Stroke etiology and white matter burden in women with and without migraine

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Stroke etiology and white matter burden in women with and without migraine

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Abstract

Background Women with migraine, especially with aura (MA), have a higher risk of white matter hyperintensities (WMH) and ischemic stroke. We aimed to assess differences in stroke etiology between women with and without migraine and the impact of migraine on WMH volume in women with stroke.

Methods We included women aged 40–60 years with a history of ischemic stroke, migraine or both. Stroke etiology was categorized using the TOAST criteria. WMH volume was measured using 3D-FLAIR images. Presence or absence of cerebellar WMH was scored. We used regression analysis to assess differences between groups, with adjustments for age, BMI, hypertension and smoking status.

Results We included 55 women with stroke, 55 with stroke and migraine, and 38 with MA. Women with stroke more often had a history of smoking than those with stroke and migraine (74% vs. 46%, $p=0.004$). Stroke of undetermined origin was more common in women with both conditions than with stroke alone (49% vs. 27%, $p=0.019$). Periventricular WMH volumes were higher in women with stroke with migraine than in those with MA alone (0.55mL vs. 0.42mL, B = 0.21, 95%CI = 0.01–0.41, $p=0.040$). There were no differences in deep WMH volume and cerebellar WMH between groups. Importantly, the addition of migraine did not affect WMH volume in women who had experienced stroke.

Conclusion Women with both stroke and migraine more often had undetermined etiology of stroke compared to women with stroke alone, and in women with stroke alone smoking was a more prevalent risk factor. Migraine did not contribute to increased WMH volume in women with stroke.

Keywords Headache, Migraine, Cerebrovascular, Stroke, White matter hyperintensities (WMH), MRI, Smoking

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Introduction

Migraine and stroke are highly prevalent diseases that exert significant impact on individuals and healthcare systems alike [1–3]. Migraine, especially migraine with aura (MA), is an established risk factor for stroke. The risk of cerebral infarction is increased more than two-fold in (young) women with MA compared to women without migraine [2, 4]. This relative risk further rises if women with migraine also smoke and use the combined oral contraceptive pill, although the absolute risk remains low for young women [5, 6]. The increased risk of cerebrovascular disease in migraine is not explained by coexistence of traditional cardiovascular risk factors or atherosclerosis [7]. Furthermore, in a recent retrospective observational study of young adults hospitalized for a first-ever ischemic stroke, no differences were found in small vessel disease lesions in stroke patients with migraine compared with stroke patients without migraine when the researchers adjusted for other vascular risk factors [8]. As such, the pathophysiological mechanisms elucidating the connection between migraine and ischemic stroke remain not fully understood. One of the mechanisms that has been implied to play a role in the relationship between migraine and stroke is cortical spreading depolarization (CSD). CSD is thought to be the underlying mechanism of migraine aura symptoms but has also shown to be implicated in stroke [9, 10]. Other potentially involved mechanisms are endothelial dysfunction, altered cerebrovascular reactivity, micro-embolism, thrombophilia, and neuroinflammation [9, 11, 12].

In both migraine and stroke, white matter hyperintensities (WMH) are seen more frequently. WMH are focal lesions without mass effect and can be seen as hyperintense on T2-weighted and fluid-attenuated inversions recovery (FLAIR) MRI sequences. Patients with migraine, especially women and those with MA, have increased WMH volumes and more often posterior circulation lesions compared to healthy controls [13–15]. In addition, women with migraine are at increased risk of developing deep WMH, regardless of migraine type [13]. Notably, these lesions progress over time, independent of attack frequency and migraine activity, suggesting that preventing migraine attacks may not be crucial in halting the progression of WMH [16]. Rather, it is indicative of underlying neurovascular processes that lead to both migraine and WMH, as supported by recent GWAS findings that link migraine-associated variants to vascular and central nervous system tissue and cell types [17]. These neurovascular mechanisms may contribute to the transformation of initially invisible microstructural changes into visible, migraine-related WMHs [18].

The coexistence of migraine and stroke, along with migraine being a risk factor for stroke, prompts inquiries into whether stroke events in patients with migraine have a similar etiology as stroke events in patients without migraine. Moreover, as of now, it is unknown if there is a potential additional effect of migraine on WMH volume in stroke patients. Consequently, our objectives were to determine stroke etiology and other (non)classic risk factors and to compare WMH volumes in middle-aged women with a history of stroke, stroke and migraine, and migraine alone.

Methods

Study participants

Participants were recruited from two cross-sectional studies with similar protocols: the "Cardiovascular Risk Profile in Women – Microvascular Status" (CREW-MIST) study, and the "White Matter Lesions in Young to Middle Aged Women with Stroke, Preeclampsia or Migraine Study" (WHISPER). Both studies were performed at the Leiden University Medical Center (LUMC) between 2016 and 2022. The CREW-MIST study investigated middle-aged women with a history of ischemic stroke with and without a history of migraine, and the WHISPER study included middle-aged women with MA without ischemic stroke. All women aged 40–60 years who presented with ischemic stroke at the in- and outpatient clinic of the Neurology Department at the LUMC were approached for participation. Additionally, participants were recruited via online advertisements through websites of our group and the Dutch Hearth Foundation. Women with MA were recruited from the validated, web-based Leiden University Medical Center Migraine Neuroanalysis program (LUMINA) cohort [19].

Thus, we included three groups of women aged 40–60 years old: (1) with a history of ischemic stroke, (2) with a history of MA, (3) with a history of both ischemic stroke and migraine (migraine without aura (MO) and/or MA). This ensured that our findings are applicable to our target population with minimal impact from age-related risk factors. Additionally, we decided to include migraine with aura patients as a control group instead of both types of migraine patients as WMH volume and stroke risk is known to be higher in migraine with aura patients [15].

Ischemic stroke was defined as acute neurological deficits lasting > 24 h with corresponding lesions seen on CT and/or MRI scan. All stroke patients received standard care and extensive work-up according to local hospital guidelines (including 24 h Holter, young stroke lab and/or transthoracic echocardiogram). Ischemic stroke was divided into five subtypes following the modified Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification: (1) large artery atherosclerosis (LAA), (2) cardiac emboli (CE), (3) small vessel disease (SVD), (4)

other cause, and (5) undetermined [20]. Neuroimaging reports (CT/MRI), clinical findings and additional diagnostic tests were used for localization and classification of stroke. Presence of hypertension and diabetes was not taken into account in classifying events [21]. For all participants, migraine diagnosis was determined by trained researchers through semi-structured interviews, and classified according to the International Classification of Headache Disorder-3 criteria [22]. A specialized headache neurologist (GT) was consulted in case of diagnostic uncertainties. For all groups, women were excluded when they had a retinal, spinal or venous infarction, any other neurological disorder, any serious illness compromising study participation, or any contra-indication for MRI.

Data and MRI acquisition

Medical charts were reviewed and participants filled in a questionnaire on general demographics, medical history, obstetric history, medication use, and vascular risk factors. Hypertension was defined as use of anti-hypertensive medication and/or reported history of hypertension by the patient. Hypercholesterolemia was defined as use of cholesterol lowering drugs and/or reported history of hypercholesterolemia by patient. Smoking was defined as current smoker or ever smoked. Overweight was defined as BMI ≥ 25 kg/m2.

All participants were scanned on a 3T Philips Ingenia MR scanner (Philips Medical Systems, Best, Netherlands) with the standard 32-channel head coil. The scanning protocol included a 3D T1-weighted (repetition time (TR) = 8.2 ms, echo time (TE) = 4.5 ms, ACQ voxel MPS = 1.00 × 1.00 × 1.00), 2D T2-weighted (TR = 4783 ms, TE = 80 ms, ACQ voxel MPS = 0.43 × 0.50 × 3.00) and 3D fluid attenuated inversion recovery (FLAIR) (TR = 4800 ms, TE = 302 ms, inversion time = 1650 ms, matrix size = 224 × 224) scan.

WMH volume assessment

All MRI scans were assessed independently by two trained researchers (AW and NW) blinded to migraine status and other clinical data. A consensus meeting was held for divergent scores with an experienced neuroradiologist (MK) to obtain a final decision. In ischemic stroke patients the presence and volume of WMH was only scored in the unaffected hemisphere, and WMH volumes were multiplied by two for comparison with migraineurs.

WMH were considered to be present if hyperintense on FLAIR, and divided in periventricular, deep and cerebellar WMH. The Fazekas score was used to assess the presence of WMH [23]. The following scoring was used for periventricular WMH: 0) absent, (1) caps or pencil-thin lining, (2) smooth halo, and (3) irregular periventricular signal extending into the deep white matter. The scoring for deep WMH was: 0) absent, (1) punctate foci, (2) beginning confluence, and (3) large confluent areas. Cerebellar lesions were scored as either present or absent.

WMH volume was determined using in-house developed semi-automatic segmentation software in MeVisLab version 3.4.1 (MeVis Medical Solutions AG) [24, 25]. WMH were defined as the voxels on bias-field corrected FLAIR images with an intensity of 2.8 SD greater than the mean, in areas normally containing only white matter [26]. Lesions were labeled as periventricular when starting from the margins of the lateral ventricle and continuing into deep white matter. Lesions were labeled as deep when completely separated from the lateral ventricle.

Statistics

WMH volumes were measured in milliliters. Because several individuals had a periventricular or deep WMH volume of 0 mL, all WMH volumes were increased by the smallest measured volume (e.g. +0.0006 mL for deep; and +0.0228 mL for periventricular WMH volumes) to allow log-transformation. Thereafter, all WMH volumes were log-transformed to obtain plausible normal distribution for further analyses. Frequencies of Fazekas scores and presence of cerebellar lesions are shown as proportions.

Differences in cohort characteristics between the three groups were assessed using Chi-square test for proportions and one-way ANOVA for continuous outcomes. Multivariate linear regression was used to analyze differences in WMH volumes across the groups. Fazekas scores were modelled with ordinal logistic regression analyses and logistic regression analysis was performed to analyze differences in presence of cerebellar WMH between groups. In all regression analyses, we adjusted for age, BMI, hypertension and (ever) smoking. All statistical analysis were performed in SPSS Statistics (IBM Corp, version 25).

Results

A total of 148 middle-aged women were included with stroke ($n = 55$), migraine and stroke ($n = 55$), and MA ($n = 38$). Age at study visit, age at stroke and BMI were similarly distributed in all groups. Table 1 shows an overview of the cohort characteristics.

Risk factors and stroke etiology

Women with ischemic stroke (with and without migraine) more frequently reported hypertension and hypercholesterolemia than those in the MA group (Fig. 1). Women with stroke more often had a history of smoking compared to those with stroke and migraine and to those with MA (74% vs. 46% and 41% respectively, $p = 0.004$ and $p = 0.004$) (Fig. 1). No differences

Table 1 Cohort characteristics

	Stroke $N=55$	Stroke + migraine $N=55$	Migraine $N=38$	*P*-value
Age at visit, mean ± SD	50.6 ± 5.1	51.3 ± 5.2	51.3 ± 4.9	0.72
Age at stroke, mean ± SD	46.5 ± 6.0	45.2 ± 6.5	–	0.27
Time between stroke and visit, median (IQR)	3.6 (1.7–5.4)	4.4 (2.0–7.4)	–	0.12
Migraine diagnosis, n (%)				
Migraine with aura	–	28 (51)	38 (100)	
Migraine without aura		27 (49)	0 (0)	
BMI, mean ± SD [a]	27.2 ± 4.6	26.7 ± 4.5	25.3 ± 4.2	0.21
Diabetes, n (%) [b]	1 (2)	2 (4)	1 (3)	0.96
Post-menopausal, n (%) [c]	23 (43)	25 (46)	19 (50)	0.78
Age menopause, mean ± SD[d]	48.0 ± 5.8	48.3 ± 6.9	45.7 ± 7.4	0.44
Stroke before menopause, n (%)[e]	7 (14)	10 (18)	–	0.50
Oral contraceptive use, n (%)				
Ever[f]	48 (92)	53 (98)	35 (95)	0.33
Current	1 (2)	1 (2)	5 (13)	0.018

Abbreviations: *BMI* body mass index, *IQR* interquartile range, *SD* standard deviation

[a] Missing values: stroke $n=6$, stroke + migraine $n=7$, migraine $n=9$

[b] Missing values: stroke $n=2$, stroke + migraine $n=1$, migraine $n=1$

[c] Missing values: stroke $n=1$

[d] Missing values: stroke $n=2$, stroke + migraine $n=1$, migraine $n=2$

[e] Missing values: stroke $n=3$, stroke + migraine $n=1$

[f] Missing values: stroke $n=2$, stroke + migraine $n=1$, migraine $n=2$

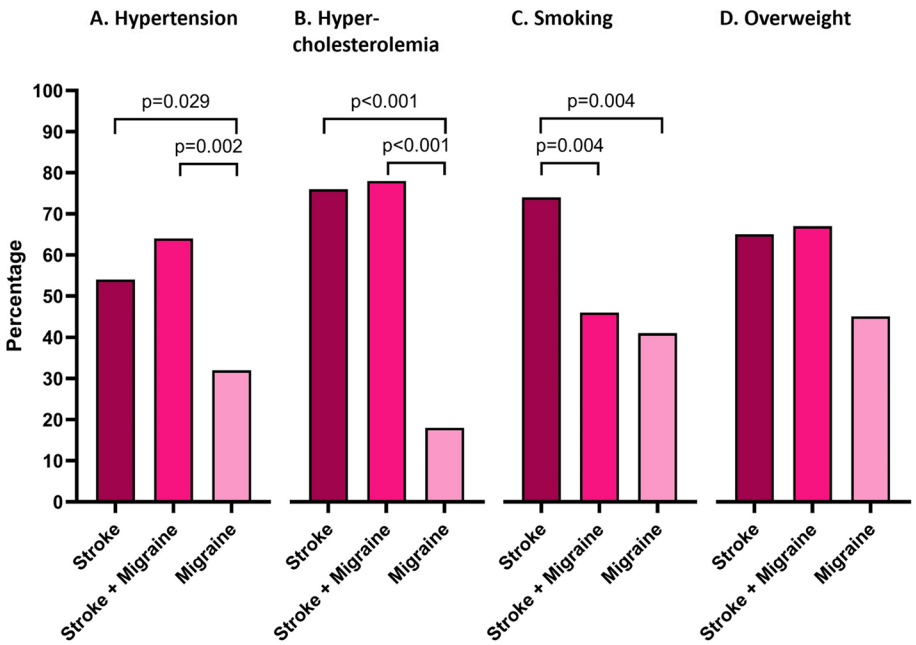

Fig. 1 Differences in cardiovascular risk factors (hypertension (**A**), hypercholesterolemia (**B**), ever smoking (**C**), and overweight (**D**)) between women with a history of stroke, stroke and migraine, and migraine with aura. Only significant *p*-values are depicted

in overweight (BMI ≥ 25 kg/m^2) were found between groups (Fig. 1). Furthermore, women with both stroke and migraine more often had a stroke of undetermined origin according to the TOAST classification (49% vs. 27%, $p=0.019$) compared to those without migraine (Fig. 2).

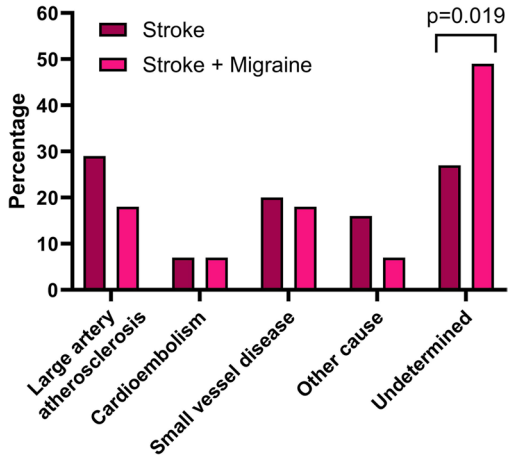

Fig. 2 TOAST classification of women with a stroke with and without migraine. Women with stroke and migraine more often had a stroke of undetermined origin ($p=0.019$). Only significant *p*-values are depicted. Abbreviations: TOAST classification = Trial of Org 10172 in acute stroke treatment classification

WMH volumes

Median (IQR) total WMH volumes were 0.64 (0.29–1.29) mL in women with stroke; 0.63 (0.36–1.33) mL in women with stroke and migraine, and 0.46 (0.25–0.73) mL in women with MA (Fig. 3). No significant differences in total WMH volumes were found between groups (Table 2).

Median (IQR) periventricular WMH volumes were 0.49 (0.27–0.95) mL in women with stroke, 0.55 (0.34–1.03) mL in women with stroke and migraine and 0.42 (0.22–0.57) mL in women with MA alone (Fig. 3). Women with stroke and migraine had higher periventricular WMH volumes than women with MA (B = 0.21, 95%CI = 0.01–0.41, $p=0.040$). No significant difference was found for women with stroke only compared to women with stroke and migraine or with migraine only (Table 2).

Median (IQR) deep WMH volumes were 0.08 (0.01–0.30) mL in women with stroke, 0.07 (0.02–0.35) mL in women with stroke and migraine, and 0.03 (0.01–0.15) mL in women with MA (Fig. 3). No differences in deep WMH volumes were found between groups (Table 2).

Fazekas scale and cerebellar WMH

The Fazekas scores of both periventricular and deep WMH did not differ significantly between groups (Supplementary Material, Table S1 and S2). The majority of patients in all groups had a Fazekas score of 1 for both periventricular WMH and deep WMH. Cerebellar lesions were present in 18% of patients with a history of stroke, in 21% of patients with a history of both stroke and migraine, and in 11% of patients with MA. There were no significant differences in the proportion of patients with cerebellar lesions between groups (Supplementary Material, Table S2).

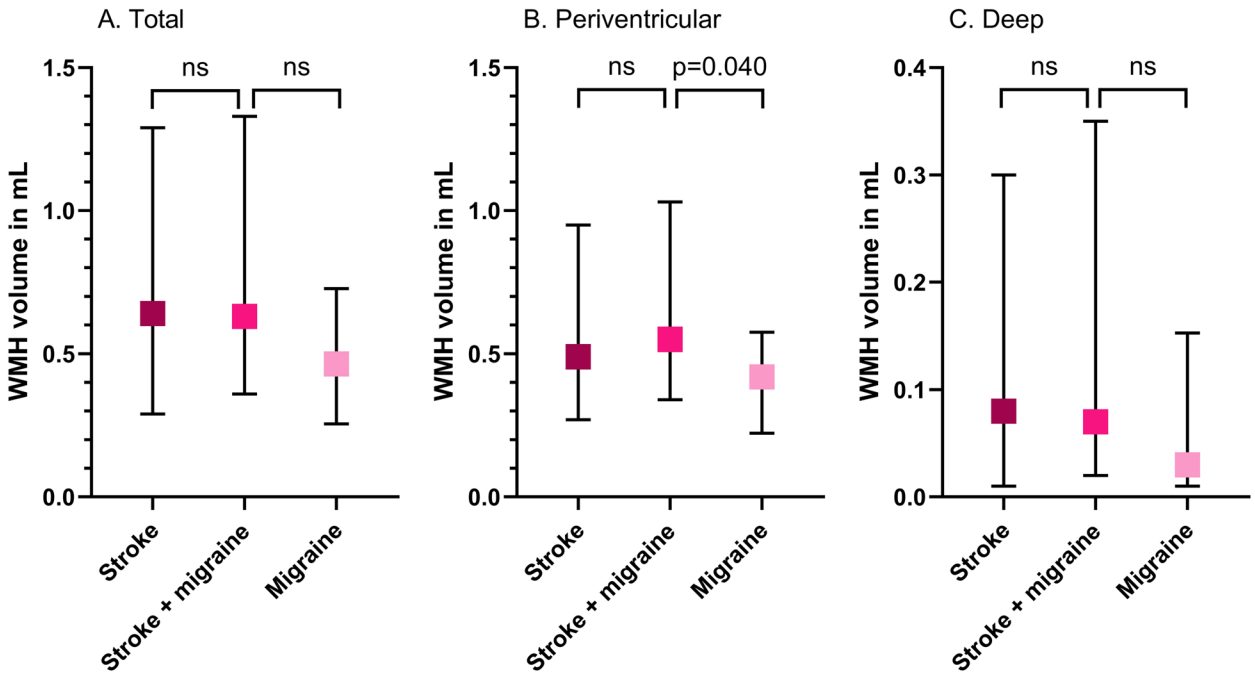

Fig. 3 Median white matter hyperintensities (WMH) volumes (IQR) of women with a history stroke, stroke and migraine, and migraine with aura. *P*-values are derived from linear regression analyses of log-transformed volumes and are corrected for age, BMI, hypertension and smoking status

Table 2 Linear regression analyses of transformed WMH volumes

	B	95% CI	*P*-value
Total WMH volume			
Stroke vs. Stroke + migraine	0.01	-0.21 – 0.22	0.95
MA vs. Stroke + migraine	-0.21	-0.46 – 0.03	0.087
MA vs. Stroke	-0.22	-0.47 – 0.03	0.086
Periventricular WMH volume			
Stroke vs. Stroke + migraine	-0.03	-0.20 – 0.15	0.76
MA vs. Stroke + migraine	-0.21	-0.41 – -0.01	**0.040**
MA vs. Stroke	-0.19	-0.39 – 0.02	0.081
Deep WMH volume			
Stroke vs. Stroke + migraine	0.10	-0.29 – 0.48	0.63
MA vs. Stroke + migraine	-0.06	-0.51 – 0.38	0.78
MA vs. Stroke	-0.16	-0.62 – 0.30	0.49

Abbreviations: *B* unstandardized coefficient, *95% CI* 95% Confidence Interval for B, *MA* migraine with aura, *WMH* white matter hyperintensities

All analyses are corrected for age, BMI, hypertension and smoking status

Discussion

Women with a history of stroke with and without migraine had different stroke etiologies according to the TOAST classification. Of the women with stroke without migraine, around one quarter had a stroke of undetermined origin, whereas in the women with stroke and migraine, half had a stroke of undetermined origin. This suggests that women with migraine have a different stroke etiology than those without migraine. Our finding that women with stroke but no history of migraine were more frequently smokers than those with a history of migraine further supports the probability of a different underlying pathophysiological mechanism between women with stroke with and without migraine. Next, we found no increase in WMH volume due to migraine in women with stroke. Periventricular WMH volumes were higher in women with stroke and migraine than in those with MA alone.

The precise mechanisms linking migraine and ischemic stroke are unclear. In this study, we demonstrate that the etiology leading to stroke in patients with and without migraine may differ. The absence of a causal factor for stroke is more common in patients with both migraine and stroke than in those with stroke alone, as supported by two prior studies [27, 28]. It is possible that these migraine patients experience strokes without requiring the involvement of other classic pathophysiological mechanisms, such as atherosclerosis or a cardio embolism. This is supported by earlier findings indicating that the increased risk of cerebrovascular disease (CVD) in migraine patients seems not to be due to (large artery) atherosclerosis caused by traditional cardiovascular risk factors [7, 29]. Our finding that women with stroke but no history of migraine were more frequently smokers than those with a history of migraine, further reinforces this hypothesis. Previous work also demonstrated that among patients with stroke and migraine fewer smoked compared to patients with stroke and no migraine (25.9% vs. 38.3%).[30] This is in line with a study on substance use in migraine patients, showing that patients with migraine are less likely to smoke, drink alcohol or use illicit drugs [31]. This of course does not prove that conventional risk factors do not play a role. In our study, women with stroke more often had a history of hypertension and hypercholesterolemia, than women with migraine alone, but there were no differences between women with stroke with and without migraine. Previous studies have found conflicting results on whether migraine increases the risk of hypertension, therefore the role it plays in the migraine stroke relationship remains controversial [32]. In general, there seems to be no clear dyslipidemia profile in patients with migraine [33, 34]. Still, sex-specific associations are indicative towards a less CVD-protective lipoprotein profile in women with migraine [33].

Several mechanisms have been implied to play a role in the relationship between migraine and stroke, such as CSD, endothelial dysfunction, altered cerebrovascular reactivity and neuroinflammation [9, 11]. Animal studies suggest that micro-emboli can trigger CSDs, potentially linking right-to-left cardiac shunting, often due to a patent foramen ovale (PFO), to migraine aura and stroke [35, 36]. CSD also affects ischemic stroke development, with peri-infarct depolarizations causing expansion of the infarct core. Transgenic hemiplegic migraine mouse models with experimentally induced stroke had larger infarcts due to a higher propensity for peri-infarct depolarizations [37]. While migraine preventive treatment protected mice from ischemic injury, clinical studies have shown inconsistent results [38]. In a large population based study the increase in WMH in migraine subjects was independent on whether subjects had active or non-active migraine and frequency of attacks [16].

Endothelial dysfunction is another suggested shared mechanism between migraine and stroke, involving reduced cerebrovascular reactivity and markers for endothelium activation, hypercoagulability, and inflammation [39]. Enhanced platelet aggregation in migraine patients suggests a potential link controlled by the endothelium [40]. Reduced vascular reactivity might partly explain the connection between migraine and stroke, as evidenced by increased arterial stiffness and impaired cerebral vasodilator function [41].

Even though the absolute risk for developing stroke remains low for (young) women with migraine, there

are implications for clinical practice [2]. The use of oral contraceptives increases the relative risk for stroke, especially in patients with MA [2]. This relative risk is further increased to a 35 times in women with MA who use oral contraceptives and also smoke [6]. Therefore, combined hormonal contraceptives are not recommended in women with MA and migraine patients who smoke. In the past, there have been worries that acute medications to treat migraine attacks, such as triptans, might increase the risk of stroke, because of their vasoconstrictive properties. A novel study found a short-term increased risk in myocardial infarction and ischemic stroke after triptan initiation, although the absolute risk remained very low in these patients [42]. However, previous clinical studies have shown that triptan use is not associated with an increase in cardiovascular events and, based on expert opinion, triptan use is considered safe in many countries [43]. Recently, selective $5HT_{1F}$ receptor agonists (ditans) have been developed that do not cause vasoconstriction, as such they may be even better suited for stroke patients [44]. There are some safety concerns related to the use of calcitonin gene related peptide (CGRP) monoclonal antibodies and small molecule CGRP antagonists in migraine patients with stroke, because of the blockage of vasodilation as an escape response [45]. There is one case report of a 41-year old woman with MO who developed a stroke after the first dose of a CGRP receptor blocker [46]. Furthermore, real world data studies showed an increase in mean blood pressure in patients treated with anti-CGRP (receptor) antibodies (compared to control migraine patients), with some patients requiring antihypertensive treatment [47, 48]. Therefore, use of anti-CGRP (receptor) antibodies is not recommended in stroke patients until the long-term safety has been established.

Our study comes with some limitations. Firstly, the sample size of all groups is relatively small and the overall WMH volumes were low, as such, subtle differences in WMH volume between patients with and without migraine and stroke might have been missed. Furthermore, as we performed a clinic based study, our results might possibly not be generalizable to all populations. This, however, led to rich medical data and a clearly defined homogeneous population. Next, based on available data, we used the TOAST classification to divide stroke in subgroups, however newer classification systems have been proposed that might be more specific [49]. We were also unable to look into differences between migraine types (MA and MO) and migraine severity. While we aimed to determine if migraine itself let to an increased WMH volume in stroke patients, as both migraine with aura and migraine without aura are at risk of sub-clinical brain lesions, future efforts should focus on whether migraine with aura might lead to a subtle increase in WMH volume that we might have missed by also including stroke patients with migraine without aura. The group of women with a history of migraine and stroke consisted of both MA and MO patients, whereas the migraine only group consisted solely of patients with MA (although it should be noted that most MA patients also experience MO attacks). As previously mentioned, MA patients without stroke were included as effect size was expected to be larger in this group compared to MO. If a difference was found in WMH volume, this would then logically also be expected to exist between stroke patients with migraine and MO patients. Lastly, the interval between stroke and the study visit was not standardized, resulting in considerable variability. Nonetheless, there was no significant difference in median time between stroke and study visit between the two stroke groups.

Strengths of our study are the use of semi-automated software on high-quality 3T MRI scans for the assessment of WMH, leading to precise estimates of volumes (Fig. 4). Moreover, we used a validated and well-defined national cohort of migraine patients, and next to

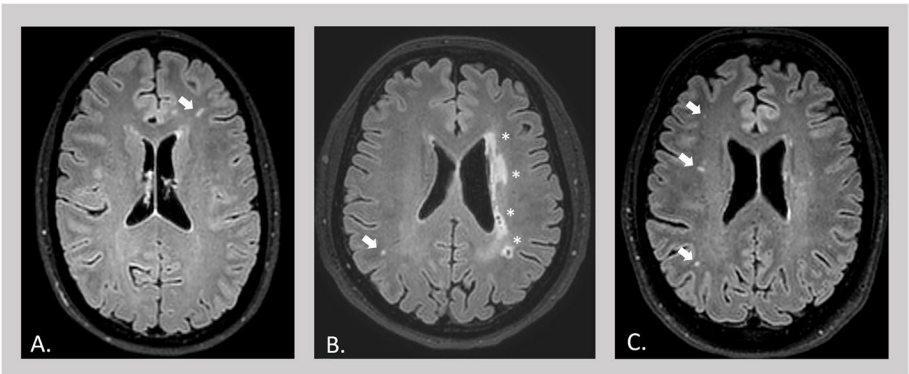

Fig. 4 Example of white matter hyperintensities (WMH) on 3D fluid-attenuated inversion recovery (FLAIR) images of three women: **A** a woman with migraine with aura, the arrow marks a deep WMH; **B** a woman with a history of stroke, the arrow marks a deep WMH, the asterisks mark the area affected by the stroke; **C** a woman with a history of migraine and stroke (stroke lesions not depicted on image)

including stroke patients from the LUMC, we included women from all over the Netherlands through online advertisement, increasing the generalizability of the study population [19]. Furthermore, the migraine diagnosis was assessed and validated by a headache specialist (GT), and the stroke diagnosis by a stroke specialist (MW). Lastly, to our knowledge, this is the first study to extensively study the presence and amount of WMH in women with stroke with and without a history of migraine.

Conclusions

To conclude, our study reveals contrasting stroke etiology between women with and without a history of migraine, highlighting smoking as a more prevalent risk factor in those with ischemic stroke but no prior migraine history. Importantly, we found no additional impact of migraine on WMH volume in middle-aged women with stroke, a positive outcome. We recommend that physicians routinely inquire about migraine history, particularly in non-smoking women presenting with ischemic stroke. This practice can help identify potential differences in stroke etiology in women and guide the development of personalized treatment strategies.

Abbreviations

BMI	Body mass index
CE	Cardiac emboli
CGRP	Calcitonin gene related peptide
CSD	Cortical spreading depolarization
CVD	Cerebrovascular disease
IQR	Interquartile range
LAA	Large artery atherosclerosis
MA	Migraine with aura
MO	Migraine without aura
PFO	Patent foramen ovale
SD	Standard deviation
SVD	Small vessel disease
TOAST classification	Trial of Org 10172 in Acute Stroke Treatment classification
WMH	White matter hyperintensities

Supplementary Information

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Supplementary Material 1. Tables S1-S2.

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Authors' contributions

KL, HO, AMB, MW and GT conceived and designed the study. MK, IB, AMB, MW, and GT advised on the interpretation of data. NW, KL, GH, and HO contributed substantially to collecting the data for the study. NW, AW, and MK performed scoring of microvascular damage on MRI. AW did the principal data analysis and writing of the manuscript. All authors contributed to revising the article, and all authors approved the final version as submitted.

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Data availability

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The Medical Ethics Committee Leiden - Den Haag - Delft (METC-LDD) approved the CREW-MIST (P15.384) and WHISPER (P18.130) study protocols and all participants provided written informed consent prior to study participation.

Competing interests

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