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Microvascular and Macrovascular Abnormalities, and Cognitive and Physical Function In Older Adults: Cardiovascular Health Study

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Abstract

Objectives—To evaluate and compare the associations of microvascular and macrovascular abnormalities with cognitive and physical function

Design—Cross-sectional analysis of the Cardiovascular Health Study (1998–1999)

Setting—Community

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Participants—2452 participants (mean age 79.5 years) with available data on ≥3 of 5 microvascular abnormalities (brain, retina, kidney) and ≥3 of 6 macrovascular abnormalities (brain, carotid artery, heart, peripheral artery)

Measurements—Standardized composite scores derived from 3 cognitive tests (Modified Mini-Mental State Examination, digit-symbol substitution test, trail making test) and 3 physical tests (gait speed, grip strength, 5-times sit-to-stands)

Results—Compared with individuals with low microvascular and macrovascular burden, those with high microvascular and macrovascular burden had the worst cognitive function (mean score difference [95% confidence interval]: −0.30 [−0.37, −0.24]) and physical function (−0.32 [−0.38, −0.26]). Individuals with high microvascular burden alone had similarly lower scores as those with high macrovascular burden alone (cognitive function: −0.16 [−0.24, −0.08] versus −0.13 [−0.20, −0.06], respectively; physical function: −0.15 [−0.22, −0.08] versus −0.12 [−0.18, −0.06], respectively). Psychomotor speed and working memory, assessed by trail making test, were only impaired in the presence of high microvascular burden. Of the 11 vascular abnormalities considered, white matter hyperintensity, cystatin C-based glomerular filtration rate, large brain infarct, and ankle-arm index were independently associated with both cognitive and physical function.

Conclusion—Microvascular and macrovascular abnormalities assessed from non-invasive tests of the brain, kidney, and peripheral artery were independently associated with poor cognitive and physical function in older adults. Future research should evaluate the usefulness of these tests in prognostication.

Keywords

Vascular disease; microvascular disease; cognitive function; physical function

INTRODUCTION

The evidence of microvascular and macrovascular abnormalities on non-invasive tests of the brain, retina, kidney, carotid artery, and peripheral artery has been linked to poor functional status, frailty, disability, and mortality in older adults.[1–7] Because the information gathered from multiple organs and vascular systems may be more useful than using information from a single organ in predicting future disease risk,[8] investigators have summarized abnormalities from multiple non-invasive tests into a single composite score that represents the overall burden of vascular disease or physiologic impairment.[6,7,9–11] Recently, we further refined this approach by assessing the burden of microvascular and macrovascular abnormalities separately.[12] While individuals with high burden of microvascular abnormalities lived a similar number of years as those with high burden of macrovascular abnormalities, the former spent longer time in disability.[12] Examining the cognitive and physical function impairment associated with microvascular and macrovascular abnormalities may elucidate the differential influences that microvascular and macrovascular abnormalities have on the disabling process. In addition, given that results from multiple tests can be correlated, a specific test that is more strongly associated with functional status may prove useful as a prognostic test.

The Cardiovascular Health Study (CHS) is a population-based cohort with measurements of microvascular and macrovascular abnormalities in a large number of older adults. We conducted a cross-sectional analysis to compare the associations of microvascular and macrovascular abnormalities and cognitive and physical function, and to identify which abnormalities that are independently associated with functional status.

METHODS

Study Population

The CHS is a population-based cohort study of cardiovascular disease (CVD) in community-dwelling adults aged 65 years or older.[13] In 1989–1990, 5201 adults were recruited from 4 United States communities and, in 1992–1993, an additional 687 African Americans were recruited.[14] In 1996–1999, non-invasive tests of the brain, retina, heart, kidney, and carotid and peripheral artery were performed. From these tests, 5 measures of microvascular abnormalities and 6 measures of macrovascular abnormalities were assessed. This cross-sectional analysis included 2452 participants who had information on ≥3 measures of microvascular abnormalities and ≥3 measures of macrovascular abnormalities and attended the 1998–1999 clinic visit. The institutional review boards of the CHS participating centers and Beth Israel Deaconess Medical Center, Boston, MA, approved this study.

Measurement of Microvascular and Macrovascular Abnormalities

Participants underwent measurements of cystatin C, urinary albumin, retinal photography, electrocardiography (EKG), ankle-arm index, carotid ultrasonography, and brain magnetic resonance imaging (MRI) in 1996–1999. Detailed procedures have been described elsewhere.[15–22] Briefly, cystatin C was measured with a particle-enhanced immunonephelometric assay using the BN II nephelometer (Dade Behring, Deerfield, IL) in stored fasting blood samples (intra-assay coefficients of variation: 2.0–2.8%, inter-assay coefficients of variation: 2.3–3.1%).[15] Cystatin C-based glomerular filtration rate (GFR) was calculated by 76.7 × cystatin $C^{-1.19}$ (ml/min/1.73 m^2).[23] Urinary albumin was measured from a random morning spot sample in the fasting state using the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA). Retinal photographs were obtained from one randomly selected eye after 5 minutes of dark adaptation. According to a standardized protocol,[16,17] trained graders who were masked to participant identity evaluated the photographs for retinopathy, arteriovenous nicking, focal arteriolar narrowing, generalized arteriolar narrowing, and generalized venular widening. A 12-lead EKG was reviewed at the reading center according to a standardized protocol.[18] The ankle-arm index was computed as the ratio of ankle to right arm systolic blood pressure and the lower value of the left or right index was used.[19] Internal and common carotid artery intima-media thickness (IMT) and carotid stenosis were measured from carotid ultrasonography.[20] White matter hyperintensity and infarct were assessed from the brain MRI by neuroradiologists blinded to clinical information.[21,22]

Based on these tests, we assessed 5 measures of microvascular abnormalities and 6 measures of macrovascular abnormalities. Each measure was categorized into 3 severity levels

(minimal, modest, or moderate-to-severe abnormality) using cut points that were clinically meaningful or previously associated with poor outcomes.[3,24–26] We then assigned scores for minimal (0 points), modest (1 point), or moderate-to-severe abnormalities (2 points) for each measure and aggregated them to construct summary indices (microvascular index: 0–10, and macrovascular index: 0–12). The prognostic value of these indices has been validated against disability and life expectancy.[12]

Measurement of Functional Status and Clinical Characteristics

During the 1998–1999 clinic examination, cognitive function was assessed using the Modified Mini-Mental State Examination (3MSE); digit symbol substitution test, a measure (number of correct items) of attention and visuomotor coordination; and trail making test part B minus part A, a measure (time [sec]) of psychomotor speed and working memory. Physical function was assessed in terms of gait speed (m/sec) from a 15-foot walk at usual speed; dominant hand grip strength (kg), the average of 3 measurements using a Jamar hand-held dynamometer[13]; and 5-time sit-to-stand test (time [sec] to perform 5 consecutive chair stands). Our primary outcomes were composite scores of cognitive function and physical function that were calculated by averaging standardized z-scores from 3 cognitive function tests and 3 physical function tests, respectively. We changed the sign of z-scores from trail making test part B minus part A and 5-time sit-to-stand test to make higher scores indicate better function. These z-scores were derived using the means and standard deviations of the CHS participants at the 1998–1999 examination. The mean (standard deviation) was 0.00 (0.81) for cognitive function score and 0.00 (0.74) for physical function score.

The following clinical characteristics were assessed: alcohol intake, smoking, physical activity (kcal/week) using the modified Minnesota Leisure-Time Activities questionnaire, and body mass index (kg/m^2). We defined hypertension as blood pressure ≥140/90 mmHg or antihypertensive medication use; and diabetes as the use of oral hypoglycemic agents or insulin in the past year, or fasting glucose ≥126 mg/dl for those who did not use any hypoglycemic agents. Clinical CVDs, including angina, myocardial infarction, congestive heart failure, peripheral arterial disease, stroke, and transient ischemic attack, were adjudicated based on medical records.[27]

Statistical Analysis

The amount of missing data varied from 2% (EKG abnormalities) to 19% (retinal microvascular signs). We performed a single multivariable imputation of missing data using sociodemographic characteristics, lifestyle, comorbidities, measures of vascular abnormalities, functional status, and disability. Our main analysis was to assess the associations of microvascular and macrovascular burden with the composite scores of cognitive and physical function. We determined the importance of microvascular burden versus macrovascular burden by comparing the difference in outcomes between those at 25^{th} percentile (low burden) and at 75^{th} percentile (high burden) of each index. Linear regression was used to model the mean difference in outcomes as a function of microvascular index, macrovascular index, their product term, and potential confounders, including age (years), sex, white race, education (years), alcohol consumption (≥1 drink/week or <1), smoking status (never, former, or current), physical activity quintile (kcal/week), and body mass

index (<25.0, 25.0–29.9, or ≥30.0 kg/m^2). For physical function, we adjusted for arthritis, but not for physical activity due to collinearity with outcomes. For more intuitive interpretation of composite scores, we contrasted adjusted mean differences in composite functional scores to mean scores for age.

As secondary analyses, we evaluated the associations of both indices with individual test scores. Spearman correlation coefficients were estimated between any 2 measures of microvascular and macrovascular abnormalities because highly correlated measures may not provide additional information on vascular disease burden. To determine which vascular measures were independently associated with functional status, we included all 11 abnormalities simultaneously in the regression model. In sensitivity analyses, we adjusted for hypertension and diabetes and restricted analyses to non-diabetics and to those without clinical CVD. All analyses were performed in Stata SE v11.2 (StataCorp, College Station, Tx) and 2-sided $p<0.05$ was considered statistically significant.

RESULTS

Compared with the 1729 participants who were excluded because of missing data on vascular abnormalities, the 2452 participants in the present analysis were younger (mean age: 79.5 versus 81.4 years) and more often male (40% versus 33%) and white (84% versus 80%). They were healthier with a lower prevalence of clinical CVD (35% versus 47%) and better cognitive (3MSE: 90.8 versus 79.7 points) and physical function (gait speed: 0.87 versus 0.72 m/sec). Other characteristics of the study population are summarized in Table 1. The correlation between any 2 measures of microvascular abnormalities from different organ systems was the strongest for retinal microvascular signs and urine albumin-to-creatinine ratio (0.10; $p<0.001$). The strongest correlation between any 2 measures of macrovascular abnormalities was observed between carotid artery stenosis and ankle-arm index (0.23; $p<0.001$). The median (25th percentile, 75th percentile) microvascular index and macrovascular index was 2 (1, 4) and 5 (3, 7), respectively.

Burden of Microvascular and Macrovascular Abnormalities and Functional Status

Compared with individuals with low microvascular and macrovascular burden, those with high microvascular and macrovascular burden had the worst cognitive function (unadjusted mean composite score difference [95% confidence interval]: −0.52 [−0.60, −0.45]; adjusted mean difference: −0.30 [−0.37, −0.24]) and physical function (unadjusted: −0.39 [−0.46, −0.33]; adjusted: −0.32 [−0.38, −0.26]) (Figure). Those with high microvascular burden alone had approximately the same decrement in composite scores as those with high macrovascular burden alone for both cognitive function (unadjusted mean difference for microvascular alone: −0.28 [−0.37, −0.18] versus macrovascular alone: −0.29 [−0.37, −0.22]; adjusted mean difference for microvascular alone: −0.16 [−0.24, −0.08] versus macrovascular alone: −0.13 [−0.20, −0.06]) and physical function (unadjusted mean difference for microvascular alone: −0.24 [−0.31, −0.15] versus macrovascular alone: −0.10 [−0.17, −0.03]; adjusted mean difference for microvascular alone: −0.15 [−0.22, −0.08] versus macrovascular alone: −0.12 [−0.18, −0.06]). There was no evidence of interaction between microvascular and macrovascular abnormalities on cognitive function ($p=0.76$) and

physical function (p=0.16), which suggests that both types of abnormalities contribute additively to functional impairment. The lower cognitive function scores in those with high microvascular burden alone, high macrovascular burden alone, and high burden of both abnormalities were equivalent to those in individuals with an age difference of 3.3 years, 2.7 years, and 6.3 years, respectively. The corresponding differences in physical functional score were 3.3 years, 2.6 years, and 7.0 years of age difference. For individual test scores, it was evident that psychomotor speed and working memory assessed by trail making test were significantly impaired only when there was high microvascular burden (Figure).

Individual Vascular Abnormalities and Functional Status

When individually examined, higher severity in each vascular measure was associated with lower cognitive and physical function scores (Table 2). When all 11 measures were simultaneously included in the regression model, not all measures were statistically significantly associated with functional status: white matter hyperintensity, cystatin C-based GFR, large brain infarct, and ankle-arm index were associated with both cognitive and physical function. However, urine albumin-to-creatinine ratio and internal carotid artery IMT were only associated with physical function.

Sensitivity Analyses

The relation between vascular burden and composite scores did not change substantially when hypertension and diabetes were additionally adjusted for or when the analysis was restricted to those without diabetes (see appendix). When the analysis was restricted to those without clinical CVD, high macrovascular burden alone was only associated with impaired physical function but not with cognitive function.

DISCUSSION

In community-dwelling older adults, having a greater burden of microvascular and macrovascular abnormalities was associated with poor cognitive and physical function. The association with cognitive and physical function was similar between microvascular and macrovascular abnormalities, except for psychomotor speed and working memory that were impaired only in the presence of high microvascular burden. Of the 5 microvascular and 6 macrovascular abnormalities considered, we found that only white matter hyperintensity, cystatin C-based GFR, large brain infarct, and ankle-arm index were independently associated with impaired cognitive and physical function.

We examined an extensive list of microvascular and macrovascular measures in relation to composite and individual test scores of cognitive and physical function. Our study complements past research that examined macrovascular burden alone[6,7,9–11] or individual microvascular abnormalities in a single organ system, such as the brain,[1,2] retina,[3] and kidney.[4,5] The degree of functional impairment among individuals with high microvascular or macrovascular burden was as large as the difference observed between those who were almost 3–7 years apart in age. In addition, the impairment in psychomotor speed and working memory was associated with high microvascular burden, as previously reported for white matter hyperintensity.[28] This may explain the greater impact of microvascular

abnormalities than macrovascular abnormalities on disability-free life expectancy in our previous analysis of the CHS cohort.[12]

Given the cross-sectional nature of our study, the temporal relationship between vascular abnormalities and functional impairment cannot be determined. As such, our findings cannot be interpreted causally. Nonetheless, based on evidence from several prospective studies in which vascular abnormalities predicted future development of functional impairment,[1,2,4,6] it seems plausible that vascular abnormalities have preceded functional decline. As vascular risk factor levels change in advanced age and their associations with clinical outcomes may weaken,[29] we speculate that the burden of microvascular and macrovascular abnormalities calculated from objective tests may better represent accumulated lifetime exposure to vascular risk factors in older adults.

Furthermore, our findings support the notion that abnormalities in multiple vascular beds may represent cumulative insults and decreased reserve in different physiologic systems that lead to frailty and functional impairment.[7,9] In previous studies,[7–9] types of vascular measures that comprised the summary index were chosen based on their availability and physiologic rationale. In our multivariable analysis, however, not all 11 vascular measures were independent predictors of functional status: only 4 measures (white matter hyperintensity, cystatin C-based GFR, large brain infarct, and ankle-arm index) were independently associated with both cognitive and physical function. These findings indicate that other measures (e.g. small brain infarct, retinal microvascular signs, carotid artery IMT, carotid artery stenosis, and EKG abnormalities) provide little additional information on functional status. This information may facilitate clinical translation of previous research findings on microvascular and macrovascular abnormalities in identifying high-risk individuals for functional decline.

Our study should be carefully interpreted with consideration of several limitations in the measurements of vascular disease burden and composite scores of cognitive and physical function. First, exclusion of sicker individuals who did not complete vascular measurements may have underestimated the associations between vascular abnormalities and functional status. Our imputation for incomplete data on vascular measurements is valid under the unverifiable assumption that we have sufficient information to predict missingness. Second, participants in our analysis were the survivors (mean age: 79.5 years) of the CHS cohort at the time of non-invasive tests, which limits generalizability of our findings to populations of different age range and further attenuates the associations with outcomes. Third, we assigned equal weights to each microvascular and macrovascular measure to create the summary scores, which might seem arbitrary. Although the use of different weights may outperform our approach in predicting certain outcomes, such weights may not work as well for other outcomes due to overfitting. The arbitrary nature of our weighting approach does not invalidate our summary scores that have been validated.[12] Fourth, we acknowledge that classification of microvascular and macrovascular abnormalities was somewhat subjective for certain measures, because EKG abnormalities or reduced cystatin-C based GFR could result from both types of abnormalities. However, other measures derived from the brain MRI, retinal photography, carotid ultrasound, and ankle-arm index were specific to either a microvascular or macrovascular process. Moreover, cystatin-C levels are affected by thyroid

function, which was not considered in our analysis. Misclassification of cystatin-C based GFR category is possible.[30] Lastly, the composite cognitive and physical function scores that we derived from 3 cognitive and 3 physical function tests have not been validated against clinical outcomes, although each component is a widely used, validated test. The use of composite scores as primary outcomes makes interpretation less intuitive, whereas it limits the number of statistical tests, thereby protecting from type I error. We attempted to provide more intuitive and clinically meaningful interpretation by comparing the coefficients of vascular burden to the coefficient of age. The results on individual tests were also presented.

These limitations notwithstanding, we showed that both microvascular and macrovascular abnormalities assessed in the brain, kidney, and peripheral artery were independently associated with clinically significant impairment in cognitive and physical function in older adults. Accumulating evidence from our study and others suggests that selective non-invasive measurements of microvascular and macrovascular abnormalities may be useful at predicting functional status, disability, and mortality in older adults.[6,7,9–12] Future research should evaluate the clinical usefulness of abnormalities on the brain MRI, cystatin C level, and ankle-arm index in treatment decision-making and prognostication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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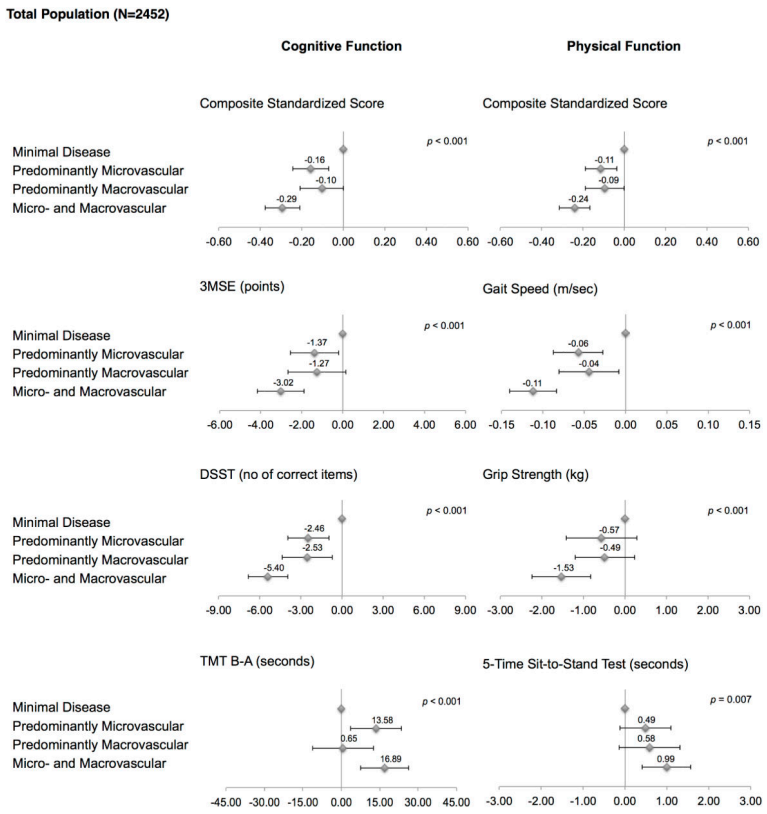

Figure. The Burden of Microvascular and Macrovascular Abnormalities and Functional Status in the Cardiovascular Health Study*

Abbreviations: 3MSE, Modified Mini-Mental State Examination; DSST, digit symbol substitution test; TMT B-A, Trail Making Test part B – part A.

* Differences in mean and 95% confidence intervals (horizontal bars) were calculated for participants with high microvascular (75^{th} percentile)/low macrovascular (25^{th} percentile) burden, low microvascular (25^{th} percentile)/high macrovascular (75^{th} percentile) burden, and high microvascular (75^{th} percentile)/high macrovascular (75^{th} percentile) burden, using participants with low microvascular (25^{th} percentile)/low macrovascular (25^{th} percentile) burden as the reference group. The results were adjusted for age (years), sex, white race, education (years), alcohol consumption (≥1 drink/week or <1), smoking status (never, former, or current), physical activity quintile (kcal/week), and body mass index category (<25.0, 25.0–29.9, or ≥30.0 kg/m^2). For physical function, arthritis requiring treatment was additionally adjusted for, but physical activity was not due to collinearity with the outcomes.

Table 1

Characteristics of Participants with Vascular Measurements in Cardiovascular Health Study

Characteristics	Summary Statistic
Sample size	2452
Clinical characteristics	
Age, mean (SD), years	79.5 (4.3)
Male	40%
White race	84%
Education, mean (SD), years	14.6 (4.6)
Alcohol consumption ≥ 1 drink/wk	24%
Smoking status	
Never	49%
Former	45%
Current	6%
Physical activity, median (IQR), kcal/wk	810 (270, 1755)
Body mass index, mean (SD), kg/m^2	27.0 (4.0)
Arthritis requiring treatment	24%
Hypertension	74%
Diabetes	15%
Hypercholesterolemia	31%
Clinical cardiovascular disease*	35%
Functional status	
3MSE, mean (SD), points	90.8 (10.2)
Digit symbol substitution test, mean (SD), points	38.3 (13.3)
Trail making test part B – part A, mean (SD), sec	84 (53, 136)
Gait speed, mean (SD), m/sec	0.87 (0.26)
Grip strength, mean (SD), kg	26.2 (9.6)
5-time sit-to-stand test, mean (SD), sec	16.1 (4.9)
Microvascular and macrovascular burden	
Microvascular index, median (IQR)	2 (1, 4)
Macrovascular index, median (IQR)	5 (3, 7)

Abbreviations: 3MSE, modified mini-mental state examination; IQR, interquartile range (25th percentile, 75th percentile); SD, standard deviation.

*Clinical cardiovascular disease includes angina, myocardial infarction, congestive heart failure, peripheral arterial disease, stroke, and transient ischemic attack.

Table 2

Cognitive and Physical Function By Microvascular and Macrovascular Abnormalities in Cardiovascular Health Study

		Composite Cognitive Function Score		Composite Physical Function Score	
Vascular Abnormalities	**N (%)**	**Mean (SD)**	**Adjusted Difference (95% CI)***	**Mean (SD)**	**Adjusted Difference (95% CI)***
Microvascular Measures					
White matter hyperintensity					
Grade 0–2	1387 (57)	0.11 (0.74)	Reference	0.13 (0.70)	Reference
Grade 3–4	742 (30)	−0.10 (0.86)	−0.11 (−0.18, −0.05)	−0.12 (0.75)	−0.08 (−0.14, −0.03)
Grade 5–9	323 (13)	−0.26 (0.90)	−0.13 (−0.22, −0.04)	−0.29 (0.75)	−0.18 (−0.26, −0.10)
			P_{trend}<0.001		P_{trend}<0.001
Small (3–20mm) brain infarct, *n*					
0	2040 (83)	0.03 (0.79)	Reference	0.04 (0.73)	Reference
1–2	305 (13)	−0.12 (0.87)	−0.04 (−0.12, 0.05)	−0.16 (0.72)	−0.05 (−0.12, 0.03)
≥3	107 (4)	−0.28 (0.95)	−0.12 (−0.26, 0.01)	−0.23 (0.72)	−0.03 (−0.15, 0.10)
			P_{trend}=0.08		P_{trend}=0.27
Retinal microvascular signs, $n^{\dagger}$					
0	1362 (55)	0.04 (0.81)	Reference	−0.01 (0.74)	Reference
1	880 (36)	−0.03 (0.83)	−0.02 (−0.07, 0.04)	0.05 (0.74)	0.06 (0.01, 0.11)
≥2	210 (9)	−0.09 (0.80)	−0.04 (−0.13, 0.06)	−0.15 (0.69)	−0.05 (−0.13, 0.04)
			P_{trend}=0.33		P_{trend}=0.69
Urine albumin-to-creatinine ratio					
≤30 mg/g	2012 (82)	0.04 (0.81)	Reference	0.03 (0.73)	Reference
31–300 mg/g	379 (15)	−0.17 (0.79)	−0.04 (−0.12, 0.03)	−0.16 (0.75)	−0.10 (−0.17, −0.04)
>300 mg/g	61 (3)	−0.26 (0.87)	0.06 (−0.12, 0.23)	−0.15 (0.70)	−0.08 (−0.23, −0.04)
			P_{trend}=0.59		P_{trend}=0.002
Cystatin C-based GFR					
≥90 ml/min/1.73m^2	381 (15)	0.16 (0.79)	Reference	0.11 (0.70)	Reference
60–89 ml/min/1.73m^2	1493 (61)	0.04 (0.79)	−0.04 (−0.12, 0.04)	0.05 (0.72)	−0.03 (−0.10, 0.04)
<60 ml/min/1.73m^2	578 (24)	−0.20 (0.85)	−0.11 (−0.20, −0.01)	−0.20 (0.77)	−0.18 (−0.27, −0.10)
			P_{trend}=0.02		P_{trend}<0.001

		Composite Cognitive Function Score		Composite Physical Function Score	
Vascular Abnormalities	**N (%)**	**Mean (SD)**	**Adjusted Difference (95% CI)***	**Mean (SD)**	**Adjusted Difference (95% CI)***
Macrovascular Measures					
Large (> 20mm) brain infarct, *n*					
0	1654 (67)	0.10 (0.76)	Reference	0.07 (0.72)	Reference
1	479 (20)	−0.14 (0.88)	−0.11 (−0.18, −0.03)	−0.08 (0.74)	−0.05 (−0.12, 0.01)
≥2	319 (13)	−0.29 (0.90)	−0.14 (−0.23, −0.05)	−0.24 (0.76)	−0.11 (−0.19, −0.03)
			P_{trend}<0.001		P_{trend}=0.007
Common carotid artery IMT					
Quintile 1 (≤0.89 mm)	493 (20)	0.11 (0.73)	Reference	0.00 (0.71)	Reference
Quintile 2–4 (0.90–1.23 mm)	1463 (60)	0.03 (0.81)	0.00 (−0.07, 0.07)	0.03 (0.72)	0.04 (−0.02, 0.10)
Quintile 5 (≥1.24 mm)	496 (20)	−0.20 (0.88)	−0.02 (−0.11, 0.07)	−0.10 (0.80)	−0.00 (−0.08, 0.07)
			P_{trend}=0.70		P_{trend}=0.84
Internal carotid artery IMT					
Quintile 1 (≤0.97 mm)	496 (20)	0.16 (0.75)	Reference	0.07 (0.72)	Reference
Quintile 2–4 (0.98–2.35 mm)	1471 (60)	−0.00 (0.81)	−0.03 (−0.13, 0.06)	0.02 (0.73)	−0.00 (−0.09, 0.09)
Quintile 5 (≥2.36 mm)	485 (20)	−0.16 (0.86)	−0.09 (−0.22, 0.04)	−0.13 (0.74)	−0.13 (−0.25, −0.02)
			P_{trend}=0.07		P_{trend}=0.004
Carotid artery stenosis					
0%	602 (25)	0.13 (0.77)	Reference	0.08 (0.70)	Reference
1–24%	1137 (46)	−0.01 (0.80)	−0.03 (−0.13, 0.06)	0.02 (0.75)	−0.01 (−0.09, 0.08)
≥25%	713 (29)	−0.10 (0.86)	−0.01 (−0.12, 0.10)	−0.10 (0.74)	−0.03 (−0.13, 0.07)
			P_{trend}=0.90		P_{trend}=0.82
Ankle-arm index					
1.01–1.40	1554 (63)	0.10 (0.76)	Reference	0.09 (0.71)	Reference
0.91–1.00 or ≥ 1.41	411 (17)	0.01 (0.80)	0.01 (−0.06, 0.08)	−0.05 (0.76)	−0.01 (−0.07, 0.06)
<0.90	487 (20)	−0.34 (0.89)	−0.13 (−0.21, −0.06)	−0.23 (0.74)	−0.10 (−0.17, −0.03)
			P_{trend}=0.001		P_{trend}=0.003
EKG‡					
No abnormalities	772 (31)	0.12 (0.77)	Reference	0.04 (0.73)	Reference
Minor abnormalities	704 (29)	−0.01 (0.80)	−0.01 (−0.08, 0.05)	−0.00 (0.70)	0.01 (−0.05, 0.07)

		Composite Cognitive Function Score		Composite Physical Function Score	
Vascular Abnormalities	**N (%)**	**Mean (SD)**	**Adjusted Difference (95% CI)***	**Mean (SD)**	**Adjusted Difference (95% CI)***
Major abnormalities	976 (40)	−0.09 (0.84)	−0.03 (−0.10, 0.03)	−0.03 (0.76)	−0.05 (−0.10, 0.01)
			P_{trend}=0.27		P_{trend}=0.10

Abbreviations: EKG, electrocardiogram; GFR, glomerular filtration rate; IMT, intima-media thickness.

*We adjusted for age (years), sex, white race, education (years), alcohol consumption (≥1 drink/week or <1), smoking status (never, former, or current), physical activity quintile (kcal/week) (only for the composite cognitive function score), body mass index (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), arthritis (only for the composite physical function score) and other vascular abnormalities in the table.

†Retinal microvascular signs include generalized arteriolar narrowing (<10th percentile of retinal arteriolar caliber), generalized venular widening (≥ 90th percentile of retinal venular caliber), retinopathy, arteriovenous nicking, and focal arteriolar narrowing.

‡Minor abnormalities include minor Q or QS waves, high R waves, minor isolated ST-T abnormalities, ST elevation, incomplete right bundle branch block, long QT interval, short PR, and right axis deviation. Major abnormalities include ventricular conduction defects, major Q or QS abnormalities, minor Q or QS with ST-T wave abnormalities, left ventricular hypertrophy, isolated major ST-T wave changes, atrial fibrillation, and first-degree atrioventricular block.