



Prospectively collected lifestyle and health information as risk factors for white matter hyperintensity volume in stroke patients

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Abstract

Most studies of white matter hyperintensity volume (WMHV) in stroke patients lack reliable information on antecedent exposure to vascular risk factors. By leveraging prospective cohort data, we explored associations between lifestyle and health factors assessed 1 year prior to stroke and WMHV in individuals who experienced an ischemic stroke. This analysis was nested within two large prospective studies of initially healthy individuals. Information on lifestyle factors and health conditions was collected prior to the stroke event through annual or biannual questionnaires. For individuals who experienced their first confirmed ischemic stroke and had available magnetic resonance imaging, we measured WMHV using a validated semiautomated method. Linear regression was used to explore associations between lifestyle factors and health conditions and log-transformed WMHV. We measured WMHV in 345 participants with a first ischemic stroke event (mean age = 74.4 years; 24.9% male). After multivariate adjustment, history of diabetes was associated with decreased WMHV (p value = 0.06) while history of transient ischemic attack (p value = 0.09) and hypertension (p value = 0.07) were associated with increased WMHV. Most lifestyle factors and health conditions measured 1 year prior to stroke were not associated with WMHV measured at the time of ischemic stroke. Future studies could examine whether long term exposure to these factors impacts diffuse microvascular ischemic brain injury among stroke patients.

Keywords Risk factors · White matter hyperintensities · Stroke

Introduction

Increased white matter hyperintensity volume (WMHV) among stroke patients is associated with greater risk of stroke recurrence [1] and poorer outcomes after stroke [2, 3].

Because WMHV impacts stroke outcomes, it is important to determine predictors of WMHV among stroke patients. Most prior studies among stroke patients explored only risk factors present at the time of the stroke event and not how risk factor status prior to stroke influenced WMHV. In addition, the severity of the stroke event limited accurate ascertainment of past risk factors, particularly lifestyle factors as these are generally self-reported.

Several lifestyle factors and health conditions measured years prior to brain imaging have been associated with white matter hyperintensity (WMH) severity among those who have not had a stroke, including smoking, physical activity, hypertension and history of cardiovascular disease [4–8]. Among stroke patients, evidence for an association between past history of smoking and WMHV is inconsistent [9–11]. No studies have been performed among stroke patients to explore the association between physical activity prior to stroke and WMHV. One study among stroke patients observed that past history of hypertension was associated with increased WMHV [11]. The same study also observed that history of transient ischemic

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attack (TIA) prior to stroke was associated with decreased WMHV [11].

To assess past risk factor status and avoid recall bias, we leveraged data from two large prospective studies, the Women's Health Study (WHS) and the VITamin D and Omega-3 Trial (VITAL). Both studies enrolled initially healthy individuals and collected information on several lifestyle factors and health conditions at baseline and followed participants prospectively for first incident ischemic stroke events. Using data from these studies, we explored the association between lifestyle factors and health conditions prior to stroke and WMHV among individuals with ischemic stroke.

Methods

Overview of studies

Participants were enrolled in the WHS or VITAL, which were randomized trials for prevention of cardiovascular disease and cancer in individuals without a history of cardiovascular disease or cancer at baseline. The studies have been described in detail previously [12–14]. Briefly, the WHS is a completed randomized trial of the effects of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39,876 female health care professionals ≥ 45 years of age at baseline in 1992–1994. After the end of the trial in 2004, women were asked if they were willing to be followed on an observational basis, and observational follow-up is currently ongoing. This analysis includes data through June 30, 2018.

VITAL is a randomized trial of the effects of vitamin D₃ and omega-3 fatty acids in the primary prevention of cardiovascular disease and cancer among 25,871 individuals (men aged ≥ 50 and women aged ≥ 55 years at baseline in 2011–2014). Active treatment ended in December 2017 and observational follow-up is currently ongoing. This analysis includes data through May 30, 2018.

All study participants have given their written informed consent and the two study protocols have been approved by the Institutional Review Board at Brigham and Women's Hospital.

Risk factor assessment

Prior to randomization, twice during the first year, and yearly thereafter, WHS and VITAL participants were mailed questionnaires asking about demographics and lifestyle characteristics. Information was also obtained on physician diagnosis of the primary trial outcomes of myocardial infarction (MI), stroke, and cancer, as well as, other health outcomes including diabetes, TIA, angina, coronary revascularization, hypertension, and high cholesterol. Risk factors

examined included smoking status (never, past, current); physical activity (< 200 kcal/week, 200 – < 600 kcal/week, 600 – < 1500 kcal/week, and ≥ 1500 kcal/week); alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, ≥ 1 drink/day); statin use (yes/no); treatment for hypertension (yes/no); post-menopausal hormone use of any type (never, past, current); body mass index (BMI) (< 25 kg/m², 25 – 29.9 kg/m², ≥ 30 kg/m²); self-report of a physician diagnosis of diabetes, TIA, angina, coronary revascularization (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) (yes/no for each); history of hypertension (yes/no, includes self-report of a physician diagnosis, use of hypertension medications, systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90); history of high cholesterol (yes/no, includes self-report of a physician diagnosis, use of cholesterol-lowering medications, or cholesterol levels ≥ 240 mg/dL); and diagnosis of incident MI (yes/no) or cancer (yes/no) since the start of the study.

Ascertainment of stroke

Both studies collected information on incident stroke events through the questionnaires which asked the participants whether they had been diagnosed with a stroke by a physician since the last questionnaire. If a participant self-reported a stroke diagnosis, an Endpoints Committee of physicians, blinded to treatment assignment, reviewed medical records to confirm or disconfirm the case according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [15]. For fatal stroke, all available sources, including death certificates, hospital records, and the National Death Index were used to confirm the event. The committee also classified confirmed stroke events into ischemic, hemorrhagic, and unknown types.

WMHV assessment from MRI

Since the start of the VITAL study and since January 1, 2011 in WHS, for each confirmed incident ischemic stroke for which there was an indication in the medical records that an MRI was performed at the time of the stroke, we requested permission to obtain electronic copies of the MRI. For those events for which we obtained MRIs, we used a semi-automated method previously developed and validated in stroke patients to measure WMHV [16–19]. After computer processing, a single study investigator (P.M.R.) reviewed each available T2 FLAIR scan to exclude hyperintense lesions not related to ischemic WMH (e.g., acute or chronic infarcts). To avoid confounding by the presence of focal white matter damage caused by the index stroke, total WMHV was calculated by doubling WMHV from the hemisphere contralateral to the cerebral infarct an approach which

has been previously validated in stroke patients [17, 20, 21]. Sagittal midline cross-sectional intracranial volume (ICA), a validated surrogate for intracranial volume [22] was used to normalize total WMHV for head size. Normalized total WMHV was calculated as WMHV multiplied by the ratio of individual ICA to mean ICA according to a previously validated method [22, 23].

Statistical analysis

The study sample was comprised of incident first ischemic stroke events occurring since January 1, 2011 in WHS or VITAL with available WMHV data. In WHS, between January 1, 2011 and June 30, 2018, 313 first ischemic stroke events were confirmed. Of these, 248 indicated in the medical record that an MRI was performed; digital copies of the MRIs were obtained from 204 of these events, and WMHV was measured in 197 participants who had a T2 FLAIR sequence available (Fig. 1). In VITAL, as of May 2018, 200 first ischemic stroke events were confirmed; 188 indicated in the medical record that an MRI was performed; MRIs were obtained from 157 of these events and WMHV was measured as observed on T2 FLAIR sequences in 149 participants. We excluded one participant from VITAL who did not complete baseline assessments of risk factors prior to stroke (Fig. 1).

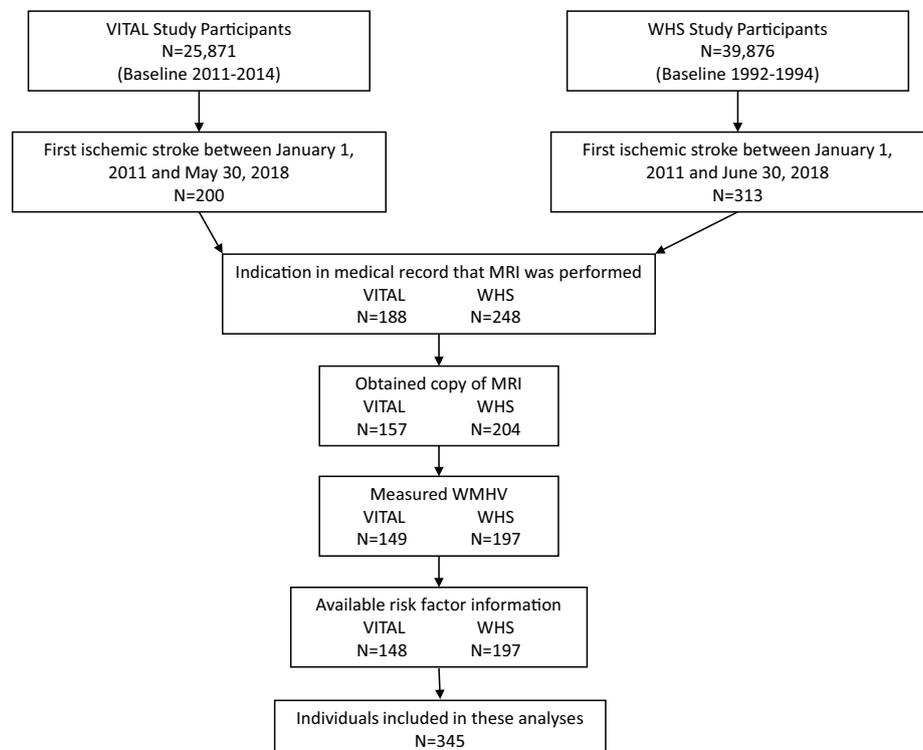
For our primary analysis, we explored the association between previous risk factor status and WMHV by using

diagnosis dates for health conditions or risk factor information from questionnaires that were at least 1 year prior to the date of the MRI. For VITAL participants who experienced a stroke event within 1 year of enrollment, we used information from the enrollment questionnaires. If relevant information was missing from the nearest questionnaire at least 1 year prior to the MRI, information from prior questionnaires was carried forward. Given the extended follow-up in the WHS, we also explored the association between risk factor status measured at least 5 and 10 years prior to the MRI and WMHV among WHS participants.

Nine individuals were missing covariate information. To impute missing data, we performed multiple imputation using the PROC MI procedure in SAS 9.4 which used an iterative form of stochastic imputation and assumed a multivariate normal distribution. All risk factors as well as log transformed WMHV, age, sex, and parent study were used in the multiple imputation procedures. Ten imputed datasets were created.

Since WMHV has a skewed distribution, we natural log transformed WMHV for all analyses. Because one participant had no WMHV present, we added 1 to all WMHVs prior to performing the log transformation. We used linear regression to explore the association between our risk factors and log-transformed WMHV. Our first analysis adjusted only for age, sex, and parent study. Our second analysis adjusted for all other risk factors in addition to age, sex, and parent study.

Fig. 1 Study flow diagram



Results

Of the 513 first ischemic stroke events, which occurred after January 1, 2011, 345 events had WMHV measured and risk factor information available. The baseline characteristics of individuals with available WMHV measurements versus those without are compared in Supplemental Table 1. Those without WMHV measurements were slightly older, less likely to be male and to currently use hormone therapy and more likely to be normal weight and to have diabetes.

Table 1 displays the baseline characteristics of the 345 participants with WMHV data, overall and by WMHV quartile. The median value of normalized WMHV in the first quartile was 1.81 cm³ while the median value of normalized WMHV in the fourth quartile was 28.60 cm³. The mean age of participants was 74.4 years and 24.9% of participants were male. Those in the highest quartile of WMHV had the oldest average age.

Table 2 presents the association between risk factors assessed at least one year prior to MRI and log normalized WMHV adjusted for age, sex, and parent study (Model 1) and all risk factors (Model 2). In Model 1, only history of hypertension was significantly associated with increased WMHV (p value = 0.03). Those with a history of TIA had higher WMHV (p value = 0.07), and those with a history of diabetes had lower WMHV (p value = 0.09) but neither difference was statistically significant.

In Model 2 the observed associations of WMHV with history of hypertension (p value = 0.08), TIA (p value = 0.08), and diabetes (p value = 0.06) remained of similar magnitude but the association with history of hypertension was no longer statistically significant.

We also explored whether risk factor status at least 5 and 10 years prior to the stroke event was associated with WMHV in the WHS (Table 3). History of diabetes at least 5 years (p value = 0.01) or 10 years (p value = 0.04) prior to stroke was significantly associated with decreased WMHV. History of TIA five years prior to stroke (p = 0.07) and treatment for hypertension 10 years prior to stroke (p = 0.08) were associated with increased WMHV although these associations were not statistically significant.

Discussion

Using prospectively collected data from two large studies, we did not demonstrate associations for most antecedent vascular risk factors and WMHV on the MRI scans of individuals who experienced an ischemic stroke. History of diabetes was associated with decreased WMHV at 5

and 10 years prior to stroke. At 1 year prior to stroke, history of TIA or hypertension was associated with increased WMHV and history of diabetes was associated with decreased WMHV but these associations were not statistically significant.

Although the pathophysiology of WMH is unclear, WMH appear to be of vascular origin and involve a loss of vascular integrity [24]. Given the link to vascular health, we hypothesized that common vascular risk factors like smoking, low alcohol consumption, lack of physical activity, diabetes, or hypertension would be associated with increased WMHV. Additionally, studies in stroke-free cohorts have found associations between several vascular risk factors and higher prevalence of white matter hyperintensities or higher WMHV [4–8]. However, few studies in stroke patients have explored the association between vascular risk factors, particularly lifestyle factors, and WMHV and evidence from these studies has been inconsistent. One study observed an association between smoking status at the time of stroke and WMHV [10] but others have not observed an association [9, 10] or found an association only among patients with early age at stroke onset (<55 years) [11]. The older average age of participants in the WHS and VITAL, as well as the small number of current smokers, may explain why we did not observe associations between smoking history and WMHV. Although one small study found no association between alcohol use and WMHV [10], larger studies (N = 1009 and N = 809) have observed higher WMHV among those who report alcohol use [9, 11]. Our study collected additional information on alcohol consumption (including alcohol consumption 5 and 10 years prior to stroke and different amounts of alcohol consumption) but we did not find an association between alcohol use and WMHV. Physical activity has been associated with reduced WMHV in healthy individuals [7], but this association has not been previously studied in stroke patients. We did not find strong associations between physical activity prior to stroke and WMHV.

In addition to exploring lifestyle factors, we examined the association between several health conditions and WMHV. Although hypertension is widely considered to be a risk factor for WMHV, the association between hypertension and WMHV was only significant among those whose age at stroke onset is <75 years [11]. One prior study among individuals with ischemic stroke observed that those with hyperlipidemia had lower WMHV than those without hyperlipidemia [10]. In contrast we did not find an association between history of high cholesterol or statin use and WMHV. Although few individuals in this study experienced a MI or had a coronary revascularization during the course of the study, we observed no association between MI or coronary revascularization and WMHV which is consistent with prior studies [9, 10, 18].

Table 1 Characteristics of participants at least 1 year prior to MRI scan in the full cohort and by WMHV quartile

Characteristic	(N = 345)	Quartile 1 (N = 87)	Quartile 2 (N = 86)	Quartile 3 (N = 86)	Quartile 4 (N = 86)
Log-transformed normalized WMHV, mean (SD)	2.22 (1.01)	0.94 (0.37)	1.86 (0.23)	2.56 (0.17)	3.53 (0.50)
Normalized WMHV, median (IQR)	8.60 (3.34, 17.09)	1.81 (0.96, 2.55)	5.53 (4.04, 6.78)	12.04 (10.05, 13.94)	28.60 (22.42, 47.19)
Days between stroke and MRI scan, median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 3)	1 (0, 2)
Age, mean (SD)	74.4 (7.3)	71.2 (7.4)	74.0 (6.5)	74.8 (6.7)	77.5 (7.1)
Male sex (%)	24.9	33.3	25.6	19.8	20.9
White race (%)	89.6	87.4	95.4	87.2	88.4
Physical activity (%)					
Missing	0.6	0	0	2.3	0
< 200 kcal/week	22.0	16.1	24.4	20.9	26.7
200–< 600 kcal/week	17.1	25.3	9.3	19.8	14.0
600–< 1500 kcal/week	29.3	26.4	27.9	30.2	32.6
≥ 1500 kcal/week	31.0	32.2	38.4	26.7	26.7
Smoking status (%)					
Missing	0.3	0	0	1.2	0
Never	47.3	43.7	54.7	44.2	46.5
Past	46.7	49.4	40.7	47.7	48.8
Current	5.8	6.9	4.7	7.0	4.7
Alcohol consumption (%)					
Missing	0.3	0	0	0	1.2
Rarely/never	38.8	35.6	29.1	48.8	41.9
1–3 drinks/month	11.9	10.3	17.4	10.5	9.3
1–6 drinks/week	33.6	39.1	36.1	25.6	33.7
1 + drinks/day	15.4	14.9	17.4	15.1	14.0
History of diabetes (%)	14.5	23.0	11.6	12.8	10.5
History of MI (%)	2.0	1.2	3.5	2.3	1.2
History of revascularization (%)	4.6	3.5	8.1	3.5	3.5
History of hypertension (%)	77.4	70.0	70.9	83.7	84.9
Treatment for high blood pressure (%)	58.0	58.6	53.5	50.0	69.8
History of high cholesterol (%)	59.4	63.2	55.8	60.5	58.1
Statin use (%)					
Missing	0.3	0	1.2	0	0
No	62.3	56.3	62.8	67.4	62.8
Yes	37.4	43.7	36.1	32.6	37.2
History of TIA (%)	2.3	0	1.2	2.3	5.8
History of angina (%)	3.8	2.3	5.8	3.5	3.5
History of cancer (%)	9.9	9.2	14.0	9.3	7.0
Hormone use among women (%)					
Missing	0.8	0	0	0	2.9
Never	28.2	31.0	28.1	30.4	23.5
Past	59.5	56.9	56.3	63.8	60.3
Current	11.6	12.1	15.6	5.8	13.2
Body mass index					
Missing	0.9	0	1.2	2.3	0
Normal weight (< 25 kg/m ²)	34.5	23.0	50.0	29.1	36.1
Overweight (25–< 30 kg/m ²)	37.4	41.4	29.1	39.5	39.5
Obese (≥ 30 kg/m ²)	27.3	35.6	19.8	29.1	24.4

IQR interquartile range (25th and 75th percentiles), SD standard deviation, WMHV white matter hyperintensity volume

Cutpoints for quartiles of log-transformed WMHV: 1.47 cm³, 2.26 cm³, 2.89 cm³

Table 2 Associations between risk factors assessed at least 1 year prior to MRI scan and log-transformed normalized white matter hyperintensity volume

	Model 1 ^a (N = 345)			Model 2 ^b (N = 345)		
	Beta	(SE)	<i>p</i> value	Beta	(SE)	<i>p</i> value
Male sex	-0.20	0.16	0.22	-0.18	0.19	0.34
Age	0.04	0.01	<0.01	0.04	0.01	<0.01
Physical activity						
< 200 kcal/week	Ref			Ref		
200–< 600 kcal/week	-0.26	0.17	0.12	-0.24	0.17	0.16
600–< 1500 kcal/week	0.03	0.15	0.84	0.07	0.16	0.64
1500+ kcal/week	-0.15	0.15	0.29	-0.10	0.16	0.53
						<i>p</i> value for trend 0.90
Smoking status						
Never	Ref			Ref		
Past	-0.01	0.11	0.92	-0.03	0.11	0.81
Current	-0.01	0.23	0.95	-0.01	0.24	0.96
						<i>p</i> value for trend 0.88
Alcohol consumption (%)						
Rarely/never	Ref			Ref		
1–3 drinks/month	-0.10	0.17	0.54	-0.11	0.18	0.56
1–6 drinks/week	-0.14	0.12	0.25	-0.16	0.13	0.22
1+ drinks/day	-0.09	0.16	0.58	-0.08	0.17	0.63
						<i>p</i> value for trend 0.41
History of diabetes	-0.25	0.15	0.09	-0.30	0.16	0.06
History of myocardial infarction	-0.16	0.37	0.66	-0.30	0.51	0.56
History of revascularization	-0.32	0.25	0.20	-0.46	0.36	0.21
History of cancer	-0.14	0.18	0.43	-0.12	0.18	0.52
History of hypertension	0.27	0.12	0.03	0.27	0.16	0.08
Hypertension treatment	0.14	0.11	0.19	0.07	0.13	0.57
History of high cholesterol	-0.07	0.11	0.56	-0.12	0.16	0.43
Statin use	-0.04	0.11	0.71	0.04	0.15	0.77
History of TIA	0.63	0.35	0.07	0.66	0.38	0.08
History of angina	-0.02	0.28	0.95	-0.05	0.31	0.86
Hormone use						
Never	Ref			Ref		
Past	0.06	0.14	0.67	0.03	0.15	0.85
Current	0.10	0.22	0.64	0.06	0.22	0.80
Body mass index						
Normal weight	Ref			Ref		
Overweight	-0.04	0.12	0.76	-0.05	0.13	0.70
Obese	-0.05	0.14	0.73	-0.05	0.15	0.76
						<i>p</i> value for trend 0.71

^aModel 1 adjusted for age, sex, and parent study^bModel 2 adjusted for all risk factors listed in addition to age, sex, and parent study

One prior study observed that history of TIA was associated with decreased WMHV among those who experienced an ischemic stroke between 55 and 75 years of age [11]. In contrast, among those aged > 75 years, they observed a

non-significant increase in WMHV for those with a history of TIA. In our cohort of elderly individuals, history of TIA was marginally associated with increased WMHV. Most studies [9–11, 18] have failed to find an association between

Table 3 Multivariable-adjusted (Model 2) associations between risk factor status at least 5 and 10 years prior to MRI scan and log-transformed normalized white matter hyperintensity volume in the Women's Health Study

	Five year (N=197)			Ten year (N=197)		
	Beta (SE)	(SE)	p value	Beta	(SE)	p value
Age	0.03	0.01	0.002	0.04	0.01	< 0.01
Physical activity						
No PA (< 200 kcal/week)	Ref			Ref		
Low PA (200–< 600 kcal/week)	–0.19	0.22	0.39	0.35	0.23	0.13
Mid PA (600–< 1500 kcal/week)	0.07	0.21	0.73	0.34	0.21	0.11
High PA (1500+ kcal/week)	0.01	0.20	0.94	0.12	0.21	0.58
Smoking status						
Never	Ref			Ref		
Past	0.03	0.14	0.82	0.09	0.15	0.55
Current	0.33	0.30	0.27	0.40	0.27	0.14
Alcohol consumption (%)						
Rarely/never	Ref			Ref		
1–3 drinks/month	–0.22	0.24	0.36	0.23	0.25	0.35
1–6 drinks/week	0.04	0.16	0.82	0.05	0.16	0.74
1+ drinks/day	–0.43	0.24	0.07	–0.32	0.24	0.18
History of diabetes	–0.66	0.24	0.01	–0.68	0.32	0.04
History of myocardial infarction	0.57	0.71	0.42	–0.04	0.93	0.96
History of revascularization	–0.84	0.55	0.13	–0.64	0.88	0.46
History of cancer	–0.27	0.23	0.24	0.06	0.30	0.83
History of hypertension	0.15	0.20	0.46	0.18	0.17	0.28
Hypertension treatment	0.17	0.16	0.29	0.31	0.17	0.08
History of high cholesterol	–0.08	0.17	0.66	0.05	0.16	0.75
Statin use	0.02	0.17	0.90	0.09	0.18	0.64
History of TIA	0.91	0.50	0.07	0.71	0.95	0.46
History of angina	0.25	0.38	0.52	0.72	0.62	0.25
Hormone use						
Never	Ref			Ref		
Past	0.10	0.17	0.56	0.01	0.19	0.95
Current	–0.16	0.22	0.47	0.11	0.17	0.54
Body mass index						
Normal weight	Ref			Ref		
Overweight	–0.18	0.17	0.29	–0.26	0.17	0.12
Obese	0.01	0.20	0.95	–0.09	0.20	0.66

Model 2 adjusted for all risk factors listed in addition to age, sex and parent study

diabetes and WMHV although one study did observe an association between hemoglobin A1c levels and increased WMHV [9]. After multivariate adjustment, we observed a non-significant inverse association between diabetes and decreased WMHV, which has not been previously observed. However, the prevalence of diabetes was higher among those individuals without measured WMHV than among those with measured WMHV which may have biased our results. Future research is needed to determine if our finding is due to bias or chance or if it reflects differences in risk factors for WMHV in diabetic patients with older age at stroke onset.

Our study also explored other potential risk factors for WMHV which have not been previously explored in stroke populations, including body mass index, post-menopausal

hormone use, history of cancer, and history of angina. We did not observe statistically significant associations between any of these risk factors and WMHV.

The strengths of this study include the use of a prospective cohort design which allowed for an in-depth, unbiased ascertainment of lifestyle behaviors such as physical activity and alcohol consumption, which are nearly impossible to reconstruct in a retrospective review of acutely ill patients admitted to the hospital with stroke. We also used a validated quantitative approach to assess WMHV instead of only relying on visual rating scales.

Some important limitations should be noted. The number of strokes were smaller than previous clinic-based studies of WMHV in ischemic stroke patients and thus we had

limited power to detect weak associations between risk factors and WMHV. Additionally, we only measured WMHV in 77% of the individuals with a first ischemic stroke who had evidence of MRI in their medical records. If risk factor status and WMHV both impact the availability of MRIs, our results may not accurately reflect the true association between risk factors and WMHV. Because we used images obtained as part of routine clinical care, there may be differences in field strength across the MRI scanners, which may result in some measurement error for WMHV. However, the scanner type is most likely unrelated to risk factor status, therefore this measurement error would be non-differential. Additionally, we assumed that WMHV in the hemisphere contralateral to the infarction was a valid proxy for WMHV in the hemisphere with the infarct. Although this is a previously validated approach [17, 20, 21], this may result in some measurement error. Finally, the reduced sample size when exploring the association between risk factor status 5 and 10 years prior to the stroke event resulted in limited power for these analyses.

This study offers an important perspective on the complexity of the underlying disease process for WMH development. The lifestyle factors examined here are known to influence overall vascular health [25]. Building on the current results, future large-scale studies are needed to determine the effect of long-term exposure to lifestyle factors and health status on the diffuse microvascular ischemic brain injury that presents as WMHV at the time of stroke. Targeted interventions involving these lifestyle behaviors as vascular risk factors may prove to become a powerful and affordable way to reduce the burden of WMHV and stroke-related disability.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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