries with a high smooth muscle component.[5,29]

In our study, the association between baPWV (i.e., 51.6 cm/s difference in baPWV for diabetes) and diabetes was intermediate between that seen for cfPWV (95.8 cm/s difference in cfPWV for diabetes) and faPWV (−17.6 cm/s difference in faPWV for diabetes). Our findings here support those from smaller studies in Asian populations that have also found that baPWV was associated with diabetes and prediabetes.[14,30,31]

Among participants with diabetes, we found that albuminuria, 10 years or greater duration of diabetes, and elevated HbA1c were associated with higher aortic stiffness. The Edinburgh Type 2 Diabetes Study (mean age 69) also observed that duration of diabetes and HbA1c was associated with higher cfPWV.[32] In addition, we observed that albuminuria was associated with baPWV but not with faPWV. In a small study of those with type 2 diabetes ($N = 134$), albuminuria and 10 years duration of diabetes were associated with large artery stiffness (aortic PWV).[33]

The mechanisms behind the associations of arterial stiffness with aging and diabetes are likely similar, reflecting adverse effects on the arterial wall and kidney related to the development of advanced glycation end products.[34] Although diabetes likely accelerates arterial stiffening through multiple pathways, the accelerated production of advanced glycation end products that cross-link with collagen and elastin resulting in diabetes-associated vascular end-organ damage has been postulated to play a role.[1,34] The Rotterdam study had similar findings, although not significant for reduced kidney function.[35]

This is the largest study to have measured PWV in a population-based US cohort of older adults with detailed measures of diabetes. Importantly, PWV was measured in central and peripheral artery segments. There are several limitations to consider. The associations described here are cross-sectional; therefore, temporality of associations cannot be inferred. A glucose load test was not performed, suggesting that some impairments could have been misclassified as normal. Due to occasional equipment malfunction not all participants had PWV measured. Lastly, aortic length was estimated over the body, which does not reflect aortic tortuosity.

In conclusion, this report contributes to the literature on arterial stiffness and diabetes with segment-specific PWV measures in a large, older population inclusive of African-American men and women. We estimate that the magnitude of the cross-sectional effect of diabetes on aortic stiffness is equivalent to 6 years of aging. Among those with diabetes, we find that duration of diabetes, reduced kidney function, and albuminuria, a known manifestation of diabetic nephropathy, strengthen the observed association with aortic stiffness. Our results document heterogeneity of associations between arterial territories such that differences in aortic stiffness measured by cfPWV are greater among those with diabetes. These results are consistent with greater age-related aortic tissue remodeling among persons with diabetes, seemingly related to duration of diabetes and an indicator of end-organ damage. Considering the adverse hemodynamic consequences of central artery stiffness, not only replication of these results, but also evaluation of the central pressure and flow pulsatility characteristics among persons with diabetes are called for.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Goh SY, Cooper ME. Clinical review: the role of advanced glycation end products in progression and complications of diabetes. *J Clin Endocrinol Metab* 2008; 93:1143–1152.
2. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008; 51:527–539.
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55:1318–1327.

4. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; 106:2085–2090.
5. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; 63:636–646.
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605.
7. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T, Artery S; European Society of Hypertension Working Group on Vascular Structure and Function; European Network for Noninvasive Investigation of Large Arteries. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30:445–448.
8. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31:1281–1357.
9. The Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31:2338–2350.
10. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, Deedwania P, Eckel RH, Ershow AG, Fradkin J, Inzucchi SE, Kosiborod M, Nelson RG, Patel MJ, Pignone M, Quinn L, Schauer PR, Selvin E, Vafiadis DK; American Heart Association Diabetes Committee of the Council on L, Cardiometabolic Health CoCCCoC, Stroke Nursing CoCS, Anesthesia CoQoC, Outcomes R, the American Diabetes A. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015; 38:1777–1803.
11. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 2001; 285:2109–2113.
12. Li CH, Wu JS, Yang YC, Shih CC, Lu FH, Chang CJ. Increased arterial stiffness in subjects with impaired glucose tolerance and newly diagnosed diabetes but not isolated impaired fasting glucose. *J Clin Endocrinol Metab* 2012; 97:E658–E662.
13. Ho CT, Lin CC, Hsu HS, Liu CS, Davidson LE, Li TC, Li CI, Lin WY. Arterial stiffness is strongly associated with insulin resistance in Chinese–a population-based study (Taichung Community Health Study, TCHS). *J Atheroscler Thromb* 2011; 18:122–130.
14. Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, Takeuchi H, Shimamoto K. Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study. *Diabetes Care* 2003; 26:437–440.
15. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. *Atherosclerosis* 2015; 238:370–379.
16. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol* 1989; 129:687–702.
17. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens* 2009; 27:2022–2027.
18. Prineas R, Crow R, Zhang Z. *The Minnesota Code Manual of Electrocardiographic Findings*. Springer-London: New York, 2010.
19. Chirinos JA, Segers P, Gillebert TC, De Buyzere ML, Van Daele CM, Khan ZA, Khawar U, De Bacquer D, Rietzschel ER, Asklepios I. Central pulse pressure and its hemodynamic determinants in middle-aged adults with impaired fasting glucose and diabetes: the Asklepios study. *Diabetes Care* 2013; 36:2359–2365.
20. Kimoto E, Shoji T, Shinohara K, Hatsuda S, Mori K, Fukumoto S, Koyama H, Emoto M, Okuno Y, Nishizawa Y. Regional arterial stiffness in patients with type 2 diabetes and chronic kidney disease. *J Am Soc Nephrol* 2006; 17:2245–2252.
21. De Angelis L, Millasseau SC, Smith A, Viberti G, Jones RH, Ritter JM, Chowienczyk PJ. Sex differences in age-related stiffening of the aorta in subjects with type 2 diabetes. *Hypertension* 2004; 44:67–71.
22. Shah AS, Wadwa RP, Dabelea D, Hamman RF, D'Agostino R Jr, Marcovina S, Daniels SR, Dolan LM, Fino NF, Urbina EM. Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. *Pediatr Diabetes* 2015; 16:367–374.
23. Webb DR, Khunti K, Silverman R, Gray LJ, Srinivasan B, Lacy PS, Williams B, Davies MJ. Impact of metabolic indices on central artery stiffness: independent association of insulin resistance and glucose with aortic pulse wave velocity. *Diabetologia* 2010; 53:1190–1198.
24. Liang J, Zhou N, Teng F, Zou C, Xue Y, Yang M, Song H, Qi L. Hemoglobin A1c levels and aortic arterial stiffness: the Cardiometabolic Risk in Chinese (CRC) Study. *PLoS One* 2012; 7:e38485.
25. Bhuiyan AR, Srinivasan SR, Chen W, Paul TK, Berenson GS. Correlates of vascular structure and function measures in asymptomatic young adults: the Bogalusa Heart Study. *Atherosclerosis* 2006; 189:1–7.
26. Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H, Emoto M, Nishizawa Y. Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. *Atherosclerosis* 2010; 211:480–485.
27. Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, Heiss G. Correlates of segmental pulse wave velocity in older adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Hypertens* 2016; 29:114–122.
28. Sugawara J, Tanaka H. Brachial-ankle pulse wave velocity: myths, misconceptions, and realities. *Pulse* 2015; 3:106–113.
29. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, De Carlo M, Gallino A, Landmesser U, Laurent S, Lekakis J, Mikhailidis DP, Naka KK, Protogerou AD, Rizzoni D, Schmidt-Trucksäss A, Van Bortel L, Weber T, Yamashina A, Zimlichman R, Boutouyrie P, Cockcroft J, O'Rourke M, Park JB, Schillaci G, Sillesen H, Townsend RR. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015; 241:507–532.
30. Ando T, Okada S, Niijima Y, Hashimoto K, Shimizu H, Tsuchiya T, Yamada M, Ohshima K, Mori M, Ono K. Impaired glucose tolerance, but not impaired fasting glucose, is a risk factor for early-stage atherosclerosis. *Diabet Med* 2010; 27:1430–1435.
31. Paik JK, Kim M, Kwak JH, Lee EK, Lee SH, Lee JH. Increased arterial stiffness in subjects with impaired fasting glucose. *J Diabetes Complications* 2013; 27:224–228.
32. Teoh WL, Price JF, Williamson RM, Payne RA, Van Look LA, Reynolds RM, Frier BM, Wilkinson IB, Webb DJ, Strachan MW; ET2DS Investigators. Metabolic parameters associated with arterial stiffness in older adults with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *J Hypertens* 2013; 31:1010–1017.
33. Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. *J Am Soc Nephrol* 2005; 16:1069–1075.
34. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation* 2006; 114:597–605.
35. Sedaghat S, Dawkins Arce FG, Verwoert GC, Hofman A, Ikram MA, Franco OH, Dehghan A, Witteman JC, Mattace-Raso F. Association of renal function with vascular stiffness in older adults: the Rotterdam study. *Age Ageing* 2014; 43:827–833.