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RESEARCH ARTICLE

Risk factors and cognitive correlates of white matter hyperintensities in ethnically diverse populations without dementia: The COSMIC consortium

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Abstract

INTRODUCTION: White matter hyperintensities (WMHs) are an important imaging marker for cerebral small vessel diseases, but their risk factors and cognitive associations have not been well documented in populations of different ethnicities and/or from different geographical regions.

METHODS: We investigated how WMHs were associated with vascular risk factors and cognition in both Whites and Asians, using data from five population-based cohorts of non-demented older individuals from Australia, Singapore, South Korea, and Sweden ($N = 1946$). WMH volumes (whole brain, periventricular, and deep) were quantified with UBO Detector and harmonized using the ComBat model. We also harmonized various vascular risk factors and scores for global cognition and individual cognitive domains.

RESULTS: Factors associated with larger whole brain WMH volumes included diabetes, hypertension, stroke, current smoking, body mass index, higher alcohol intake, and insufficient physical activity. Hypertension and stroke had stronger associations with WMH volumes in Whites than in Asians. No associations between WMH volumes and cognitive performance were found after correction for multiple testing.

CONCLUSION: The current study highlights ethnic differences in the contributions of vascular risk factors to WMHs.

KEYWORDS
cognition, ethnic differences, population-based studies, vascular risk factors, white matter hyperintensities

1 | INTRODUCTION

White matter hyperintensities (WMHs) are an important imaging marker for cerebrovascular diseases. A rich body of research has examined risk factors for WMHs[1,2] and associations between WMHs and cognition.[3,4] In particular, studies have found a heavier burden of WMHs with hypertension,[5] higher blood pressure in normal range,[6,7] diabetes,[8] cardiovascular disease,[9] excessive alcohol consumption,[10] and insufficient physical activity.[3,10,11] Poorer performance in the cognitive domains of processing speed[1] and executive function[12] has also been associated with WMHs. Further, a meta-analysis of 22 longitudinal studies found that WMH accumulations were associated with increased dementia and stroke risks, and mortality.[3]

Ethnicity differences in the prevalence of WMHs, and their associations with risk factors and cognition, have not been well documented, although studies in different ethnicities exist. For example, a population-based study of 688 elderly Japanese reported that higher systolic blood pressure, current drinking, lower total cholesterol, and poorer cognitive function were associated with higher WMH volumes.[13] A study of 1748 population-based Whites showed that higher WMH volumes were associated with more cigarette smoking per day, a higher prevalence of cardiovascular disease, poorer memory, and reduced organization skills.[14,15] The current study aimed to examine associations of WMHs with risk factors and cognition, and ethnicity differences in their associations, by pooling magnetic resonance imaging (MRI) data from five population-based studies of non-demented older adults in Cohort Studies of Memory in an International Consortium (COSMIC[16]).

The primary advantage of using COSMIC data is the availability of population-based, community-dwelling older individuals from different countries in the world, with participant-level clinical and MRI data available for analyses. The major challenge arises from the need to harmonize data pertaining to risk factors, neuropsychological assessments, and MRI. To address these challenges, COSMIC has introduced comprehensive protocols, and the harmonization of risk factors and neuropsychological data has been largely achieved.[17]

2 | AIM

Our aim was to examine the associations of WMH volumes with vascular risk factors and cognition, and ethnicity differences in their associations, in a pooled sample of population-based studies of non-demented individuals from four countries.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. A rich body of research has examined risk factors for white matter hyperintensities (WMHs) and associations between WMHs and cognition. However, ethnicity differences in the prevalence of WMHs, and their associations with risk factors and cognition, have not been well documented.
2. **Interpretation**: Our findings reveal that WMH volumes are associated with diabetes, hypertension, stroke, smoking, body mass index, alcohol intake, and physical activity. Hypertension and stroke have stronger associations with WMH volumes in the White, compared to Asian, subsample.
3. **Future directions**: To further understand the underlying mechanisms of the observed ethnic differences, future research could investigate the genetic factors. Also, longitudinal studies would be interesting to explore the progression of WMHs and the long-term effects on cognitive decline in diverse ethnic groups.

3 | METHODS

3.1 | Participating studies

Five COSMIC studies with MRI scans were included in the current study, namely, Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD),[18] the Gothenburg H70 Birth Cohort Study (H70 Study),[19] Singapore Longitudinal Aging Studies (SLAS-I and SLAS-II),[20] Sydney Memory and Ageing Study (MAS),[21] and the Personality and Total Health (PATH) Through Life study (≥ 60 years).[22] Baseline data were used for all studies except PATH to maximize the sample size. Wave 2 data of PATH were included because cognitive data to assess executive function and processing speed were not available at baseline. Five participants from KLOSCAD and 27 from SLAS with dementia were excluded.

3.2 | MRI acquisition

We analyzed T1- and T2-weighted fluid attenuated inversion recovery (FLAIR) scans acquired across seven MRI scanners. KLOSCAD and H70 Study used Philips 3T Achieva scanners (Philips Medical Systems),[19,23] and PATH used a Philips 1.5T Gyroscan scanner.[22] Of the 474 MAS participants, 240 were scanned with a Philips 3T Intera Quasar scanner, and the remaining 234 with a Philips 3T Achieva Quasar Dual scanner.[21] SLAS-I and SLAS-II used a Siemens 3T Tim Trio and a GE Healthcare 1.5T HDXT scanner, respectively. Detailed imaging acquisition parameters are summarized in Table S1 in supporting information.

3.3 | WMH segmentation and quantification

WMH volumes were quantified using UBO Detector.[24] Briefly, FLAIR scans were linearly registered to T1 images. Tissue segmentation was then conducted, and the warp field from native T1 space to Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL[25]) space was generated. The warp fields were applied to FLAIR images in native T1 spaces to bring FLAIR scans to the DARTEL space. After removing non-brain tissue, FSL FAST was applied to segment DARTEL-space FLAIR into candidate clusters. By considering intensity, anatomical location, and cluster size features, a k nearest neighbor classifier (with default setting $k = 5$ and probability threshold = 0.7) was applied to separate non-WMH from WMH clusters. As described in the methodology paper,[24] WMH voxels <12 mm^3 from lateral ventricles were considered periventricular WMH (PVWMH) voxels, and those ≥ 12 mm^3 were classified as deep WMH (DWMH) voxels. Quality control was conducted by visualizing the resultant WMH masks superimposed onto corresponding FLAIR images. Seventy-eight scans were excluded due to inaccurate segmentations (Table S2 in supporting information).

3.4 | Harmonization of non-imaging variables

The harmonization of body mass index (BMI), diabetes, hypertension, hypercholesterolemia, atrial fibrillation (AF), cardiovascular disease, stroke, physical activity, and smoking, followed the protocols in a previous COSMIC study[17] (Tables S3–S7 in supporting information). Physical activity was categorized as inactive (scored as 0), occasional exercise (scored as 1), and frequent (scored as 2; Tables S3–S7).

Because SLAS only acquired data for the frequency of alcohol drinking, and 97.1% of participants reported never/rarely drinking, it was excluded from the analyses of alcohol consumption. The harmonization of alcohol consumption in other cohorts followed another COSMIC study[26] (Tables S3–S7). AF data were not acquired for PATH participants.

The harmonization of global cognition (Mini-Mental State Examination), memory (delayed world list recall), language (semantic fluency—animals), processing speed (Trail Making Test A), and executive function

(Trail Making Test B), also followed COSMIC protocols[17] (Supplementary Text 1 and Table S8 in supporting information). Trail Making Test A and B completion times were multiplied by −1 for better interpretation. Processing speed and executive function data were not available for the H70 Study. For some SLAS participants, memory ($N = 100$), language ($N = 115$), processing speed ($N = 120$), and executive function ($N = 138$) data were not available.

3.5 | Harmonization of WMH volumes

The comparison of different harmonization methods for WMH volumes is summarized in Supplementary Text 2 in supporting information. Age effects and Kolmogorov–Smirnov tests were used to assess the performance of harmonization (Figures S1–S2 in supporting information). ComBat-harmonized WMH volumes were used for further analyses.

3.6 | Statistical analyses

F tests and chi-square tests were used to examine the differences in risk factors between cohorts. Controlling for age and sex, the association between risk factors and WMH was examined with structural equation models (SEM) implemented in the Lavaan[27] package in R. Maximum likelihood estimator with robust standard errors and a scaled test statistic were used. Full information maximum likelihood was used to deal with missing values. To test the associations of risk factors on WMH, all vascular risk factors were used as independent variables of interest. The *P* value threshold was adjusted to 0.005 (0.05/10) in the Bonferroni correction, considering the presence of 10 risk factors. Differences in the effect of each risk factor on PVWMH and DWMH were also examined with SEM. The associations between cognition and WMH volumes, and the mediation effects of WMH volumes in the associations between vascular risk factors and cognition, were also examined in SEM (details see Supplementary Text 3 and Figure S3 in supporting information). Similar to risk factors, the *P* value threshold was adjusted to 0.01 (0.05/5) for cognition test in the Bonferroni correction. The moderating effects of ethnicity (three White and two Asian cohorts) in the association between vascular risk factors and WMH were tested. For associations in which the interaction term between ethnicity and risk factor had a *P* value less than 0.05, we ran regression analyses in White and Asian subsamples separately to investigate the ethnicity differences. In the tests for ethnicity differences, only White and Asian participants were included. Non-White (21 MAS and 12 PATH participants) and non-Asian (one SLAS participant) individuals were excluded. Outliers for WMH volumes and the cognitive scores were removed through applying a three standard deviation threshold.

4 | RESULTS

4.1 | Sample characteristics

Participants were aged 56 to 94 years at the time of data acquisition, and 54.8% were female. The excluded participants (WMH quality control and WMH outliers, $n = 125$) were aged 62 to 74 (mean age 71), and 55.2% were female. The *F* tests for all continues variables indicated significant differences across cohorts ($F = 6.9–505.7$, $P < 0.001$). The chi-square tests for all category variables showed significant differences across overall cohorts ($\chi^2 = 7.1–761.5$, $P < 0.001$). Participants in the SLAS had fewer years of education compared to those in other studies. Gothenburg H70 reported higher levels of physical activity among its participants relative to other studies. Additionally, SLAS had a higher proportion of female participants compared to other studies. There were no differences in sex distribution between the excluded participants and the whole sample ($\chi^2 = 0.018$, $P = 0.991$). Sample characteristics are summarized in Table 1. The details of excluded participants (WMH quality control and WMH outliers) are summarized in Table S9 in supporting information.

4.2 | Associations between vascular risk factors and WMH

The associations between vascular risk factors and WMH volumes are summarized in Table 2. Hypertension ($\beta = 0.056–0.087$, $P = 0.001–0.005$), current smoking (but not past smoking; $\beta = 0.096–0.114$, $P = 0.001–0.007$) and higher BMI ($\beta = 0.005–0.006$, $P = 0.006–0.009$) were associated with higher whole brain WMH (WBWMH), PVWMH, and DWMH volumes. After applying the Bonferroni correction, the associations of current smoking with both DWMH and PVWMH volumes remained significant. The associations of hypertension with WBWMH, PVWMH, and DWMH volumes also remained significant.

Higher number of drinks per week ($\beta = 0.005$, $P = 0.031–0.037$) and insufficient physical activity ($\beta = 0.028–0.032$, $P = 0.020–0.039$) were associated with higher WBWMH and PVWMH volumes. Participants with diabetes had higher WBWMH volumes ($\beta = 0.043$, $P = 0.047$), especially in the periventricular regions ($\beta = 0.051$, $P = 0.022$). History of stroke was associated with higher WBWMH volumes ($\beta = 0.085$, $P = 0.039$), especially in deep white matter regions ($\beta = 0.143$, $P = 0.009$). However, the above association did not survive Bonferroni correction. The associations between stroke and DWMH volumes were significantly stronger than the associations between stroke and PVWMH volumes ($P = 0.004$).

The differences in WMH volumes between different levels in smoking and physical activity are summarized in Figure 1. As shown in Figure 1, the frequent and occasional exercise groups

TABLE 1 Sample characteristics.

Parameters		H70 Study	KLOSCAD	MAS	PATH	SLAS	Total	F/χ^2 [c]
N (total/QC/outliers)[a]		704/700/668	260/257/255	497/474/468	414/384/380	196/178/175	2071/1994/1946	–
Age (mean [range])		71 [70,72]	72 [59,89]	79 [70,90]	67 [64,70]	74 [56,94]	72 [56, 94]	505.7***
Sex (female)		52.9%	57.6%	54.2%	43.8%	74.8%	54.8%	25.6***
Diabetes		15.7%	43.1%	12.9%	9.4%	21.3%	18.1%	147.2***
Hypertension		74.2%	85.5%	80.4%	64.3%	69.0%	74.6%	63.1***
Hypercholesterolemia		47.1%	74.0%	67.7%	36.3%	61.6%	55.2%	163.5***
Atrial fibrillation		4.1%	6.1%	4.3%	–	3.5%	4.4%	7.1***
Cardiovascular disease		6.9%	19.1%	22.8%	14.1%	10.5%	13.9%	62.3***
Stroke		8.3%	8.0%	2.3%	0.0%	29.1%	8.0%	52.6***
Current smoking		7.7%	5.3%	3.4%	6.8%	28.7%	8.9%	165.1***
Physical activity (occasional)		11.9%	66.4%	50.1%	72.1%	81.1%	45.3%	761.5***
Physical activity (frequent)		85.7%	12.2%	34.2%	18.3%	7.6%	44.3%	
Alcohol (drinks/week)[b]		8 [0, 68.7]	2 [0, 42]	6.3 [0, 56]	3.8 [0, 63.4]	-	3.8 [0, 68.7]	151.2***
BMI		26.0 ± 4.4	23.5 ± 2.8	26.7 ± 4.2	26.6 ± 4.2	23.4 ± 4.1	26.0 ± 4.3	24.2***
Education (years)		13.3 ± 4.1	12.1 ± 4.5	11.7 ± 3.6	14.0 ± 2.8	3.6 ± 3.7	12.0 ± 4.7	260.0***
Cognition	MMSE	29 ± 1.3	26.8 ± 3	28.9 ± 1.4	29.1 ± 1.4	25.1 ± 4.4	28.3 ± 2.5	42.2***
	Memory	8.6 ± 1.6	5.4 ± 2.4	7.5 ± 3.5	6.0 ± 2.5	5.4 ± 3.4	6.8 ± 3.1	6.9***
	Language	24.2 ± 6.1	16.7 ± 5.1	15.8 ± 4.6	–	12.1 ± 2.8	19.5 ± 4.7	40.6***
	Processing speed	–	57.6 ± 46	46 ± 16.1	34.4 ± 11.0	103.7 ± 51.3	50.5 ± 34.9	7.4***
	Executive function	–	163.8 ± 87	117.9 ± 55.6	79.8 ± 30.4	184.4 ± 61.5	121.5 ± 68.6	8.0***

Notes: Physical activity (occasional/frequent)—refer to Tables S3–S7 in supporting information for specific definitions in different studies. Executive function, Executive function test score, using Trail Making Test B in seconds; Language, Language test score, using semantic fluency test; Memory, Memory test score, using delayed world list recall; MMSE, the total score of the Mini-Mental State Examination; Processing speed, Processing speed test score, using Trail Making Test A in seconds

Abbreviations: BMI, body mass index; H70 Study, Gothenburg H70 Birth Cohort Study; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; MAS, Sydney Memory and Ageing Study; MMSE, Mini-Mental State Examination; PATH, Personality and Total Health Through Life study; QC, quality control; SLAS, Singapore Longitudinal Aging Studies; WMH, white matter hyperintensity.

[a]Total—the sample size of each cohort without dementia; QC—the sample size of each cohort without dementia after WMH quality control; Outliers—the sample size of each cohort without dementia after WMH quality control and outlier removal.

[b]10 g alcohol = 1 standard drink, the median with ranges was showed.

[c]For continuous variable, using *F* test; for category variable, using χ^2 test.

***$P < 0.001$.

TABLE 2 Associations between vascular risk factors and harmonized WMH volumes.

	Whole brain WMH			Periventricular WMH			Deep WMH		
	β	CI lower	CI upper	*β*	CI lower	CI upper	*β*	CI lower	CI upper
Diabetes	0.043*	0.001	0.087	0.051*	0.007	0.095	0.037	−0.025	0.098
Hypertension	0.059**†	0.021	0.098	0.056**†	0.005	0.096	0.087***†	0.034	0.140
Hypercholesterolemia	−0.025	−0.062	0.013	−0.025	−0.063	0.013	−0.022	−0.075	0.031
Atrial fibrillation	0.012	−0.083	0.107	0.010	−0.084	0.104	−0.013	−0.160	0.135
Cardiovascular disease	0.033	−0.015	0.082	0.021	−0.028	0.070	0.051	−0.016	0.144
Stroke	0.085*	0.004	0.146	0.043	−0.007	0.107	0.143**	0.033	0.254
Smoking	0.096**	0.035	0.157	0.099***†	0.039	0.159	0.114**†	0.031	0.198
Body mass index	0.005**	0.001	0.011	0.006**	0.001	0.012	0.005**	0.001	0.008
Physical activity	−0.032*	−0.059	−0.005	−0.028*	−0.055	−0.001	−0.035	−0.074	0.003
Alcohol consumption	0.005*	<0.001	0.009	0.005*	<0.001	0.009	0.003	−0.001	0.012

Note: The table lists all the regression coefficients for the risk factors. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. †Remains significant after Bonferroni correction.

Abbreviations: CI, 95% confidence interval; WMH, white matter hyperintensity.

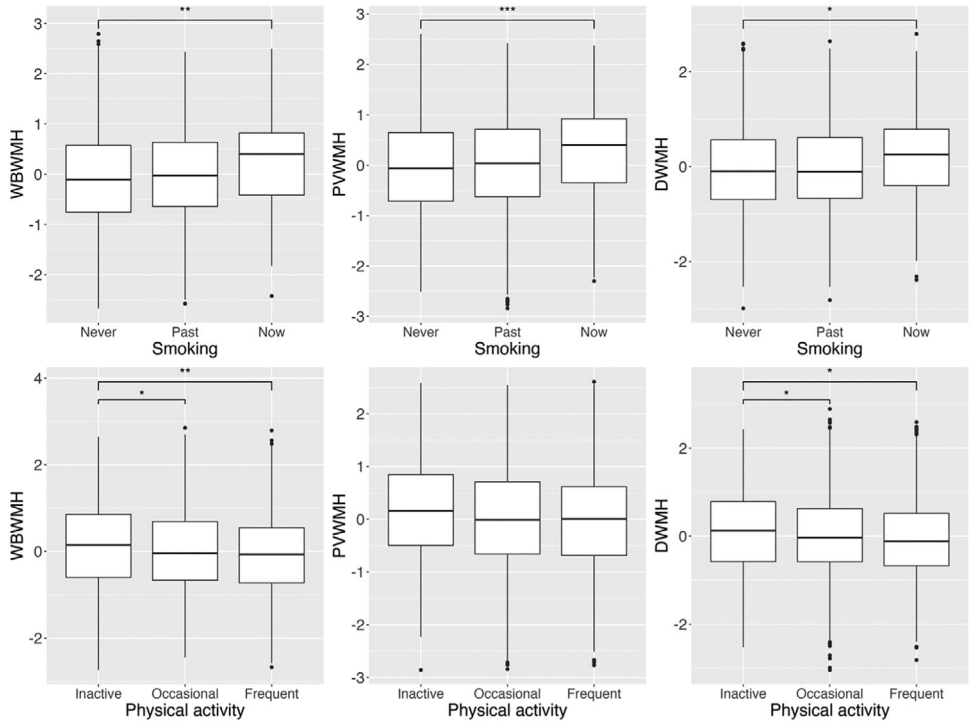

FIGURE 1 The differences in WMH volumes between different levels of physical activities (first row) and smoking (second row). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. DWMH, deep white matter hyperintensities; PVWMH, periventricular white matter hyperintensities; WBWMH, whole brain white matter hyperintensities; WMH, white matter hyperintensity

TABLE 3 Associations between WMH volumes and cognition.

	Whole brain WMH			Periventricular WMH			Deep WMH		
Cognition	***β***	**CI lower**	**CI upper**	***β***	**CI lower**	**CI upper**	***β***	**CI lower**	**CI upper**
Mini-Mental State Examination	−0.040	−0.082	0.002	−0.027	−0.069	0.014	−0.033	−0.102	0.037
Memory	−0.035	−0.105	0.034	−0.040	−0.110	0.030	−0.039	−0.108	0.029
Language	−0.020	−0.088	0.046	−0.015	−0.083	0.052	−0.024	−0.091	0.041
Processing speed	−0.049	−0.107	0.008	−0.043	−0.099	0.013	−0.067*	−0.137	−0.003
Executive function	−0.057*	−0.113	<0.001	−0.041	−0.098	0.015	−0.063*	−0.127	<0.001

Note: The table lists all the regression coefficients for cognitive variables. *P* values for the associations were shown as *$P < 0.05$.
Abbreviations: CI, 95% confidence interval; WMH, white matter hyperintensity.

had less WBWMH (mean difference = 0.092–0.106, $P = 0.002$–0.016) and DWMH (mean difference = 0.083–0.093, $P = 0.037$–0.045) volumes than the inactive group. No significant differences were found between the frequent and occasional exercise groups ($P > 0.805$).

4.3 | Associations between WMH and cognition

Associations between WMH volumes and cognition are summarized in Table 3. Higher DWMH volumes were associated with worse performance in the processing speed domain ($\beta = -0.067$, $P = 0.026$). Higher WBWMH ($\beta = -0.057$, $P = 0.040$) and DWMH ($\beta = -0.063$, $P = 0.037$) volumes were associated with worse performance in the executive function domain.

However, these findings did not survive Bonferroni correction for multiple tests. No mediation effects of WMH were found in the associations between vascular risk factors and cognition (Table S10 in supporting information).

4.4 | Moderation effects of ethnicity in the associations between vascular risk factors and WMH

The differences in WMH volumes between White and Asian groups are summarized in Figure 2, but were not statistically significant when

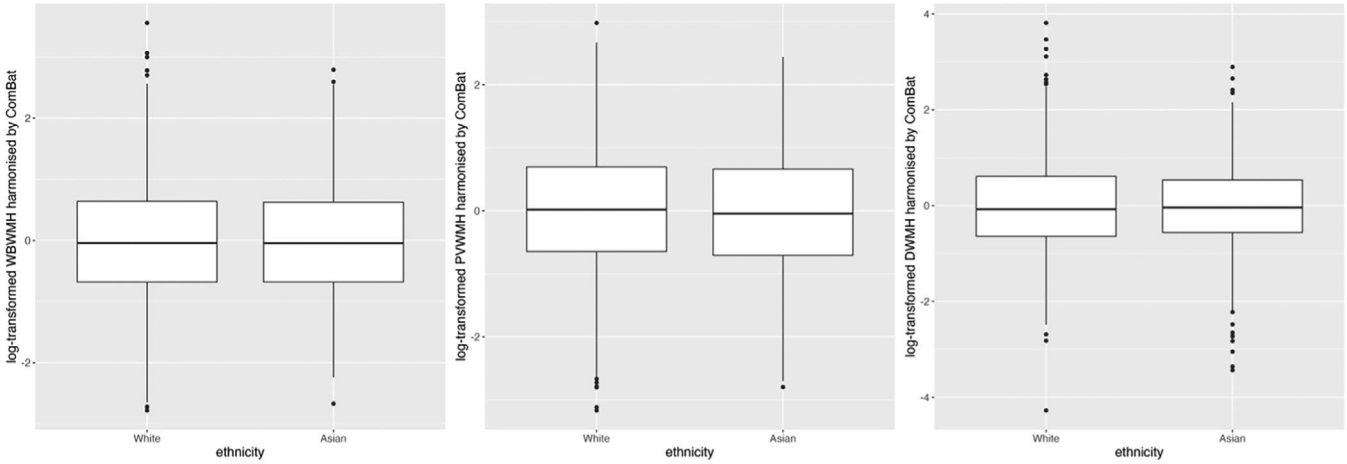

FIGURE 2 The differences in WMH volumes between White and Asian participants. DWMH, deep white matter hyperintensities; PVWMH, periventricular white matter hyperintensities; WBWMH, whole brain white matter hyperintensities; WMH, white matter hyperintensity

TABLE 4 Differences in the associations of risk factors with WMH between White and Asian individuals.

		Whites			Asians		
Risk Factors	**WMH measure**	**β**	**CI lower**	**CI upper**	**β**	**CI lower**	**CI upper**
Stroke	WBWMH	0.124**	0.029	0.220	0.006	−0.127	0.139
Stroke	PVWMH	0.083	−0.002	0.176	0.001	−0.127	0.129
Stroke	DMWH	0.176*	0.021	0.331	0.050	−0.137	0.230
Hypercholesterolemia	WBWMH	−0.005	−0.044	0.034	−0.081*	−0.164	−0.002
Hypercholesterolemia	PVWMH	−0.019	−0.042	0.036	−0.084*	−0.168	−0.001
Hypercholesterolemia	DWMH	−0.003	−0.076	0.038	−0.061	−0.177	0.055

Note: The table shows regression coefficients for risk factors in White and Asian subsamples. Only factors for which an interaction term between risk factor and ethnicity had $P < 0.1$ are included. *$P < 0.05$, **$P < 0.01$.
Abbreviations: CI, 95% confidence interval; DWMH, deep white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; WBWMH, whole brain white matter hyperintensity; WMH, white matter hyperintensity.

adjusting for age and sex (mean differences < 0.002, *P* value > 0.305).

Interaction terms between ethnicity and risk factors with a *P* value < 0.05 were found for stroke and hypercholesterolemia (WBWMH/PVWMH/DWMH). We further investigated these associations by splitting the whole sample into White and Asian subsamples (Table 4). The associations between hypercholesterolemia and less WBWMH ($\beta = -0.081$, $P = 0.021$) and PVWMH ($\beta = -0.084$, $P = 0.039$) volumes were significant in the Asian subsample only. The associations of stroke with higher WBWMH ($\beta = 0.124$, $P = 0.011$) and DWMH ($\beta = 0.176$, $P = 0.026$) volumes were statistically significant in the White subsample only.

5 | DISCUSSION

WMH volumes were examined in relation to vascular risk factors and cognitive function, using samples from five international studies from the COSMIC consortium. Diabetes, hypertension, history of stroke, current smoking, high BMI, physical inactivity, and higher alcohol consumption were associated with larger WBWMH volumes. WMH volume, especially in the deep white matter regions, was negatively associated with executive function, and higher DWMH volume was significantly associated with poorer performance in processing speed and executive function. The associations of hypertension and stroke with WMH volumes were stronger in White participants, whereas a negative association between hypercholesterolemia and WMH was stronger in Asians.

Our finding of associations between WMH volumes and cardiovascular factors is consistent with previous studies for diabetes,[8] hypertension,[28] and BMI.[29] A few population-based studies reported no association between alcohol consumption and WMH volumes.[30,31] However, the current study showed a significant association between higher alcohol intake and higher WMH volumes. A systematic review showed a linear association between higher alcohol consumption and higher prevalence of hypertension and heart failure.[32] Cardiovascular dysfunction was strongly associated with WMH.[9] Some pathology

studies found that ethanol may affect endothelial function[33] and cause vascular oxidative stress,[34] contributing to the accumulation of WMH.

Current smoking was a significant risk factor for WMH volumes, but not past smoking, consistent with previous findings.[35] Interestingly, there is no sufficient evidence to support a difference between former smokers and non-smokers. Furthermore, a previous study also reported a positive association between the progression of WMH and an increase in the pack-years of smoking.[35] At the same time, there was no association between years since quitting and WMH progression among former smokers. However, only 6% of participants quit smoking within 6 years. Future research should track more smokers to investigate the impact of the duration after quitting smoking on WMH.

The results of the current study suggest that a moderate level of physical activity was sufficient enough to be associated with WMH volume. This is consistent with a systematic review that found less WMH to be associated with more physical activity, but only in individuals without severe neurological disorders.[36] The optimal amount of physical activity associated with reduced levels of WMH remains to be determined.

We found executive function and processing speed to be associated with both WBWMH and DWMH, though with marginal statistical significance. Some previous studies have also found these cognitive domains to be associated with lower WMH volumes, in both general population-based and high vascular risk samples.[37] However, other research has reported contradictory findings of no association of WMH volumes with either global cognition[38,39] or any specific cognitive domain.[38] In the current study, each of the participating cohorts used different neuropsychological test batteries, and we were only able to use one test for each cognitive domain that was common across cohorts. Because one neuropsychological test may not necessarily be representative of a specific cognitive domain, this lack of a broader range of cognitive measures may have contributed to the marginal nature of the association seen in our study.

The current study did not find significant differences in WMH volumes between White and Asian cohorts. However, it is worth noting that the Asian cohorts included in the current study (Korea and Singapore) are from relatively high-income countries. A recent systematic review found a higher presence of moderate to severe WMH in low-income countries (moderate to severe WMH: 28.4%, mean age > 60) than in middle-income countries (moderate to severe WMH: 19.0%, 61.5% articles mean age > 60, 38.5% mean age 55–60).[40] A systematic review included participants with a mean age of 61 years who reported a higher presence of moderate to severe WMH in community-based cohorts in high-income countries (Rotterdam, Austria, moderate to severe WMH > 65%).[41] However, one study in the United States reported that Black individuals had higher WBWMH volumes than White individuals.[42] Future research is needed to investigate (1) ethnicity differences in WMH volumes in countries with similar income levels, and (2) the association between WMH volumes and income level using a similar data acquisition protocol.

As for hypercholesterolemia, the current study found no association between hypercholesterolemia and WMH volumes, which is consistent with both Asian[43] and White[44] large-scale studies. Although some community-based studies showed that higher low-density lipoprotein cholesterol was associated with higher WMH burden,[45,46] one cohort (n = 2635) noted a significant association between higher high-density lipoprotein cholesterol and higher prevalence of cerebral microbleeds.[47] In the tests for ethnicity differences, hypercholesterolemia was associated with lower WMH volumes in Asian subsamples. A well-presented review[48] proposed that cholesterol-lowering medication (e.g., statins) may moderate the effects of cholesterol on brain imaging measurement[49] and neurocognitive disorders.[50] As for the ethnic differences in response to medicines, a previous report showed that Japanese individuals with lower statin doses led to a similar risk reduction of cardiovascular disease than White individuals with higher doses.[51] A pharmacokinetic study of statins indicated that the overall quantity of statin successfully reaching the systemic circulation in Asian individuals is double compared to White individuals,[52] which may contribute to brain imaging measurements. Future studies about hypercholesterolemia should consider the effect of statins, especially in research on elderly populations.

There are some limitations in this study. First, harmonizing non-imaging risk factors in multi-cohort studies is challenging. Some studies collected detailed information, such as self-reports, medical history, and clinical data, while others only acquired self-reports. Regarding lifestyle-related risk factors, each study had different protocols for data collection, particularly for physical activity (e.g., only some studies reported the number of hours per week). Second, each cognitive domain performance score was based on the results of a single test, which may not comprehensively represent ability in any given domain. Third, the criteria of hypercholesterolemia only considered total cholesterol. Future studies should focus more specifically on high-density or low-density lipoprotein cholesterol. Fourth, the placement of cohorts from South Korea and Singapore into a single "Asian" group ignores the ethnic and genetic diversity within and between these populations. We hope that future studies with sufficient numbers from different ethnicities within Asia will conduct more refined analyses. Last, one cohort did not have data for AF, and the smaller overall number of participants may have limited our ability to find any associations between this vascular risk factor and WMH volumes.

6 | CONCLUSION

This multi-national study confirmed previous findings on the associations of WMHs with vascular risk factors and cognition. Hypertension and stroke were found to have strong associations with higher WBWMH volumes in White participants only. In comparison, hypercholesterolemia was found to be associated with lower WMH volumes in Asian individuals only.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data were provided by the contributing studies to COSMIC on the understanding and proviso that the relevant study leaders be contacted for further use of their data and additional formal data sharing agreements be made. Researchers can apply to use COSMIC data by completing a COSMIC Research Proposal Form available from https://cheba.unsw.edu.au/consortia/cosmic/research-proposals.

CONSENT STATEMENT

All human subjects involved in this study provided their informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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