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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.

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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 CAHHM (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 described[13] (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 CAHHM 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 SBI[8] 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

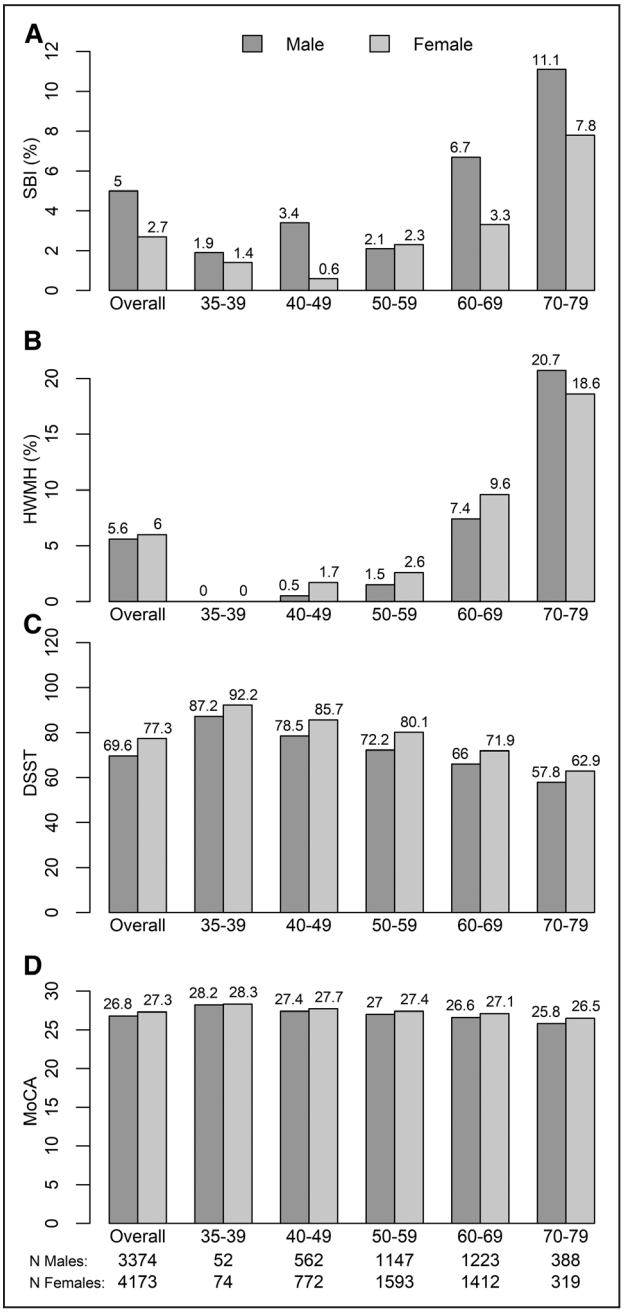

Figure 1. Prevalence of silent brain infarctions (SBI) and high white matter hyperintensity (HWMH) as well as mean scores of Digital Symbol Substitution test (DSST) and Montreal Cognitive Assessment (MoCA) in the overall study population and by age and sex. Bars represent proportion of participants in 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 test[21] 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_{trend}<0.001, Figure 1A and 1B). Conversely, with increasing age, DSST and MoCA scores declined significantly (P_{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)	68.1*† (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_{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 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

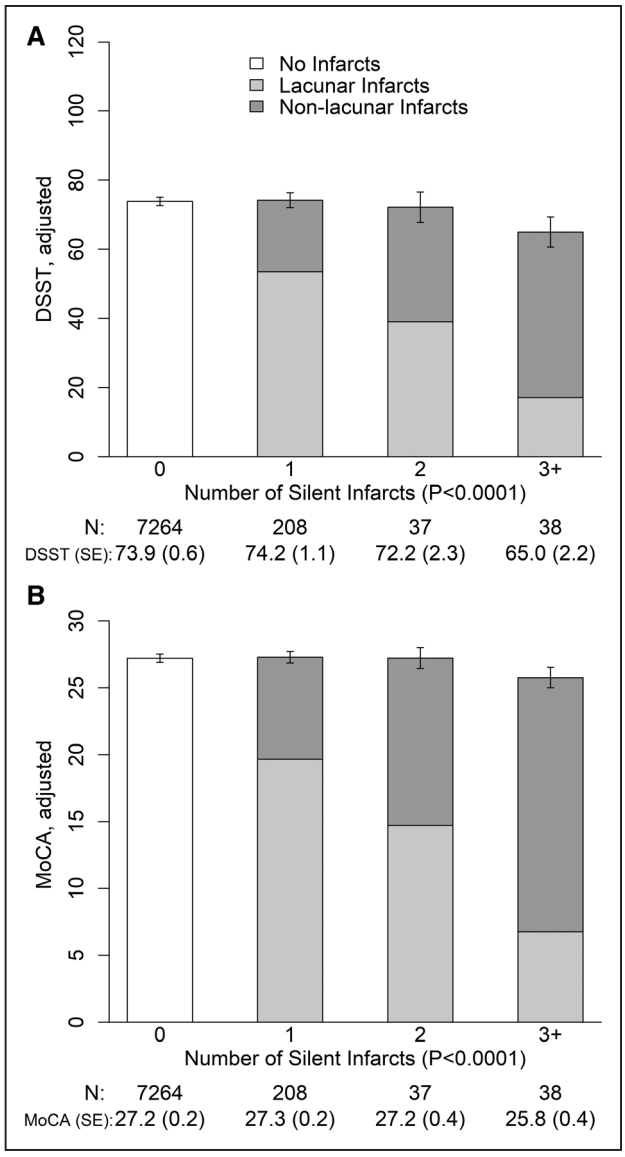

Figure 2. Cognitive function by number of silent brain infarction. Mean Digital Symbol Substitution test (DSST) (**A**) and Montreal Cognitive Assessment (MoCA; **B**) scores adjusted for age, sex, education, INTERHEART risk score, and high white matter hyperintensity by number of silent brain infarcts. 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.

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 stroke[22] 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 populations[4] 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.

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