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Association of Central Arterial Stiffness and Pressure Pulsatility with Mild Cognitive Impairment and Dementia. The Atherosclerosis Risk in Communities Study - Neurocognitive Study (ARIC-NCS)

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Abstract

Background—The association of central arterial stiffness and pressure pulsatility with mild cognitive impairment and dementia is not well characterized in the population-based setting.

Objective—The aim of this study was to quantify the cross-sectional association of arterial stiffness and pressure pulsatility with mild cognitive impairment and dementia among 4,461 older white and black adults from the population-based Atherosclerosis Risk in Communities Study-Neurocognitive Study.

Methods—We used race-stratified multinomial logistic regression to evaluate associations of percentile cut points of carotid-femoral pulse wave velocity, central systolic blood pressure, central pulse pressure, and pulse pressure amplification with mild cognitive impairment and dementia versus no cognitive impairment.

Results—Among whites, those with carotid-femoral pulse wave velocity or central systolic blood pressure ≥75th percentile had a higher prevalence of mild cognitive impairment compared to participants <75th percentile (conditional odds ratio (OR); 95% confidence interval (CI): 1.27 (1.02, 1.56) and 1.28 (1.04, 1.57), respectively) and those with central pulse pressure ≥75th percentile had a higher prevalence of mild cognitive impairment (OR 1.27 (95% CI: 1.03, 1.58))

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and dementia (OR 1.76 (95% CI: 1.06, 2.92) compared to participants <75th percentile. Also among whites, those with pulse pressure amplification ≤25th percentile had a higher prevalence of dementia compared to participants >25th percentile (OR 1.65; (95% CI: 1.01, 2.70). Weaker associations were seen among black participants.

Conclusion—Higher arterial stiffness and pulsatility were associated with mild cognitive impairment and dementia in white participants. Longitudinal characterization of the observed associations is warranted to assess whether arterial stiffness and pressure pulsatility predict mild cognitive impairment and dementia among older adults.

Keywords

pulse wave velocity; brain; cognition; mild cognitive impairment; dementia; Alzheimer's disease

Introduction

Elevated central arterial stiffness and pressure pulsatility are emerging risk factors for cerebral small vessel disease, mild cognitive impairment (MCI), and Alzheimer's disease (AD)-related dementias [1–5]. As a consequence of central arterial stiffening, the cerebral vasculature is subjected to increased pressure and pulsatility [6], leading to cerebral hypoperfusion and microvascular ischemia. Chronic cerebral hypoperfusion and repeat occurrences of microvascular ischemia may lead to tissue damage [7, 8] manifested in the brain as white matter hyperintensities, focal brain infarcts, and brain atrophy [9] that are associated with cognitive decline and dementia [10–13]. Studies of the association of arterial stiffness and pressure pulsatility with MCI and dementia are few and their results are inconsistent [1, 5, 14–18]. Prior studies used various methods to quantify central artery stiffness and were limited in the number of cases identified as MCI and AD dementia. Differences in these associations by race are also relatively unexplored, despite indications that blacks in the United States have an adverse risk profile including hypertension and diabetes with unfavorable implications for cerebral microvascular damage, cognitive decline, and dementia. Limited data suggest that blacks in the United States might have a high risk of dementia and AD dementia compared with whites [19–22].

The burden of MCI and dementia is a salient and growing public health concern as populations age [23, 24]. This study examined the cross-sectional associations of central arterial stiffness and pressure pulsatility with MCI and dementia among older black and white adults in a population-based study. Understanding these associations and their impact in diverse populations may offer insights for reductions in the population burden of MCI and dementia.

Materials and Methods

Study population

The Atherosclerosis Risk in Communities-Neurocognitive (ARIC) study is a population-based, longitudinal study of 15,792 participants aged 45–64 years at the time of their enrollment in 1987–1989 from the following four US communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland.

Details of the baseline visit have been previously described [25]. This investigation included 6,538 participants aged 70–89 who attended the visit 5 examination between 2011 and 2013. Participants provided written informed consent and the ARIC-NCS study was approved by the Institutional Review Boards at all field centers and other study agencies.

We excluded participants with missing information on PWV (n=863), body mass index (BMI) ≥40 kg/m^2 (n=204) or missing BMI (n=14), major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2; n=190), Minnesota code 8-1-2 with low quality PWV waveforms (n=30), aortic aneurysms/abdominal aorta diameter ≥5 cm by ultrasound (n=5), self-reported history of aortic or peripheral revascularization or aortic graft (n=94), echocardiographic evidence of aortic stenosis (n=28), moderate or greater aortic regurgitation (n=25), and missing covariates of interest (systolic blood pressure, heart rate, *APOE e4* carriage, education, smoking, and physical activity, n=557), and missing determination of cognitive status (no cognitive impairment, MCI, or dementia, n=27) [26]. Participants who self-identified as Asian from any site (n=15), whites from Jackson (n=2), and blacks from Minnesota and Maryland sites (n=23) were also excluded due to small numbers. The final analytic set included 4,461 participants after the exclusions (see supplemental table S2 for comparison of those included and excluded from this analysis).

At visit 5 participants were asked to bring all prescription and nonprescription medications taken within the prior two weeks, to not consume food or drinks, and refrain from tobacco and vigorous physical activity after midnight prior to the clinic visit or for 8 hours prior to the visit. Participants underwent a blood draw, B-mode scan of the abdominal aorta, standard 12-lead electrocardiogram (ECG), anthropometric measurements, extensive neuropsychometric testing, cerebral magnetic resonance imaging (MRI) on a subset of participants, assessment of functional abilities, and interviewer-administered questionnaires to obtain medical history and lifestyle information. Body weight was measured to the nearest 0.1 kilogram and height was recorded to the nearest centimeter. Three seated blood pressure measurements were obtained after a five-minute rest using an oscillometric automated sphygmomanometer (Omron HEM-907 XL, Omron Co. Ltd., Kyoto, Japan) and the average of the last two measurements was used.

Hypertension was defined as SBP ≥140 mm/Hg, diastolic blood pressure (DBP) ≥90 mm/Hg, or anti-hypertensive medication use. Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, anti-diabetic medication use, or self-reported physician diagnosis of diabetes. Prevalent coronary heart disease (CHD) and stroke were defined by baseline status and ARIC cohort surveillance data through the data of the participant's visit 5 examination. Standard resting 12-lead ECGs were digitally acquired using a GE MAC 1200 electrocardiograph (GE, Milwaukee, WI) at 10 mm/mV calibration and a speed of 25 mm/s. ECGs were centrally processed using GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin) at the Epidemiological Cardiology Research Center at the Wake Forest School of Medicine. Physical activity was assessed using the Baecke questionnaire [27]. Participants self-reported up to four sport activities and the frequency (hours/week) and duration (months/year) with which the activity was performed within the last year. Each sport activity was assigned a metabolic equivalent [28] thereby allowing for the estimation of Metabolic Equivalent of Task (MET)-min/week of activity performed. The

MET-min/week was then summed across the four reported activities. Participants that self-reported not engaging in a sport activity were assigned a MET-min/week value of 0. Physical activity was then categorized into tertiles of MET-min/week yielding the following groups: 0, tertile 1 ≤676.49, tertile 2 >676.49 & ≤1311.09, tertile 3 >1311.09 of the total MET-min/wk.

Pulse wave velocity

Details of the PWV methodology for ARIC-NCS have been reported [29]. Briefly, technicians measured PWV using the automated waveform analyzer VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan) [30] after participants were supine for 5 to 10 minutes. Carotid and femoral arterial pressure waveforms were acquired by applanation tonometry sensors on the left common carotid artery and left common femoral artery. Bilateral brachial and posterior-tibial arterial pressure waveforms were detected by plethysmographic and an oscillometric pressure sensor wrapped on both arms and ankles.

PWV was calculated as distance divided by transit time. Distance for carotid femoral PWV (cfPWV) was measured with a segmometer (Rosscraft, Surray, Canada) and calculated as the carotid to femoral distance minus the distance between the suprasternal notch to carotid. Measures of blood pressure were calculated simultaneously on all limbs by the VP-1000 Plus to obtain measures of estimated central systolic blood pressure (cSBP), central pulse pressure (cPP; [cSBP – right brachial DBP]), and pulse pressure amplification (PA; [(right brachial SBP- right brachial DBP) / cPP]. Technicians obtain at least two measurements and results were averaged. Outliers, defined as values three standard deviations above or below the mean, were winsorized for the analyses. Higher values of cfPWV, cSBP, and cPP indicate arterial stiffness and pressure pulsatility, whereas lower PA indicates greater pressure pulsatility. Repeat visits were conducted for a subset of participants at each field center approximately 4–8 weeks later (n = 79; mean age 75.7 years; 46 females). The intra-class correlation coefficients and 95% confidence intervals (95% CIs) for single measurements were 0.70 (0.59, 0.81) for cfPWV [31], 0.58 (0.45, 0.71) for cSBP, 0.60 (0.48, 0.72) for cPP, and 0.25 (0.09, 0.41) for PA.

Diagnosis of MCI and dementia

The current analyses were limited to ARIC-NCS participants who were seen in person [26]. MCI and dementia were ascertained based on the National Institute on Aging-Alzheimer's Association criteria [32, 33] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th edition [34]. Details of the classification of MCI and dementia have been described [26]. Briefly, the criteria incorporated neuropsychometric information (e.g. change in digit symbol substitution test (DSST), delayed word recall task (DWRT), and word fluency test (WFT) scores from previous visits 2, 3, and 4 and the current visit 5); the Mini-Mental State Examination Test (MMSE) score; the clinical dementia rating score (CDR) [35]; and the functional activities questionnaire (FAQ; Figure 1) [36]. The ARIC-NCS Classification Committee reviewed participants with suspected MCI or dementia and a diagnosis was confirmed by one physician and one neuropsychologist with adjudication by a third reviewer if applicable. MCI and dementia were considered as mutually exclusive where those with dementia were not considered to have MCI. Etiologic diagnoses were assigned

for participants who were seen in person and classified as having MCI or dementia, as previously described [26]. A panel of physicians and neuropsychologists assigned one primary etiologic diagnosis and could specify secondary etiologies. In this analysis, we evaluated only those with a primary etiology AD or cerebrovascular disease (CeVD). AD was defined following the criteria from the National Institute on Aging-Alzheimer's Association working groups [33] and CeVD was operationally defined. Specifically, a diagnosis of CeVD was considered primary or secondary according to an algorithm based on the core criteria from the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria [37]. The core criteria included neurological examination findings consistent with a cerebrovascular origin, a history of stroke, a history of sudden worsening of cognitive function in conjunction with a clinically diagnosed stroke, or imaging evidence of either extensive white matter hyperintensity burden or infarcts.

Statistical analysis

Participant characteristics by race and cognitive status were estimated as means and standard deviations or frequencies and percent, where appropriate. We calculated means and the 95% confidence intervals (CI) for cfPWV and pressure pulsatility measures by race and cognitive status and adjusted for age, sex, and education.

Multivariable, multinomial logistic regression was used to evaluate associations of 75^{th} percentile cut points for cfPWV, cSBP, and cPP and a 25^{th} percentile cut point for PA with MCI, dementia, versus no cognitive impairment (referent) and conditional odds ratios are reported. The upper 75^{th} percentile cut points were ≥1,324.0 cm/s for cfPWV, ≥157.0 mmHg for cSBP, and ≥82.4 mmHg for cPP. The lower 25^{th} percentile cut point was ≤0.853 for PA. Analyses were stratified by race and adjusted for age, sex, heart rate, education, study center (for whites only due to small numbers in blacks), *APOE* genotype, smoking status, and physical activity. As a priori hypotheses, we also tested interactions by race, hypertension, and diabetes. Analyses were stratified by race because of a statistically significant race interaction ($P<0.1$). P-values were two-sided with statistical significance of $P<0.05$ (SAS, version 9.2, SAS Institute, Inc., Cary, NC).

Results

Participant characteristics

Among the ARIC-NCS participants seen in person, 703 (19.8%) white participants were identified with MCI and 98 (2.8%) with dementia, and 178 (19.5%) black participants were identified with MCI and 39 (4.3%) with dementia. The mean age ranged from 74.0 ± 4.7 to 79.4 ± 4.5 years, and mean BMI ranged from 26.4 ± 4.8 to 29.4 ± 4.8 kg/m^2 across race-cognitive status groups (Table 1). Among whites and blacks, those with MCI or dementia were older, had higher SBP, arterial stiffness and pressure pulsatility, had a lower education, and were more likely to have diabetes, prevalent CHD, and prevalent stroke compared to those with no cognitive impairment (Table 1).

Relationships between cfPWV and pressure pulsatility with cognitive status

The age, sex, and education-adjusted, estimated means of cfPWV and pressure pulsatility by cognitive status and race are shown in the supplemental table S2. Among whites, after adjusting for heart rate, age, sex, education, center, APOE genotype, smoking status and physical activity, those with cfPWV or cSBP ≥75th percentile had a higher prevalence of MCI compared to participants <75th percentile (odds ratio (OR); 95% CI: 1.27 (1.02,1.56) for cfPWV and 1.28 (1.04, 1.57) for cSBP) and those with cPP ≥75th percentile had a higher prevalence of MCI and dementia compared to participants <75th percentile (OR:1.27 (1.03, 1.58) for MCI and OR: 1.76 (1.06, 2.92) for dementia; Table 2). Also among whites, those with PA ≤25th percentile had a higher prevalence of dementia compared to participants >25th percentile (OR: 1.65 (1.01, 2.70)). Associations of cfPWV, cSBP, cPP and PA with MCI and dementia were not statistically significant and estimates had a large variance among black participants. There was no evidence for effect modification by hypertension or diabetes, and all results were robust to additional adjustment for hypertension or diabetes. Adjustment for mean arterial pressure slightly increased the variance of the estimates, but did not visibly change the magnitude of the association between cfPWV and MCI or dementia. We thus present the main results unadjusted for mean arterial pressure

Association of cfPWV and pressure pulsatility with the primary etiology of MCI and dementia

AD was more frequent than CeVD as the primary etiology of MCI and dementia among whites and blacks (Table 3). Among whites with MCI and among blacks with dementia, those with CeVD as the primary etiology had higher cfPWV compared to AD as the primary etiology. Among whites, those with AD as the primary etiology had consistently higher cSBP, cPP and lower PA compared to those with CeVD as the primary etiology among MCI and dementia, although the differences were not statistically significant. Conversely, among blacks, those with CeVD as the primary etiology had consistently higher cfPWV, cSBP, and cPP compared to those with AD as the primary etiology among MCI and dementia, although the differences were not statistically significant.

Discussion

We evaluated the association between central arterial stiffness and pressure pulsatility with the prevalence of MCI and dementia in a cohort of white and black older adults in the United States. Our results show that higher central arterial stiffness and pressure pulsatility were associated with the prevalence of MCI and dementia in whites. We also showed that the association between cfPWV and pressure pulsatility with the prevalence of MCI and dementia varied across central arterial stiffness and pulsatility measures, although, cPP was consistently associated with the prevalence of MCI and dementia among whites.

Central arterial stiffness is associated with impaired cognitive function in community-based studies [38–42], as well as in systematic reviews and meta-analyses [1–4]. In contrast, studies of the association of central arterial stiffness and pressure pulsatility with MCI and dementia yielded inconsistent results [1, 14–18]. While most prior studies distinguished between CeVD and AD dementia, CeVD and AD dementia diagnoses are almost always

clinical and therefore subject to substantial imprecision. Furthermore, the two pathologies often overlap and most dementias in the elderly are a mix of both [43].

PWV was reported to be higher among those with CeVD, AD dementia, and MCI of either etiology compared to those with normal cognitive function among elderly adults reporting memory impairment in an outpatient setting [14]. Similarly, a meta-analysis report showed that PWV was higher among those with CeVD compared to those with AD dementia or controls [16], although these analyses pooled studies that used heterogeneous methods of CeVD and AD dementia diagnostic classification, different PWV methods, as well as studies reporting on brachial-ankle PWV (baPWV). The resulting heterogeneity is of concern, not least because baPWV reflects both central and peripheral arterial stiffness and may bias associations with central arterial stiffness, i.e. the property that is more related to cardiovascular disease and end-organ function.

One of the two prospective studies in the literature, the Framingham Offspring study, reported cfPWV to be associated with the 10-year incidence of MCI among all study participants and with the incidence of all-cause dementia among those without diabetes [5]. Further analysis showed that cPP was not associated with the risk of MCI or dementia. The other prospective evaluation - the Rotterdam Study - did not detect an association between cfPWV and the risk of CeVD or dementia after a mean follow-up of 4.4 years, although the number of cases of CeVD was small (11 incident cases of CeVD) and MCI was not ascertained [15]. In the current study, estimates between cfPWV and the prevalence of MCI among whites were slightly higher than for dementia, but the opposite was seen for cPP, suggesting that it may be informative to evaluate multiple measures of arterial stiffness and pressure pulsatility.

Our primary analyses did not rely on etiological subtypes of dementia (CeVD versus AD dementia), because the majority of our dementia cases have more than one etiologic diagnosis [26], and because we recognize that a clinical diagnosis of CeVD has poor sensitivity and specificity [44, 45]. In secondary analyses, we evaluated cfPWV and pressure pulsatility among those with a primary etiologic diagnosis of CeVD or AD. Our results showed that cfPWV was higher for CeVD compared to AD in all subgroups, but statistically significant for whites with MCI and blacks with dementia. Pressure pulsatility, however, was consistently higher for those with AD diagnosis compared to those with CeVD diagnoses among whites, but higher for CeVD compared to AD among blacks. Although cfPWV and pressure pulsatility may have stronger associations with CeVD than AD dementia, evidence suggests that both individuals with CeVD and AD dementia have higher cfPWV than those with MCI and normal cognitive function [14]. Moreover, cfPWV is associated with increases in cerebral β-amyloid deposition among older adults [46], suggesting that central arterial stiffness could contribute to the accumulation of β-amyloid that is associated with AD-related dementias. More precise etiological diagnoses using biomarkers for cerebrovascular and Alzheimer disease will be needed to refine relationships between cfPWV, pressure pulsatility, and disease mechanisms.

We add to the literature an evaluation of central arterial stiffness and pressure pulsatility measures among a large sample of white and black older adults with a detailed and up-to-

date characterization of MCI and dementia. The evidence relating central arterial stiffness and pressure pulsatility to MCI and dementia is based on studies of predominantly white individuals. Interestingly, we detected an effect modification by race by which the observed associations were stronger among whites. This is in contrast to what we expected, since blacks have a high prevalence of risk factors for vascular disease and dementia such as hypertension, diabetes, and stroke. The cumulative effects of these risk factors, arterial stiffness, and pressure pulsatility over the life course may have larger effects on the neurovascular system and cognitive status than PWV measured later in life when the association is attenuated. Longitudinal characterization of the observed associations is warranted to assess whether arterial stiffness and pressure pulsatility predict MCI and dementia among white and black older adults, particularly since the ARIC-NCS study documented a higher prevalence of cerebral infarcts at baseline [22] and a greater increase in white matter hyperintensities over a median of 10.6 years among black compared with white participants [21].

Increased central arterial stiffness and pressure pulsatility have been posited to contribute to cerebral microvascular damage, cognitive impairment, and dementia by reducing mean cerebral blood flow and increasing pulsatile stress in the brain. Additional pathways contributory to cognitive decline and dementia associated with cerebral hypoperfusion have been proposed [47, 48]. Individuals with dementia have lower mean cerebral blood flow and higher pulsatile flow velocity in middle cerebral arteries, compared to those with normal cognition [49]. PWV [50] and cPP [51] are associated with these hemodynamic alterations in the middle cerebral artery, and cerebral β-amyloid deposition among older adults [46], as further links between PWV and cerebral microvascular damage, cognitive impairment and dementia.

Our study has several limitations. The cross-sectional design precludes the assessment of temporality (and of causality) in the observed associations. ARIC-NCS visit 5 participants that were excluded from these analyses were older, had a higher BMI and MAP, and a higher prevalence of hypertension and coronary heart disease compared to participants included in the analysis. Thus, the observed associations may have been attenuated since participants included in the analysis were healthier than those we excluded. Associations with PA may also have been attenuated due to the lower measurement repeatability of PA. The estimated ICC for an average of 2 measurements of PA in this study would be 0.45, according the Spearman-Brown formula [52]. An ICC of 0.45 is fair according to Fleiss [53], but additional replicates would improve the repeatability. Future studies, therefore, should evaluate their repeatability estimates and take an average of measures that would optimize their ICC. On occasion, some PWV measurements were not collected due to technical difficulties, participant factors, and scheduling conflicts. Since black participants in the ARIC-NCS cohort predominantly reside in Jackson, MS, the observed associations may not generalize to blacks as a diverse demographic group. An additional limitation to consider is the potential for survival bias due to attrition over the course of >25 years of follow-up, which predominantly affected the black members of the cohort. Differential survival by race may have contributed to differences in risk factor profiles and in associations among whites and blacks in ARIC-NCS. The surviving cohort members likely are healthier and more vigorous than those who did not take part in the examination, which would – in general –

tend to attenuate the observed associations. The internal validity of the associations estimated in this study is supported by our multivariable statistical adjustment for participant characteristics that influenced attrition, and we deem our results from this population-based cohort to be generalizable to other populations of older adults of comparable demographic characteristics. Although we were able to subdivide our MCI and dementia groups by presumed etiology, assignment of a vascular etiology has challenges that may lead to loss of sensitivity and specificity, and it further reduced subgroup sizes, especially in blacks.

Central artery stiffening is largely age-related, but also modifiable and may be a possible target for intervention intended to prevent and reduce cerebrovascular disease. Arterial de-stiffening has been observed with blood pressure control [54, 55] and with lifestyle interventions such as habitual physical activity [56–59]. In addition to physical exercise, weight loss, smoking cessation, salt reduction [59], and dietary interventions [56] have also been shown to have promise in reducing central arterial stiffness.

In conclusion, central arterial stiffness and pressure pulsatility are associated with the prevalence of MCI and dementia among white older adults. Persuasive epidemiologic evidence suggests that central arterial stiffness and pressure pulsatility contribute to cerebrovascular disease and dementia. Knowledge of the degree to which central arterial stiffness and pressure pulsatility adversely impact brain structure and function is therefore relevant to strategies to reduce or reverse central arterial stiffness as potential opportunities to influence the development of MCI and dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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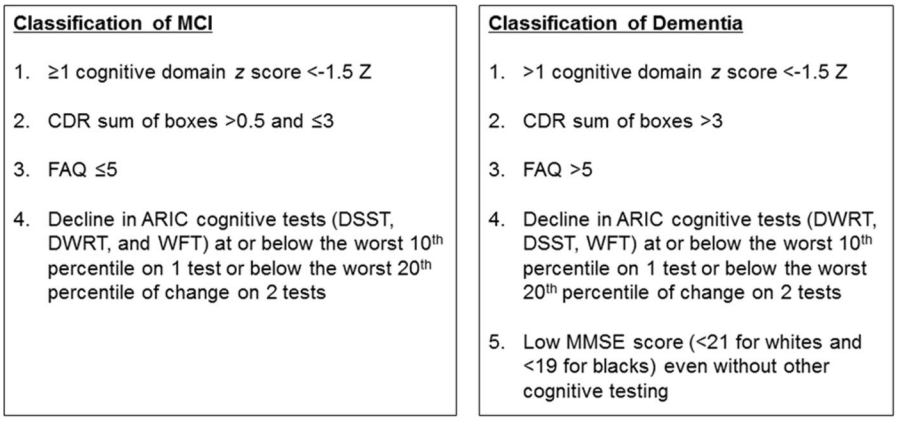

Figure 1.

Classification of MCI and dementia included neuropsychometric information (change in digit symbol substitution test (DSST), delayed word recall task (DWRT), and word fluency test (WFT) scores from previous visits 2, 3, and 4 and the current visit 5); Mini-Mental State Examination Test (MMSE); clinical dementia rating score (CDR); and the functional activities questionnaire (FAQ).

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Table 1

ARIC-NCS participant characteristics by race and cognitive status, N= 4461

Variable	Whites n=3550			Blacks n=911		
	Normal n=2749 (77%)	MCI n=703 (20%)	Dementia n=98 (3%)	Normal n=694 (76%)	MCI n=178 (20%)	Dementia n=39 (4%)
Female, n (%)	1622 (59.0)	343 (48.8)	49 (50.0)	464 (66.9)	122 (68.5)	24 (61.5)
Age, years	75.2 ± 4.9	76.8 ± 5.2	78.7 ± 5.1	74.0 ± 4.7	75.8 ± 5.1	79.4 ± 4.5
Body mass index, kg/m^2	27.7 ± 4.4	27.6 ± 4.4	26.6 ± 4.3	29.4 ± 4.8	29.1 ± 4.8	26.4 ± 4.8
Heart rate, bpm	61.2 ± 9.4	61.9 ± 10.3	62.3 ± 12.5	63.9 ± 10.4	63.8 ± 18.8	65.1 ± 10.8
Systolic blood pressure, mmHg	128.5 ± 17.0	130.6 ± 18.3	133.3 ± 17.4	133.3 ± 18.0	135.2 ± 18.8	135.6 ± 19.1
Diastolic blood pressure, mmHg	65.7 ± 10.1	65.1 ± 10.7	65.1 ± 9.6	70.0 ± 10.1	69.2 ± 10.9	68.7 ± 10.7
Education, n (%)						
< High school	227 (8.3)	66 (9.4)	23 (23.5)	168 (24.2)	51 (28.7)	22 (56.4)
High school	1027 (37.4)	249 (35.4)	27 (27.6)	145 (20.9)	41 (23.0)	7 (17.9)
> High school	1495 (54.4)	388 (55.2)	48 (49.0)	381 (54.9)	86 (48.3)	10 (25.6)
APOE genotype, number of ε4 alleles						
0	2098 (76.3)	498 (70.8)	47 (48.0)	437 (63.0)	97 (54.5)	18 (46.2)
1	615 (22.4)	192 (27.3)	43 (43.9)	236 (34.0)	67 (37.6)	13 (33.3)
2	36 (1.3)	13 (1.8)	8 (8.2)	21 (3.0)	14 (7.9)	8 (20.5)
Current/former smoker (vs. never), n (%)	1605 (58.4)	408 (58.0)	56 (57.1)	314 (45.2)	90 (50.6)	23 (59.0)
Physical Activity, MET-min/week						
0	696 (25.3)	199 (28.3)	38 (38.8)	264 (38.0)	75 (42.1)	22 (56.4)
Tertile 1, ≤ 676.49	580 (21.1)	189 (26.9)	24 (24.5)	185 (26.7)	58 (32.6)	10 (25.6)
Tertile 2, >676.49 & ≤1311.09	675 (24.6)	171 (24.3)	18 (18.4)	149 (21.5)	27 (15.2)	5 (12.8)
Tertile 3 >1311.09	798 (29.0)	144 (20.5)	18 (18.4)	96 (13.8)	18 (10.1)	2 (5.1)
Type 2 diabetes, n (%)	713 (26.1)	217 (31.0)	34 (35.4)	263 (38.3)	81 (46.0)	19 (48.7)
Hypertension, n (%)	1857 (68.0)	494 (71.2)	66 (71.0)	598 (86.4)	157 (88.2)	30 (81.1)
Prevalent CHD, n (%)	379 (14.0)	102 (14.7)	28 (29.2)	57 (8.2)	21 (12.0)	5 (13.2)
Prevalent Stroke, n (%)	53 (1.9)	27 (3.8)	7 (7.1)	26 (3.7)	13 (7.3)	2 (5.1)
cfPWV >75th percentile, n (%)	518 (20.7)	182 (28.9)	26 (31.3)	213 (32.5)	61 (35.9)	22 (64.7)
cSBP >75th percentile, n (%)	558 (22.4)	166 (26.6)	21 (25.3)	215 (33.0)	54 (32.3)	13 (38.2)
cPP >75th percentile, n (%)	556 (22.5)	165 (26.5)	29 (34.9)	197 (30.4)	52 (31.0)	9 (27.3)

Variable	Whites n=3550			Blacks n=911		
	Normal n=2749 (77%)	**MCI n=703 (20%)**	**Dementia n=98 (3%)**	**Normal n=694 (76%)**	**MCI n=178 (20%)**	**Dementia n=39 (4%)**
PA <25th percentile, n (%)	605 (24.7)	146 (23.7)	28 (34.1)	171 (26.4)	45 (26.9)	4 (12.1)

Values are Number (%) or mean ± SD

MCI: mild cognitive impairment; cfPWV: carotid femoral pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure; PA: pulse pressure amplification

Cut points were ≥1,324.0 cm/s for cfPWV, ≥157.0 mmHg for cSBP, ≥82.4 mmHg for cPP, and ≤0.853 for PA

Table 2

Multivariate regression analysis of cfPWV and pressure pulsatility with cognitive status (no cognitive impairment, MCI, dementia): ARIC-NCS visit 5

Measure	Cognitive Status referent = normal	Whites		Blacks	
		Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
cfPWV, ≥ 75th percentile	MCI	1.28 (1.03, 1.57)	1.27 (1.02, 1.56)	0.97 (0.66, 1.41)	0.95 (0.65, 1.39)
	Dementia	1.26 (0.77, 2.08)	1.25 (0.75, 2.09)	2.11 (0.96, 4.62)	1.97 (0.89, 4.36)
cSBP, ≥ 75th percentile	MCI	1.29 (1.05, 1.58)	1.28 (1.04, 1.57)	0.86 (0.59, 1.26)	0.85 (0.58, 1.24)
	Dementia	1.16 (0.69, 1.93)	1.17 (0.69, 1.97)	0.82 (0.37, 1.82)	0.81 (0.36, 1.81)
cPP, ≥75th percentile	MCI	1.31 (1.06, 1.62)	1.27 (1.03, 1.58)	0.84 (0.56, 1.25)	0.83 (0.56, 1.24)
	Dementia	1.89 (1.16, 3.09)	1.76 (1.06, 2.92)	0.49 (0.20, 1.20)	0.49 (0.20, 1.23)
PA, ≤ 25th percentile	MCI	1.00 (0.81, 1.24)	0.98 (0.79, 1.21)	0.95 (0.63, 1.44)	0.95 (0.63, 1.44)
	Dementia	1.69 (1.04, 2.72)	1.65 (1.01, 2.70)	0.32 (0.10, 1.01)	0.34 (0.11, 1.06)

MCI: mild cognitive impairment; cfPWV: carotid femoral pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure; PA: pulse pressure amplification

Model 1 includes adjustment for heart rate, age, sex, education, and center (for whites only)

Model 2 is model 1 plus adjustment for *APOE* genotype, smoking (current/former vs never), and physical activity (0, tertile 1 ≤676.49, tertile 2 >676.49 and ≤1311.09, and tertile 3 >1311.09 total MET-min/week

Cut points were ≥1,324.0 cm/s for cfPWV, ≥157.0 mmHg for cSBP, ≥82.4 mmHg for cPP, and ≤0.853 for PA

P-values for race interaction: 0.05 in model 1 and 0.13 in model 2 for cfPWV; 0.53 for model 1 and 0.50 for model 2 for cSBP; 0.28 in model 1 and 0.22 in model 2 for cPP; and 0.06 in model 1 and 0.06 in model 2 for PA

Table 3

Adjusted means (95% confidence limits) of cfPWV and pressure pulsatility by primary etiology of MCI and dementia by race

	MCI		Dementia	
Whites	AD (n=486)	CeVD (n=56)	AD (n=62)	CeVD (n=20)
cfPWV, cm/s	1154.5 (1120.3, 1188.7)	1286.8 (1200.3, 1373.2)	1158.7 (1074.0, 1243.4)	1216.7 (1078.7, 1354.6)
cSBP, mmHg	144.1 (141.8, 146.4)	142.5 (136.6, 148.4)	143.9 (138.1, 149.7)	140.8 (131.5, 150.1)
cPP, mmHg	73.7 (71.7, 75.7)	70.9 (65.8, 76.0)	74.5 (69.5, 79.5)	72.3 (64.2, 80.4)
PA	0.92 (0.91, 0.93)	0.94 (0.91, 0.97)	0.89 (0.86, 0.92)	0.91 (0.86, 0.96)
Blacks	AD (n=139)	CeVD (n=19)	AD (n=29)	CeVD (n=9)
cfPWV, cm/s	1244.4 (1183.3, 1305.5)	1381.2 (1224.8, 1537.6)	1291.0 (1156.7, 1425.2)	1668.6 (1433.9, 1903.3)
cSBP, mmHg	146.1 (142.2, 150.0)	154.7 (144.8, 164.6)	147.2 (138.8, 155.7)	157.8 (142.9, 172.6)
cPP, mmHg	73.4 (69.6, 77.1)	77.2 (66.9, 87.4)	71.6 (63.3, 80.0)	75.6 (61.2, 90.0)
PA	0.92 (0.90, 0.94)	0.88 (0.83, 0.93)	0.91 (0.87, 0.95)	0.93 (0.86, 1.01)

Values are means (95% confidence limits) adjusted for age, sex, and education

AD: Alzheimer's disease; CeVD: cerebrovascular disease; MCI: mild cognitive impairment; cfPWV: carotid femoral pulse wave velocity; cSBP: central systolic blood pressure; cPP: central pulse pressure; PA: pulse pressure amplification