

Western University
Scholarship@Western

Medical Biophysics Publications

Medical Biophysics Department

3-4-2020

Reduced Cognitive Assessment Scores Among Individuals With Magnetic Resonance Imaging-Detected Vascular Brain Injury

Sonia S Anand

Matthias G Friedrich

Dipika Desai

Karleen M Schulze

Philip Awadalla

See next page for additional authors

Follow this and additional works at: <https://ir.lib.uwo.ca/biophysicspub>



Part of the [Medical Biophysics Commons](#)

Citation of this paper:

Anand, Sonia S; Friedrich, Matthias G; Desai, Dipika; Schulze, Karleen M; Awadalla, Philip; Busseuil, David; Dummer, Trevor J B; Jacquemont, Sébastien; Dick, Alexander; Kelton, David; Kirpalani, Anish; Lear, Scott A; Leipsic, Jonathan; Noseworthy, Michael D; Parker, Louise; Parraga, Grace; Poirier, Paul; Robson, Paula; Tardif, Jean-Claude; Teo, Koon; Vena, Jennifer; Yusuf, Salim; Moody, Alan R; Black, Sandra E; and Smith, Eric E, "Reduced Cognitive Assessment Scores Among Individuals With Magnetic Resonance Imaging-Detected Vascular Brain Injury" (2020). *Medical Biophysics Publications*. 218.

<https://ir.lib.uwo.ca/biophysicspub/218>

Authors

Sonia S Anand, Matthias G Friedrich, Dipika Desai, Karleen M Schulze, Philip Awadalla, David Busseuil, Trevor J B Dummer, Sébastien Jacquemont, Alexander Dick, David Kelton, Anish Kirpalani, Scott A Lear, Jonathan Leipsic, Michael D Noseworthy, Louise Parker, Grace Parraga, Paul Poirier, Paula Robson, Jean-Claude Tardif, Koon Teo, Jennifer Vena, Salim Yusuf, Alan R Moody, Sandra E Black, and Eric E Smith

Reduced Cognitive Assessment Scores Among Individuals With Magnetic Resonance Imaging–Detected Vascular Brain Injury

Sonia S. Anand¹, MD, PhD; Matthias G. Friedrich, MD;

Dipika Desai, MSc; Karleen M. Schulze, MMath; Philip Awadalla, PhD; David Busseuil, PhD; Trevor J.B. Dummer, PhD; Sébastien Jacquemont, MD; Alexander Dick, MD; David Kelton, MD; Anish Kirpalani, MD, MASC; Scott A. Lear, PhD; Jonathan Leipsic, MD; Michael D. Noseworthy, PhD, PEng; Louise Parker, PhD; Grace Parraga, PhD; Paul Poirier, MD, PhD; Paula Robson, PhD; Jean-Claude Tardif, MD; Koon Teo, MBBCh, PhD; Jennifer Vena, PhD; Salim Yusuf, MBBS, Dphil; Alan R. Moody, MBBS; Sandra E. Black, MD; Eric E. Smith, MD, MPH; on behalf of the Canadian Alliance for Healthy Hearts and Minds Cohort

Background and Purpose—Little is known about the association between covert vascular brain injury and cognitive impairment in middle-aged populations. We investigated if scores on a cognitive screen were lower in individuals with higher cardiovascular risk, and those with covert vascular brain injury.

Methods—Seven thousand five hundred forty-seven adults, aged 35 to 69 years, free of cardiovascular disease underwent a cognitive assessment using the Digital Symbol Substitution test and Montreal Cognitive Assessment, and magnetic resonance imaging (MRI) to detect covert vascular brain injury (high white matter hyperintensities, lacunar, and nonlacunar brain infarctions). Cardiovascular risk factors were quantified using the INTERHEART (A Global Study of Risk Factors for Acute Myocardial Infarction) risk score. Multivariable mixed models tested for independent determinants of reduced cognitive scores. The population attributable risk of risk factors and MRI vascular brain injury on low cognitive scores was calculated.

Results—The mean age of participants was 58 (SD, 9) years; 55% were women. Montreal Cognitive Assessment and Digital Symbol Substitution test scores decreased significantly with increasing age ($P < 0.0001$), INTERHEART risk score ($P < 0.0001$), and among individuals with high white matter hyperintensities, nonlacunar brain infarction, and individuals with 3+ silent brain infarctions. Adjusted for age, sex, education, ethnicity covariates, Digital Symbol Substitution test was significantly lowered by 1.0 (95% CI, -1.3 to -0.7) point per 5-point cardiovascular risk score increase, 1.9 (95% CI, -3.2 to -0.6) per high white matter hyperintensities, 3.5 (95% CI, -6.4 to -0.7) per nonlacunar stroke, and 6.8 (95% CI, -11.5 to -2.2) when 3+ silent brain infarctions were present. No postsecondary education accounted for 15% (95% CI, 12–17), moderate and high levels of cardiovascular risk factors accounted for 19% (95% CI, 8–30), and MRI vascular brain injury accounted for 10% (95% CI, -3 to 22) of low test scores.

Received October 29, 2019; final revision received January 23, 2020; accepted February 5, 2020.

From the Department of Medicine, McMaster University, Hamilton, Ontario, Canada (S.S.A., K.M.S., K.T., S.Y.); Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (S.S.A., K.T., S.Y.); Population Health Research Institute, Hamilton Health Sciences, Ontario, Canada (S.S.A., D.D., K.M.S., K.T., S.Y.); Department of Medicine and Diagnostic Radiology, McGill University, Montreal, Quebec, Canada (M.G.F.); Department of Electrical and Computer Engineering, School of Biomedical Engineering, Department of Molecular Genetics, Ontario Institute for Cancer Research, University of Toronto, Canada (P.A.); Research Centre, Montreal Heart Institute, Université de Montréal, Quebec, Canada (D.B., J.-C.T.); School of Population and Public Health, University of British Columbia, and BC Cancer Agency, Vancouver, Canada (T.J.B.D.); Department of Medicine and Pediatrics, Université de Montréal, CHU Sainte Justine, Quebec, Canada (S.J.); Division of Cardiology, University of Ottawa Heart Institute, University of Ottawa, Ontario, Canada (A.D.); Diagnostic Imaging, Brampton Civic Hospital, William Osler Health System, Brampton, Ontario, Canada (D.K.); Department of Medical Imaging, St. Michael's Hospital, University of Toronto, Ontario, Canada (A.K.); Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada (S.A.L.); Department of Radiology, University of British Columbia, St. Paul's Hospital, Vancouver, British Columbia, Canada (J.L.); Department of Electrical and Computer Engineering, School of Biomedical Engineering, McMaster University, and Diagnostic Imaging, St. Joseph's Health Care, Hamilton, Ontario, Canada (M.D.N.); Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada (L.P.); Department of Medical Biophysics, and Robarts Research Institute, Western University, London, Ontario, Canada (G.P.); Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Canada (P.P.); Cancer Research and Analytics, Cancer Control Alberta, Alberta Health Services, Edmonton, Canada (P.R.); Cancer Research and Analytics, Cancer Control Alberta, Alberta Health Services, Richmond Road Diagnostic and Treatment Centre, Calgary, Canada (J.V.); Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada (A.R.M.); Department of Medicine (Neurology) and Hurvitz Brain Sciences Research Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada (S.E.B.); Hotchkiss Brain Institute, Department of Clinical Neurosciences, University of Calgary, Alberta, Canada (E.E.S.).

The Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.028179>.

Correspondence to Sonia S. Anand, MD, PhD, Population Health Research Institute, 237 Barton St E, Hamilton, ON Canada L8L 2X2. Email anands@mcmaster.ca

© 2020 American Heart Association, Inc.

Stroke is available at <https://www.ahajournals.org/journal/str>

DOI: 10.1161/STROKEAHA.119.028179

Conclusions—Among a middle-aged community-dwelling population, scores on a cognitive screen were lower in individuals with higher cardiovascular risk factors or MRI vascular brain injury. Much of the population attributable risk of low cognitive scores can be attributed to lower educational attainment, higher cardiovascular risk factors, and MRI vascular brain injury. (*Stroke*. 2020;51:1158-1165. DOI: 10.1161/STROKEAHA.119.028179.)

Key Words: brain ■ cardiovascular disease ■ cognition ■ infarction ■ risk factors

Silent brain infarctions (SBI), or silent strokes where symptoms are absent or unrecognized, are subcortical cavities (lacunes) or cortical areas of atrophy and gliosis, which are presumed to be caused by previous infarction.¹ White matter hyperintensities (WMHs) are also presumed to be caused by brain ischemia.¹ Prior epidemiological studies indicate these vascular brain injuries are associated with cognitive decline, incident stroke, dementia, and death.²⁻⁴

The presence of SBI is higher in people with traditional cardiovascular risk factors including hypertension, diabetes mellitus, smoking, and cholesterol.⁵⁻⁸ These risk factors are also associated with increased cognitive decline in older populations.⁴ However, the results of clinical trials using medications to alter cardiovascular risk factors have not consistently shown reductions in cognitive decline.⁹⁻¹²

We hypothesized that cardiovascular risk factors and silent vascular brain injury, as detected by magnetic resonance imaging (MRI), would be significantly associated with reduced cognitive function. Therefore, we investigated if scores on 2 tests, a cognitive screen and a test of processing speed, are lower in individuals with higher cardiovascular risk and those with subclinical vascular brain injury in a large population-based sample.

Methods

The authors declare that all supporting data are available within the article and the [Data Supplement](#). The CAHMM (Canadian Alliance of Healthy Hearts and Minds) is a prospective cohort study where the majority of participants (>80%) were recruited through existing cohorts as previously described¹³ (Table I in the [Data Supplement](#)). Research Ethics Board approval was obtained, and all participants provided informed consent. Participants were eligible if they were between ages 35 and 69 years at the time of enrollment into their parent cohort and willing to have additional questionnaires, physical measurements, and an MRI scan completed. Participants were excluded if they had contraindications to an MRI scan.¹³ Details of the CAHMM MRI protocol have been previously published.^{8,13} Nonlab-based INTERHEART (A Global Study of Risk Factors for Acute Myocardial Infarction) risk score (IHRS) is a previously validated score which quantifies cardiovascular risk burden, and shown to be incrementally associated with SBI⁸ and quantified cardiovascular risk factor burden. IHRS includes age, sex, smoking status, diabetes mellitus, high blood pressure, family history of myocardial infarction, waist-to-hip ratio, home or work stress, depression, simple dietary questions, and physical activity.^{14,15} IHRS scores range from 0 to 48; low risk is defined as a score of 0 to 9, moderate risk as 10 to 16, and high risk as 17+. For educational level, participants were classified as having high school (or less), trade/technical, college or a university earned certificate, bachelor's degree, or a graduate degree.

Key Brain Injury Measures

Participants underwent a short noncontrast enhanced scan using a 1.5 Tesla or 3 Tesla magnet.¹³ Brain infarcts were identified on a high-resolution 3-dimensional T1-weighted sequence and 2-dimensional fluid-attenuated inversion recovery sequence by either magnetic

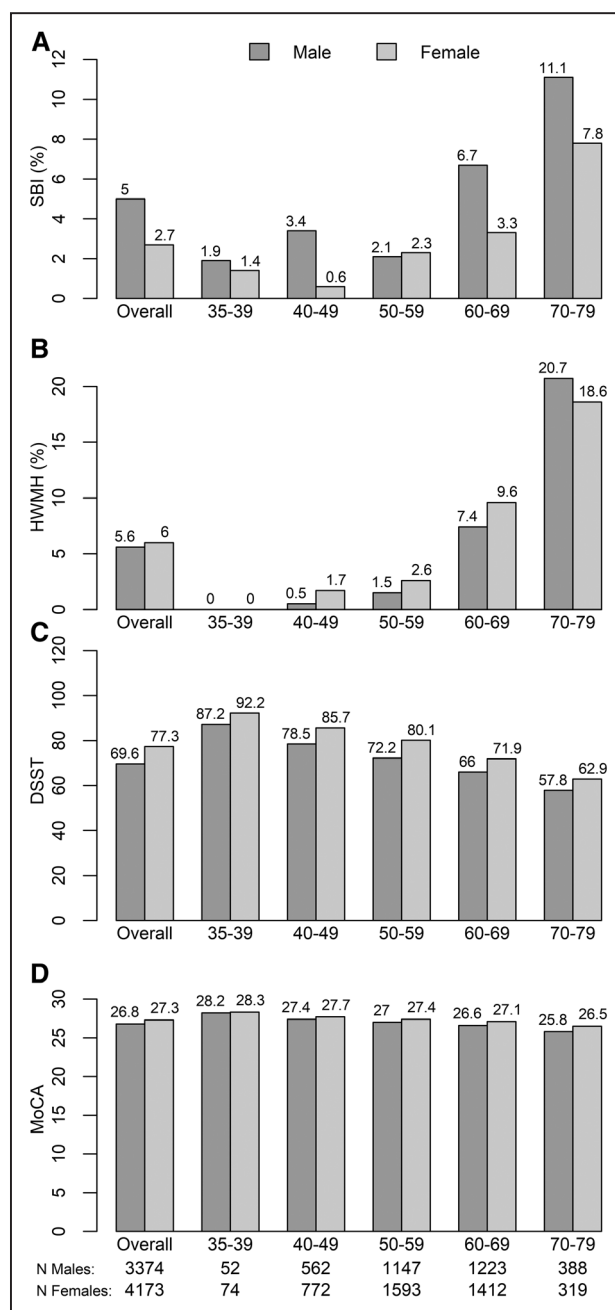


Figure 1. Prevalence of silent brain infarctions (SBI) and high white matter hyperintensity (HWMH) as well as mean scores of Digital Symbol Substitution test (DSST) and Montreal Cognitive Assessment (MoCA) in the overall study population and by age and sex. Bars represent proportion of participants in age and sex group with (A) SBI or (B) HWMH and mean (C) DSST or (D) MoCA scores by age groups and sex. Proportions (%) and means presented above bars; counts presented at the bottom. Overall proportion in far-left group. Sex-specific test for trend for each measure is $P < 0.0001$.

resonance readers or a blinded neuroradiologist or neurologist. Key brain injury measures included high WMH (HWMH) burden and SBIs. WMH was rated on the Fazekas score, a visual rating scale validated to correlate with volumetric measurements.¹⁶ High was defined as Fazekas score ≥ 4 (summing the periventricular and subcortical grades), which indicates beginning confluent or confluent WMH.¹³ Infarcts were subcategorized based on location and size as small (≤ 15 mm axial diameter) subcortical lacunes, following Standards for Reporting Vascular Changes on Neuroimaging,¹⁷ versus larger (>15 mm axial diameter) or cortical infarcts.¹⁸ Thalamic infarcts were classified as lacunar. The number of infarcts was calculated as the sum of all infarcts in all locations.

Cognitive Tests

Two measures were used. The Digital Symbol Substitution test (DSST) is a 2-minute test requiring participants to match symbols with numbers according to a code.¹⁹ Potential scores range from 0 to 133, and lower scores indicate worse performance. The DSST is commonly used in large cohorts and clinical trials, owing to its ability to display age-related effects over the age of 40 to 70 years, predict clinically important events including falls and mortality, language-independence and sensitivity to change over time, and mildly impaired cognition.^{9,20} Cutoff values of 1 and 2 SD below the mean DSST are commonly used clinical thresholds for mild cognitive impairment and to define frank cognitive impairment, respectively. The Montreal Cognitive Assessment (MoCA) is a global cognitive screening test²¹ taking 10 to 15 minutes to administer and evaluates delayed recall, verbal fluency, visuospatial skills, executive functions, calculation, abstraction, language, orientation, attention, and concentration.²¹ Scores range from 0 to 30, and a score of ≥ 26 denotes normal cognitive function. Education level was included in all of the score analyses as an adjusting factor.

Statistical Analysis

The primary outcomes of DSST and MoCA were analyzed as linear continuous variables. Vascular brain injury frequency and cognitive function scores were examined by increasing age ranges stratified by sex, and P_{Trend} was calculated using linear contrasts for continuous measures and the Cochran Armitage Test for bivariate measures. Generalized linear mixed models with random intercepts for center, using an unstructured covariance matrix, were used for the comparison of cognitive function scores in participants: (1) categorized by their IHRS category, (2) with a normal brain MRI (no SBI) to those with SBI subdivided by lacunar and nonlacunar types, and (3) with HWMH to those without. Minimally adjusted cognitive scores included age, sex, ethnicity, and educational level, and maximally adjusted models also included the presence of HWMH (when the exposure of interest is SBI), SBI (when HWMH is the exposure of interest), and cardiovascular risk factors. Pairwise comparisons were calculated by Tukey-Kramer adjusted pairwise comparisons. Linear mixed models, with center as a random effect, were constructed to determine the joint effects of HWMH, stroke type, stroke count adjusted for age, sex, ethnicity, education level, and the IHRS on the mean change in cognitive function score. To aid clinical interpretation, the differences in cognitive function scores are also expressed in equivalent years of cognitive aging (derived from the beta coefficient for age in the fully adjusted models). The population attributable risk (PAR)²² of each modifiable factor was calculated using logistic regression, by dichotomizing the DSST to <1 SD below the mean, the MoCA score to <26 , and including center and ethnicity as a fixed effect. The IHRS was categorized into low, moderate, or high-risk categories, and education was dichotomized into completed high school or less versus any further education. The PAR quantifies the proportion of preventable events if the identified factor(s) were eliminated while other factors were held unchanged. SAS 9.4 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

Table 1. Baseline Characteristics by IHRS Category

	IHRS Category				
	Overall	Low Risk (0–9)	Moderate Risk (10–16)	High Risk (17+)	P_{Trend}
N	7547	3793	2407	1311	
IHRS, mean (SD)	10.1 (5.8)	5.5 (2.6)	12.2 (1.7)	19.4 (3.3)	
Age, mean (SD)	57.8 (8.9)	56.0 (8.8)	59.1 (8.9)	60.5 (8.0)	
Female, %	55.3 (4173/7547)	65.4 (2479/3793)	48.8 (1174/2407)	38.4 (503/1311)	
Highest level of education					
High school or less, %	13.2 (971/7382)	10.1 (374/3713)	13.6 (321/2361)	21.2 (270/1274)	
College or trade, %	31.9 (2355/7382)	28.9 (1073/3713)	33.7 (796/2361)	37.3 (475/1274)	
Bachelor degree, %	32.7 (2412/7382)	35.7 (1324/3713)	31.8 (750/2361)	25.7 (327/1274)	
Graduate degree, %	22.3 (1644/7382)	25.4 (942/3713)	20.9 (494/2361)	15.9 (202/1274)	
White, %	80.4 (6064/7545)	78.8 (2989/3791)	80.1 (1928/2407)	85.3 (1118/1311)	
DSST,* mean (SE)	73.9 (72.7 to 75.0)	74.6 (73.4 to 75.9)	73.7 (72.5 to 75.0)	71.9 (70.6 to 73.3)	<0.0001
DSST Z,* mean (SE)	0.00 (–0.07 to 0.08)	0.05 (–0.02 to 0.13)	–0.01 (–0.09 to 0.07)	–0.12 (–0.21 to –0.03)	<0.0001
MoCA,* mean (SE)	27.2 (26.9 to 27.5)	27.3 (27.0 to 27.6)	27.2 (26.9 to 27.5)	27.0 (26.7 to 27.4)	0.004
MoCA,* % with score ≥ 26 (SE)	82.5 (78.6 to 85.8)	83.7 (79.9 to 86.9)	82.1 (77.9 to 85.7)	79.4 (74.6 to 83.6)	<0.0001
HWMH, %	5.8 (439/7541)	3.7 (142/3790)	6.6 (159/2405)	10.4 (136/1310)	<0.0001
Silent brain infarction, %	3.7 (283/7547)	2.5 (94/3793)	4.7 (113/2407)	5.6 (73/1311)	<0.0001
Lacunar, %	2.4 (180/7547)	1.6 (62/3793)	2.7 (66/2407)	3.8% (50/1311)	
Nonlacunar, %	1.4 (103/7547)	0.8 (32/3793)	2.0 (47/2407)	1.8 (23/1311)	

P_{Trend} calculated using linear contrasts for continuous outcomes and the Cochran Armitage Test for bivariate outcomes. DSST indicates Digital Symbol Substitution test; HWMH, high white matter hyperintensity; IHRS, INTERHEART risk score; and MoCA, Montreal Cognitive Assessment.

*Cognitive score estimates adjusted for age, sex, ethnicity, and education, with center as random intercepts.

Results

Between 2014 and 2018, 7547 participants free of clinical stroke or cardiovascular disease completed an MRI scan and cognitive tests. Fifty-five percent were women, the mean age was 58 years, and 20% were nonwhite. The mean MoCA score was 27.1 (SD, 2.3), and the mean DSST was 73.8 (SD, 15.7).

Age and Sex Distribution of HWMH, SBI, and Cognitive Scores

In both women and men with increasing age, the proportion with MRI-detected HWMH and SBI increased significantly ($P_{\text{trend}} < 0.001$, Figure 1A and 1B). Conversely, with increasing age, DSST and MoCA scores declined significantly ($P_{\text{trend}} < 0.001$, Figure 1C and 1D). Similarly, SBI and HWMH increased while DSST and MoCA scores decreased across low, moderate, and high IHRS categories (Table 1). Specifically, a 5-unit change in IHRS was associated with a -0.1 (95% CI, -0.1 to -0.04) reduction in MoCA (equivalent to 2.5 years of additional cognitive aging) and a -1.0 (95% CI, -1.3 to -0.7) change in DSST (equivalent to 1.4 years of cognitive aging).

Cognitive Scores and HWMH

The 5.8% of participants with HWMH were older and had a higher burden of cardiovascular risk factors (Table 2). Lower scores for both DSST (72.0 [95% CI, 70.3–73.7] versus 74.0 [95% CI, 72.8–75.1]; $P=0.003$), equivalent to 2.9 years of cognitive aging, and MoCA (27.0 [95% CI, 26.6–27.3] versus 27.2 [95% CI, 26.9–27.5]; $P=0.01$), equivalent to 5 years of cognitive aging, were observed compared to participants with and without HWMH.

Cognitive Scores and SBI

Of 3.7% (283/7547) of participants with SBI, 64% (180/283) were lacunar brain infarcts, and 36% (103/283) were nonlacunar brain infarcts. Participants with SBI were older and had a higher IHRS compared with those with no MRI-detected brain infarction. DSST and MoCA scores were not lower in participants with lacunar strokes compared with participants without SBI: (DSST, 75.0 [95% CI, 72.8–77.3] versus 73.9 [95% CI, 72.8–75.1]; MoCA: 27.3 [95% CI, 26.9–27.8] versus 27.2 [95% CI, 26.9–27.5]), whereas DSST and MoCA scores were significantly lower among participants with nonlacunar stroke (DSST: 68.6 [95% CI, 65.8–71.3]; MoCA: 26.5 [95% CI, 26.0–27.1]; Table 2). The DSST and MoCA difference

Table 2. Cognitive Function Scores by Presence of Silent Vascular Brain Injury

	Silent Brain Infarctions				High WMH		
	No Brain Infarction	Lacunar Brain Infarction	Nonlacunar Brain Infarction	P Value	No HWMH	HWMH	P Value
N	7264	180	103		7102	439	
Age, mean (SD)	57.6 (8.9)	62.6 (8.5)	63.1 (8.2)		57.3 (8.8)	65.5 (7.0)	
Female, %	55.9	39.4	41.7		55.2	56.7	
Highest level of education							
High school or less, %	13.1	14.3	17.0		12.9	17.3	
College or trade, %	31.9	30.3	34.0		31.7	35.7	
Bachelor degree, %	32.8	32.0	25.0		33.0	27.3	
Graduate degree, %	22.2	23.4	24.0		22.4	19.6	
White, %	80.2	83.9	88.3		79.9	88.2	
IHRS, mean (SD)	10.0 (5.7)	12.1 (6.5)	12.1 (5.6)		9.9 (5.7)	12.6 (6.1)	
Minimally adjusted outcomes (95% CI)							
DSST, mean	73.9 (72.7 to 75.1)	74.5 (72.3 to 76.7)	68.6*† (65.3 to 70.9)	<0.0001	74.0 (72.8 to 75.2)	71.6 (69.9 to 73.3)	<0.001
MoCA, mean	27.2 (26.9 to 27.5)	27.3 (26.8 to 27.7)	26.5*† (26.0 to 27.0)	0.003	27.2 (26.9 to 27.5)	26.9 (26.5 to 27.3)	0.003
MoCA, % with score of 26+	82.6 (78.7 to 85.9)	80.4 (72.7 to 86.3)	71.0* (60.0 to 80.0)	0.008	82.6 (78.6 to 85.9)	79.0 (73.1 to 84.0)	0.05
Final adjusted outcomes (95% CI)							
DSST, mean	73.9 (72.8 to 75.1)	75.0 (72.8 to 77.3)	68.6*† (65.8 to 71.3)	<0.001	74.0 (72.8 to 75.1)	72.0 (70.3 to 73.7)	0.003
MoCA, mean	27.2 (26.9 to 27.5)	27.3 (26.9 to 27.8)	26.5*† (26.0 to 27.1)	0.005	27.2 (26.9 to 27.5)	27.0 (26.6 to 27.3)	0.01
MoCA, % with score of 26+	82.7 (78.8 to 86.0)	81.5 (74.0 to 87.2)	71.8* (60.9 to 80.7)	0.02	82.7 (78.8 to 86.0)	80.2 (74.4 to 85.0)	0.17

Cognitive score estimates minimally adjusted for age, sex, ethnicity, and education, using a random intercept (center) model. Final score estimates adjusted for age, sex, ethnicity, education, and IHRS; SBI analysis further adjusted for HWMH and HWMH further adjusted for Brain Infarctions categories. Differences between no stroke and lacunar stroke were not statistically significant. DSST indicates Digital Symbol Substitution test; HWMH, high WMH; IHRS, INTERHEART risk score; MoCA, Montreal Cognitive Assessment; SBI, silent brain infarction; and WMH, white matter hyperintensity.

Tukey-Kramer adjusted pairwise comparisons:

* $P < 0.05$ between no stroke and nonlacunar stroke.

† $P < 0.05$ between lacunar and nonlacunar stroke groups.

was equivalent to 7.6 years and 17 years of cognitive aging, respectively.

DSST and MoCA scores were significantly lower in individuals with more brain infarcts compared to individuals with less ($P < 0.0001$) in the maximally adjusted model. Nonlacunar infarcts made up >50% of infarcts in participants with 3+ brain infarctions (Figure 2). An increase in HWMH frequency from 5.4% among those with a normal MRI to 28.9% among those with 3+ infarcts was observed ($P_{\text{trend}} < 0.0001$; data not shown). In the multivariable cognitive score models, the DSST scores were lower by 7.0 (95% CI, -7.4 to -6.7) points for every 10 years increase in age, by 1.0 (95% CI, -1.3 to -0.7) per 5-unit change in the IHRS, by 1.9 (95% CI, -3.2 to -0.6) for HWMH, by 3.5 (95% CI, -6.4 to -0.7), if a nonlacunar stroke was identified, and by 6.8 (95% CI, -11.5 to -2.2) for presence of 3+ SBI. Conversely, DSST was higher among women compared with men with a score increase of 6.5 (95% CI, 5.9–7.1) and among those with any postsecondary education. A similar pattern was observed for MoCA scores (Table 3).

To show the relative importance of modifiable factors associated with reduced cognitive function from a population perspective, the PAR of each modifiable factor (which incorporates the frequency of the factor and its strength of association with the outcome) was calculated (1 SD DSST score below the mean and MoCA <26, Table 4). PAR estimates show the proportion of people with cognitive dysfunction could be reduced by 15% (95% CI, 12–17) with increased postsecondary education, by 19% (95% CI, 8–30) if a moderate and high level of cardiovascular risk factors were prevented, and by 10% (95% CI, -3 to 22) by preventing MRI-detected vascular brain injury. MoCA scores showed similar contributions (Table 4).

Discussion

In this large middle-aged population of adults with no prior history of cardiovascular disease, MRI-detected covert vascular brain injury was associated with lower scores on a cognitive screening test and a neuropsychological test of processing speed. These novel findings were especially apparent among older-aged individuals with a higher burden of cardiovascular risk factors, nonlacunar brain infarctions, and among those with 3+ SBI of any type. The relationships between MRI-detected covert vascular brain injury and cognitive scores persist after adjustment for known covariates and cardiovascular risk factors. These differences in cognitive scores, whereas modest and not of immediate clinical significance, could increase the risk for later-life symptomatic cognitive decline if they persist and worsen. Additionally, they support a need for good vascular risk factor control in midlife to prevent vascular brain injury.

Our large study allowed us to separately identify associations between infarct subtypes and cognitive scores, whereas most prior studies were smaller and by necessity grouped all infarcts together.^{23–25} Interestingly, in our relatively young population, the proportion of lacunar to nonlacunar infarcts was relatively low (1.75:1) compared with studies of the elderly (13:1).⁴ We showed that individuals with nonlacunar cortical infarcts had lower cognitive scores compared with those without. This was not observed for lacunar infarctions. Individuals with nonlacunar brain infarction had a 3.5 point

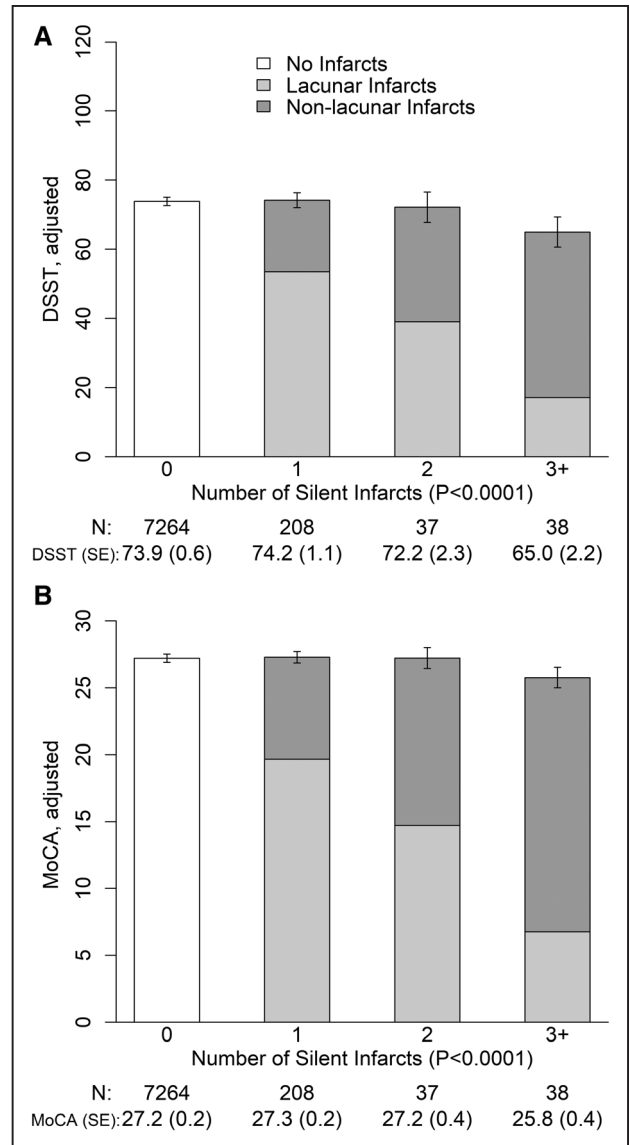


Figure 2. Cognitive function by number of silent brain infarction. Mean Digital Symbol Substitution test (DSST) (A) and Montreal Cognitive Assessment (MoCA; B) scores adjusted for age, sex, education, INTERHEART risk score, and high white matter hyperintensity by number of silent brain infarcts. The grayscale shows the proportion of participants, represented by that bar, with no infarcts, lacunar, or nonlacunar infarcts. Note: Although participants were between the ages of 35 and 69 y at the time of enrollment, some participants were over the age of 69 y at the time of magnetic resonance imaging and cognitive function testing.

lower DSST compared with those without, which translates into ≈ 5 years of cognitive aging. Also, an increasing number of SBI (of any type, though predominantly nonlacunar) was significantly related to reduced cognitive function scores. This relationship between cortical infarctions and lower cognition is supported by the Rotterdam study.²⁴ Together with prior literature, our findings suggest that infarct type and cognition may vary over the life span, with increasing vulnerability to small vessel disease (manifest as lacunes) and susceptibility to their effects evolving as people transition from midlife to older age.

We also observed that HWMH are not benign, as they were associated with lower cognitive scores, independent of

Table 3. Multivariable Models of Factors Associated With Cognitive Function Scores

	DSST Model		MoCA Model	
	Mean Score Change (95% CI)	P Value	Mean Score Change (95% CI)	P Value
Age (per 10 y)	-7.0 (-7.4 to -6.7)	<0.0001	-0.4 (-0.4 to -0.3)	<0.0001
Female	6.5 (5.9 to 7.1)	<0.0001	0.5 (0.4 to 0.6)	<0.0001
Highest level of education				
High school or less	-6.5 (-7.5 to -5.4)	<0.0001	-1.6 (-1.8 to -1.4)	<0.0001
College or trade	-4.4 (-5.2 to -3.6)		-1.0 (-1.1 to -0.9)	
Bachelor degree	-1.2 (-2.1 to -0.4)		-0.3 (-0.4 to -0.1)	
Graduate degree (ref)				
IHRS (per 5-unit change)	-1.0 (-1.3 to -0.7)	<0.0001	-0.1 (-0.1 to -0.0)	<0.0001
HWMH	-1.9 (-3.2 to -0.6)	0.005	-0.3 (-0.5 to -0.0)	0.03
Nonlacunar stroke	-3.5 (-6.4 to -0.7)	0.02	-0.3 (-0.8 to 0.2)	0.22
3+ brain infarctions vs 0-2 brain infarctions	-6.8 (-11.5 to -2.2)	0.004	-1.3 (-2.1 to -0.6)	<0.001

DSST indicates Digital Symbol Substitution test; HWMH, high white matter hyperintensity; IHRS, INTERHEART risk score; and MoCA, Montreal Cognitive Assessment.

SBI and cardiovascular risk factors, in a middle-aged population. This is important, given that a previous US study did not observe an association between WMH and cognitive function,²⁶ whereas this association was observed in a smaller yet older-aged US cohort,²⁷ the Framingham offspring cohort,²⁸ and in the PURE MIND study (Prospective Urban Rural Epidemiologic MIND Sub-Study).^{6,29} Our findings are consistent with a recent meta-analysis, showing that HWMH in the elderly were associated with an increased risk of future stroke 2.4 (95% CI, 1.9-3.8), dementia 1.8 (95% CI, 1.4-2.4), Alzheimer disease 1.5 (95% CI, 1.2-1.8), and a 2-fold increase in death (95% CI, 1.7-2.4).²

The PAR analysis shows the relative contribution of each modifiable risk factor for low scores on the DSST and the MoCA. Increasingly, PAR is being used to identify the relative contribution of risk factors for stroke²² and dementia.³⁰

The impact of educational attainment is substantial and indicates postsecondary education as a potentially modifiable factor on cognitive health.³¹ Also, the impact of cardiovascular risk factors and vascular brain injury on lowered cognitive function occurs partially through the development of SBI and HWMH, but not exclusively. This indicates other probable pathways by which cardiovascular risk factors are associated with cognitive decline.

Our data suggest that prevention and treatment of cardiovascular risk factors should reduce vascular brain injury and prevent cognitive decline, and it may be reasonable to begin such treatment midlife. These findings extend prior work on SBI in older populations⁴ to an earlier stage in the life-course. Currently, there are no guidelines for the management of asymptomatic MRI-defined SBI or HWMH due to few clinical trials which have robustly shown benefit.¹ Recently, SPRINT

Table 4. Determinants and Their PAR of Reduced Cognitive Function

	Odds of DSST <59 (1 SD Below Mean)			Odds of MoCA <26		
	Odds (95% CI)	P Value	Partial PAR (95% CI)	Odds (95% CI)	P Value	Partial PAR (95% CI)
Age (per 10 y)	2.73 (2.49 to 3.01)	<0.0001		1.46 (1.36 to 1.57)	<0.0001	
Female	0.41 (0.35 to 0.47)	<0.0001		0.76 (0.67 to 0.85)	<0.0001	
Any postsecondary education	0.48 (0.40 to 0.58)	<0.0001	14.6 (12.1 to 17.1)	0.43 (0.37 to 0.51)	<0.0001	14.9 (11.3 to 18.5)
IHRS high risk (score 17+) vs IHRS low risk (score 0-9)	1.46 (1.21 to 1.75)	<0.0001	19.1 (7.7 to 30.1)	1.44 (1.23 to 1.69)	<0.0001	13.8 (5.0 to 22.5)
IHRS moderate risk (score 10-16) vs IHRS low risk (score 0-9)	1.19 (1.01 to 1.40)	0.03		1.16 (1.02 to 1.33)	0.03	
HWMH	1.54 (1.21 to 1.95)	<0.001	6.7 (2.1 to 11.2)	1.18 (0.94 to 1.48)	0.16	1.6 (-0.8 to 4.0)
Nonlacunar stroke	1.56 (0.91 to 2.62)	0.10	2.1 (-1.8 to 6.0)	1.40 (0.84 to 2.27)	0.18	1.0 (-1.2 to 3.3)
3+ SBI vs less	2.65 (1.18 to 6.05)	0.02	2.3 (-1.5 to 6.2)	2.56 (1.19 to 5.55)	0.02	1.4 (-1.0 to 3.8)

Note: For all PAR models, age, sex, ethnicity, and center are included as fixed effects. For DSST, the partial PAR for the combined Brain Injury variables is 10.0 (-2.7 to 22.4), Full PAR 92.7 (80.1 to 97.4); for MoCA, the partial PAR for combined Brain Injury variables is 3.6 (-4.0 to 11.1), Full PAR 66.7 (32.6 to 85.4). Postsecondary education is defined as obtaining any postsecondary education. DSST indicates Digital Symbol Substitution test; HWMH, high white matter hyperintensities; IHRS, INTERHEART risk score; MoCA, Montreal Cognitive Assessment test; PAR, population attributable risk; and SBI, silent brain infarction.

(Systolic Blood Pressure Intervention Trial) blood pressure-lowering trial showed that intensive compared with standard blood pressure management reduced the combined incidence of mild cognitive impairment or dementia (hazard ratio, 0.81 [95% CI, 0.69–0.95]) and was associated with fewer HWMH on MRI.¹⁰ Additionally, the INFINITY (Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People) blood pressure-lowering trial showed a reduction in HWMH in the intensive compared to liberal blood pressure-lowering group.¹¹ These results support aggressive blood pressure-lowering, although other trials of cardiovascular risk factor modification have shown inconsistent benefits.^{9,12,32} This may be partially due to weak effects of risk factor modification over a short time period, underpowered studies, the assumption that cardiovascular risk effect on cognition occurs through the development of clinical stroke, or not considering the other pathways, including HWMH. Future randomized trials targeting one or multiple cardiovascular risk factors, or new pathways,³³ which incorporate a sensitive measure of cognitive function and imaging biomarkers, are needed.

Strengths and Limitations

The strengths of CAHHM include: (1) its large size and inclusion of a large cohort of middle-aged adults, with sufficient sample size to test associations with infarct location and number, (2) all MRIs were performed as per a standardized protocol and read in a core lab, and (3) we used the PAR to measure the relative contributions of several factors, including education and cardiovascular risk factors in addition to MRI measures of vascular brain injury. The main limitation is the brief cognitive assessment with only a general cognitive screen and a neuropsychological test of processing speed, which prevents us from making inferences about most cognitive domains and falls short of what is currently considered state-of-the-art.³⁴ Another limitation is the cross-sectional analysis, in which we are unable to determine the temporal relationship between vascular risk factors, subclinical vascular brain injury, and cognition. However, as the MRI findings are subclinical, any changes in health behaviors or medication use are expected to be minimal, such that the risk factor to cognitive function and brain MRI findings should not be strongly influenced by reverse causation.

Conclusions

Scores on a cognitive screen are lower in individuals with a higher burden of cardiovascular risk factors, and those with MRI-detected vascular brain injury, including HWMH and SBI, predominantly the nonlacunar type. Interventions designed to optimize modifiable factors, including educational attainment, cardiovascular risk factors, and covert vascular brain injury, are needed.

Sources of Funding

CAHHM (Canadian Alliance of Healthy Hearts and Minds) was funded by the Canadian Partnership Against Cancer, Heart and Stroke Foundation of Canada, and Canadian Institutes of Health Research. Financial contributions were also received from the Population Health Research Institute, Dr Anand (Canadian Institutes of Health Research

Foundation Grant FDN-143255), Dr Tu (Canadian Institutes of Health Research Foundation grant FDN-143313), and Dr Smith (Canadian Institutes of Health Research Foundation Grant FDN-154317). In-kind contributions from Drs Moody and Black for magnetic resonance imaging reading costs, and Bayer AG. The Canadian Partnership for Tomorrow Project is funded by the Canadian Partnership Against Cancer, BC Cancer Foundation, Genome Quebec, Ontario Institute for Cancer Research and Alberta Health and the Alberta Cancer Prevention Legacy Fund, Alberta Cancer Foundation. The PURE Study was funded by multiple sources. The Montreal Heart Institute Biobank is funded by Mr André Desmarais and Mrs France Chréten-Desmarais and the Montreal Heart Institute Foundation. Dr Anand is supported by a Tier 1 Canada Research Chair in Ethnicity and Cardiovascular Disease, and Heart and Stroke Foundation Chair in Population Health. Dr Awadalla was supported by a Ministry of Research and Innovation of Ontario Investigator Award. Dr Black was supported by the Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, and the Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto. Dr Larose was supported by the Laval University Chair of Research & Innovation in Cardiovascular Imaging and the Fonds de recherche du Québec—Santé. Dr Parraga holds a Tier 1 Canada Research Chair in Lung Imaging to Transform Outcomes and was supported by a Western Faculty Scholar Award. Dr Leipsic holds a Canada Research Chair Tier 2 in Advanced Cardiopulmonary Imaging at University of British Columbia. Dr Parker holds the Canadian Cancer Society Chair in Population Cancer Research at Dalhousie University. Dr Tardif holds the Tier 1 Canada Research Chair in translational and personalized medicine and the Université de Montréal Pfizer endowed research chair in atherosclerosis. Dr Yusuf was supported by the Heart & Stroke Foundation/Marion W. Burke Chair in Cardiovascular Disease.

Disclosures

Dr Anand has received grants from the Canadian Partnership Against Cancer, Heart and Stroke Foundation of Canada and Canadian Institutes of Health Research, personal fees from Bayer AG and in-kind support from the Population Health Research Institute. D. Desai is supported by grants from the Canadian Partnership Against Cancer, Heart and Stroke Foundation of Canada and Canadian Institutes of Health Research. Dr Dummer is supported by the Canadian Partnership Against Cancer grant. Dr Jacquemont is supported by grants from the Canadian Institutes of Health Research. Dr Leipsic has received personal fees from Consultant Circle CVI and HeartFlow. Dr Robson is supported by grants from the Alberta Cancer Foundation, the Alberta Cancer Prevention Legacy Fund, the Canadian Partnership Against Cancer and is a paid employee for Alberta Health Services. Dr Smith is supported by grants from the Canadian Partnership Against Cancer, Heart and Stroke Foundation of Canada, and the Canadian Institutes of Health Research. Dr Tardif is supported by grants from the Government of Canada, RegenXBio and Esperion, has received personal fees from Amarin, Astra-Zeneca, DalCor, Pfizer, Sanofi, and Servier and holds a license for pharmacogenomics-guided CETP (cholesteryl ester transfer protein) inhibition. The other authors report no conflicts. Some of the data used in this research were made available by the Canadian Partnership for Tomorrow Project along with BC Generations Project, Alberta's Tomorrow Project, Ontario Health Study, CARTaGENE, and the Atlantic PATH. Data were harmonized by Maelstrom and access policies and procedures were developed by the Centre of Genomics and Policy in collaboration with the cohorts.

References

1. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, et al; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e44–e71. doi: 10.1161/STR.000000000000116

2. DeBette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol.* 2019;76:81–94. doi: 10.1001/jamaneurol.2018.3122
3. DeBette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke.* 2010;41:600–606. doi: 10.1161/STROKEAHA.109.570044
4. VermeerSE, PrinsND, denHeijerT, HofmanA, KoudstaalPJ, BretelerMM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348:1215–1222. doi: 10.1056/NEJMoa022066
5. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke.* 2003;34:1126–1129. doi: 10.1161/01.STR.0000068408.82115.D2
6. Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, et al. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. *Stroke.* 2008;39:2929–2935. doi: 10.1161/STROKEAHA.108.516575
7. Windham BG, Griswold ME, Shibata D, Penman A, Catellier DJ, Mosley TH Jr. Covert neurological symptoms associated with silent infarcts from midlife to older age: the Atherosclerosis Risk in Communities study. *Stroke.* 2012;43:1218–1223. doi: 10.1161/STROKEAHA.111.643379
8. Anand SS, Tu JV, Desai D, Awadalla P, Robson P, Jacquemont S, et al. Cardiovascular risk scoring and magnetic resonance imaging detected subclinical cerebrovascular disease. *Eur Heart J Cardiovasc Imaging.* 2019;00:1–9. doi: 10.1093/ehjci/jez226
9. Bosch J, O'Donnell M, Swaminathan B, Lonn EM, Sharma M, Dagenais G, et al; HOPE-3 Investigators. Effects of blood pressure and lipid lowering on cognition: results from the HOPE-3 study. *Neurology.* 2019;92:e1435–e1446. doi: 10.1212/WNL.00000000000007174
10. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA.* 2019;321:553–561. doi: 10.1001/jama.2018.21442
11. White WB, Wakefield DB, Moscufo N, Guttman CRG, Kaplan RF, Bohannon RW, et al. Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY). *Circulation.* 2019;140:1626–1635. doi: 10.1161/CIRCULATIONAHA.119.041603
12. Offer A, Arnold M, Clarke R, Bennett D, Bowman L, Bulbulia R, et al; Heart Protection Study (HPS), Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), and Treatment of HDL (High-Density Lipoprotein) to Reduce the Incidence of Vascular Events (HPS2-THRIVE) Collaborative Group. Assessment of vascular event prevention and cognitive function among older adults with preexisting vascular disease or diabetes: a Secondary Analysis of 3 Randomized Clinical Trials. *JAMA Netw Open.* 2019;2:e190223. doi: 10.1001/jamanetworkopen.2019.0223
13. Anand SS, Tu JV, Awadalla P, Black S, Boileau C, Busseuil D, et al; CAHHM Study Investigators. Rationale, design, and methods for Canadian alliance for healthy hearts and minds cohort study (CAHHM) - a Pan Canadian cohort study. *BMC Public Health.* 2016;16:650. doi: 10.1186/s12889-016-3310-8
14. McGorrian C, Yusuf S, Islam S, Jung H, Rangarajan S, Avezum A, et al; INTERHEART Investigators. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART modifiable risk score. *Eur Heart J.* 2011;32:581–589. doi: 10.1093/eurheartj/ehq448
15. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al; PURE Investigators. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* 2014;371:818–827. doi: 10.1056/NEJMoa1311890
16. Valdés Hernández Mdel C, Morris Z, Dickie DA, Royle NA, Muñoz Maniega S, Aribisala BS, et al. Close correlation between quantitative and qualitative assessments of white matter lesions. *Neuroepidemiology.* 2013;40:13–22. doi: 10.1159/000341859
17. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al; Standards for Reporting Vascular changes on neuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
18. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014;13:429–438. doi: 10.1016/S1474-4422(13)70310-7
19. Kaplan E, Wechsler D. *Wais-r ni for use with wais-r: Wais-r as a neuropsychological instrument: Manual.* San Antonio, TX: Psychological Corporation; 1991.
20. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al; ACCORD MIND Investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011;10:969–977. doi: 10.1016/S1474-4422(11)70188-0
21. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53:695–699. doi: 10.1111/j.1532-5415.2005.53221.x
22. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al; INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet.* 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3
23. Wright CB, Festa JR, Paik MC, Schmiedigen A, Brown TR, Yoshita M, et al. White matter hyperintensities and subclinical infarction: associations with psychomotor speed and cognitive flexibility. *Stroke.* 2008;39:800–805. doi: 10.1161/STROKEAHA.107.484147
24. Riba-Llena I, Koek M, Verhaaren BF, Vrooman HA, van der Lugt A, Hofman A, et al. Small cortical infarcts: prevalence, determinants, and cognitive correlates in the general population. *Int J Stroke.* 2015;10(suppl A100):18–24. doi: 10.1111/ij.s.12543
25. Sigurdsson S, Aspelund T, Kjartansson O, Gudmundsson EF, Jonsdottir MK, Eiriksdottir G, et al. Incidence of brain infarcts, cognitive change, and risk of dementia in the general population: the AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study). *Stroke.* 2017;48:2353–2360. doi: 10.1161/STROKEAHA.117.017357
26. Warren MW, Weiner MF, Rossetti HC, McColl R, Peshock R, King KS. Cognitive impact of lacunar infarcts and white matter hyperintensity volume. *Dement Geriatr Cogn Dis Extra.* 2015;5:170–175. doi: 10.1159/000370109
27. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, et al; ARIC Neurocognitive Investigators. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke.* 2015;46:433–440. doi: 10.1161/STROKEAHA.114.007847
28. Bangen KJ, Preis SR, Delano-Wood L, Wolf PA, Libon DJ, Bondi MW, et al. Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the Framingham Offspring Study. *Alzheimer Dis Assoc Disord.* 2018;32:50–56. doi: 10.1097/WAD.0000000000000215
29. Smith EE, O'Donnell M, Dagenais G, Lear SA, Wielgosz A, Sharma M, et al; PURE Investigators. Early cerebral small vessel disease and brain volume, cognition, and gait. *Ann Neurol.* 2015;77:251–261. doi: 10.1002/ana.24320
30. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390:2673–2734. doi: 10.1016/S0140-6736(17)31363-6
31. Bancks M, Alonso A, Allen N, Yaffe K, Carnethon M. Temporal trends in cognitive function of older US adults associated with population changes in demographic and cardiovascular profiles. *J Epidemiol Community Health.* 2019;73:612–618. doi: 10.1136/jech-2018-211985
32. Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, et al; ONTARGET and TRANSCEND Investigators. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. *Lancet Neurol.* 2011;10:43–53. doi: 10.1016/S1474-4422(10)70250-7
33. Sharma M, Hart RG, Smith EE, Bosch J, Yuan F, Casanova A, et al. Rationale, design, and baseline participant characteristics in the MRI and cognitive substudy of the cardiovascular outcomes for people using anticoagulation strategies trial. *Int J Stroke.* 2019;14:270–281. doi: 10.1177/1747493018784478
34. Elias MF, Torres RV, Davey A. Clinical trials of blood pressure lowering and antihypertensive medication: is cognitive measurement state-of-the-art? *Am J Hypertens.* 2018;31:631–642. doi: 10.1093/ajh/hpy033