Prevalence and clinical characteristics of white matter hyperintensities in Migraine: A meta-analysis

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ARTICLE INFO

ABSTRACT

Background: Current evidences show an increased risk of white matter hyperintensities (WMHs) in migraineurs compared to age-matched controls. However, WMHs prevalence and the associations between WMHs and clinical characteristics in migraineurs have not been systematically evaluated using a *meta*-analytical approach. This study explored the pooled prevalence of WMHs and the associations of WMHs with the clinical characteristics in patients with migraine.
Methods: A systematic review and *meta*-analysis of observational studies reporting the occurrence and clinical characteristics of patients with WMHs attributed to migraine was performed. We searched the PubMed, Web of Science, and Embase databases. Random-effects models were used to calculate the pooled prevalence rate, odds ratio (OR), or mean difference (MD) with corresponding 95% confidence intervals (CIs).
Results: Thirty eligible studies were identified including 3,502 migraineurs aged 37.2 (mean) years. The pooled WMHs prevalence was 44 %, 45 %, and 38 % in migraine, migraine with aura, and migraine without aura groups, respectively. In migraineurs with WMHs, the frontal lobe and subcortical white matter were the most susceptible area. Compared with non-migraine controls, patients with migraine had increased odds for WMHs (OR 4.32, 95 % CI = 2.56–7.28, I^2 = 67 %). According to reported univariable results from included studies, pooled analysis showed that clinical characteristics including age, presence of aura, disease duration, hypertension, diabetes mellitus and right-to-left shunt were associated with the presence of WMHs. Migraine pain and aura characteristics were not related to WMHs.
Conclusions: These data suggest that WMHs are common in migraine, especially in those who are older or have aura, hypertension, diabetes mellitus, or right-to-left shunt. A better understanding of the WMHs attributed to migraine is needed in future studies.

1. Introduction

Migraine affects approximately 14 % of the global population and is the second leading cause of disability (Ashina et al., 2021; Stovner et al., 2022). Young people, especially females, have the highest prevalence of migraine, and their work productivity, career potential, and daily life are greatly impaired (Ashina et al., 2021). In addition to its immediate impact, patients with migraine have a 1.62-fold risk of stroke and a 1.26-fold risk of dementia compared to controls without migraine (Qu et al., 2022; Zhang et al., 2022).

White matter hyperintensities (WMHs) of presumed vascular origin are subclinical brain injuries that represent damage to brain's small vessels, including arterioles, capillaries, and venules (Wardlaw et al., 2019). WMHs are typically seen as hyperintense brain lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. Age-related and vascular risk-factor-related small vessel disease and cerebral amyloid angiopathy are main etiologies for WMHs (Pantoni, 2010). Blood–brain barrier damage, reduced cerebral blood flow, and neuroinflammation are the main pathogenesis of WMHs (Pantoni, 2010; Wardlaw et al., 2019). Owing to the increased blood–brain barrier permeability caused by normal ageing and high prevalence rate of hypertension and cerebral amyloid angiopathy in old people (Farrall and

Wardlaw, 2009), WMHs are common in the elderly, with a reported prevalence of 72.0 % in subjects over 50 years old (Zhuang et al., 2018). Interestingly, a *meta*-analysis showed that the prevalence of WMHs in migraineurs was higher than that in the age-matched controls (Bashir et al., 2013). Migraine is a neurovascular disease involving vascular and central nervous system (Hautakangas et al., 2022). Neurovascular mechanisms may lead to increased risk of WMHs in migraine.

The reported prevalence of WMHs in migraine varies widely across studies, ranging from 9.9 % to 78.4 % (Honningsvåg et al., 2016; Sacmaci et al., 2019). The correlations between WMHs and demographics or migraine characteristics (e.g., migraine subtypes and attack frequency) are also inconsistent across studies. The aim of this systematic review and *meta*-analysis was to explore the pooled prevalence of WMH and the associations of WMHs with the clinical characteristics in patients with migraine.

2. Methods

This systematic review was performed in accordance with a predefined protocol (PROSPERO registration number: CRD42022330025), following the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) (Supplementary Table 1) (Page et al., 2021). Ethical approval was not required because no individual-level data were utilized.

2.1. Search strategy

We systematically searched the PubMed, Web of Science, and Embase from inception to April 2022. The detailed search strategy was as follows: ("white matter hyperintensit*" OR "white matter lesion*" OR "white matter change*" OR "white matter disease*" OR "white matter damage*" OR "leukoaraiosis" OR "leukoencephalopath*" OR "Binswanger's disease") AND ("migraine" OR "headache" OR "cephalalgia"). The references of eligible articles and relevant reviews were also manually searched for comprehensive screening.

2.2. Study selection

We included studies that reported the prevalence of WMHs or focused on the associations between the clinical characteristics and the presence of WMHs in migraine patients in this *meta*-analysis. The diagnosis of migraine should be made by neurologists according to the International Classification of Headache Disorders (ICHD). Patients with major central nervous system diseases, such as demyelinating disorders, stroke, and neoplasm, are usually excluded (Al-Hashel et al., 2022; Ersoy et al., 2020; Iyigundogdu et al., 2018). WMHs were identified by hyperintense focal lesions in the white matter on the FLAIR sequence (Fig. 1). Investigators evaluating WMHs were blinded to the clinical data

Table 1
Meta-regression analysis of heterogeneity introduced by study characteristics.

Variables	Coefficient	SE	t	P>/t/	95 % CI
Geographical region (Non-East Asia vs East Asia)	−0. 394	0.303	−1.30	0.19	−0.988–0.201
Diagnostic criteria (ICHD-3 vs ICHD-2)	0.129	0.238	0.54	0.59	−0.337–0.595
Sample size	−0.001	0.002	−0.60	0.55	−0.005–0.003
Mean age	−0.049	0.021	−2.38	0.02	−0.089 -0.009
Female ratio	1.252	1.454	0.86	0.39	−1.598–4.102
MRI field strength (3T vs Non-3T)	0.010	0.261	0.04	0.97	−0.501–0.521
Quality score	−0.020	0.112	−0.18	0.86	−0.239–0.199

CI, confidence interval; ICHD, International Classification of Headache Disorders; MRI, magnetic resonance imaging; SE, standard error.

of the participants. The following studies were excluded: (1) studies on patients with migraine attack secondary to other diseases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), posterior reversible encephalopathy syndrome (PRES) and mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS); (2) studies on migraineurs aged <18 years; (3) studies with a sample size of migraineurs <50; (4) <1.5 Tesla or unknown magnetic resonance imaging (MRI) field strength; (5) studies without reported prevalence of WMHs (e.g., WMHs were analyzed as a continuous variable); (6) meeting abstracts; (7) studies not written in English. If overlapping data were found in different studies, only the study with the largest sample size was included.

Our predefined primary outcome measures were twofold: (i) the pooled prevalence rate of WMHs in migraine; and (ii) the potential differences in demographics and clinical features of migraine between groups of patients stratified by the presence of WMHs. The secondary outcomes of interest were: (i) the WMHs prevalence in migraineurs compared to non-migraine controls, and (ii) the distribution of the anatomical location of WMHs in migraine patients. A prearranged procedure for the selection of eligible literature was independently performed by two investigators (WZ and ZC). First, the researchers screened potential studies by reviewing their titles and abstracts. Second, they checked the full texts for eligibility according to the inclusion and exclusion criteria. References of eligible studies were manually searched to identify additional studies. Discrepancies between investigators were addressed by a third investigator (FF), who joined the discussion.

2.3. Data extraction

A prespecified template was used by two independent reviewers (WZ and ZC) to extract information on study characteristics (first author, publication year, country, sample size), demographics (mean age, sex), WMHs assessment (number of patients with WMHs, MRI field strength and slice thickness), and clinical features (aura, onset age, disease duration, chronic migraine, migraine attack frequency, migraine attack duration, painful days, aura frequency, aura duration, pain severity, degree of disability, family history of migraine, vascular risk factors [hypertension, diabetes mellitus, hyperlipidemia, smoking, body mass index, right-to-left shunt]). Among the included relevant studies, pain severity was recorded using the Visual Analog Scale (VAS) (Wewers and Lowe, 1990), and the degree of disability was recorded using the Migraine Disability Assessment Scale (MIDAS) (Stewart et al., 1999). When the data were not in the correct format for analysis (i.e., medians instead of means), we transformed the median into the mean using the Box-Cox method (McGrath et al., 2020). Relevant missing data were requested by emailing the corresponding authors wherever possible.

2.4. Quality assessment

The risk of bias in the study design was evaluated by two independent reviewers (WZ and ZC) using the Joanna Briggs Institute's (JBI) Critical Appraisal Checklist, a useful tool for descriptive studies including prevalence study and analytic cross-sectional studies (Munn et al., 2015). The checklist consists of 9 items with a total quality score rangeing from 0 to 9 points. A score equal to or exceeding 7 points indicates a high-quality study. Discrepancies were resolved by a third reviewer (FF).

2.5. Statistical analysis

The prevalence of WMHs in migraineurs was calculated by dividing the number of migraineurs with WMHs by the total number of patients with migraine. After implementing the logit transformation, a random effects model of *meta*-analysis (DerSimonian Laird method) was used to calculate the pooled estimates (Dersimonian and Laird, 1986).
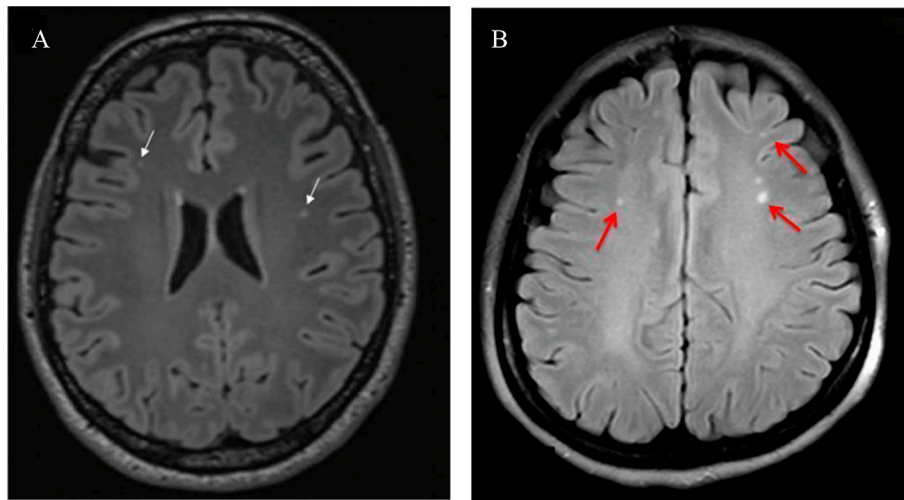
Fig. 1. White matter hyperintensities (arrows) in axial FLAIR MRI sequence.

Heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 metric; $I^2 > 50$ % was considered statistically significant heterogeneity (Higgins et al., 2003). The source of heterogeneity was explored via *meta*-regression and subgroup analyses according to multiple variables, including geographical region, study design, diagnostic criteria, sample size, mean age, female ratio, MRI field strength and quality score. Publication bias was assessed using funnel plot and Egger's test (Egger et al., 1997). The distribution of WMHs location was calculated by dividing the number of migraineurs with WMHs in different cerebral lobes or white matter areas by the total number of migraineurs with WMHs. The random effects model was used to calculate the pooled estimates after the implementation of logit transformation. Data from studies reporting WMHs prevalence in migraineurs and non-migraine controls were used to calculate a crude odds ratio (OR) using 2 × 2 tables for each study and combined using the random effects model to generate the pooled estimates.

To determine the clinical characteristics associated with the presence of WMHs, we used a random effects model to calculate the pooled mean difference (MD) and OR for continuous and categorical variables, respectively. Between groups of patients divided according to the presence of WMHs, the MD for each continuous variable was calculated using the sample sizes, means, and standard deviations, and the OR for each categorical variable was calculated using event sizes and sample sizes. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$. Statistical analyses were performed using the R version 4.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Literature search

Fig. 2 shows the study screening and selection process. The systematic database search yielded 1324, 1339, and 1788 records from the PubMed, Web of Science, and Embase, respectively. After excluding duplicates and reviewing the titles and abstracts, 146 articles were considered potential studies on WMHs in patients with migraine. After reviewing the full texts and conducting a manual search, 30 studies were included in the *meta*-analysis on the prevalence of WMHs in migraine, and 23 studies were included in the *meta*-analysis on the association of clinical characteristics with the presence of WMHs. In addition, 10 studies were included to compare the risk of WMH between migraine and control groups.

3.2. Study characteristics

The characteristics of the included studies are summarized in Supplementary Table 2. Most studies were conducted in Europe and America, Turkey was the country with the most studies (n = 8), and six studies were conducted in East Asia. Twenty-nine studies were cross-sectional design and only one study was cohort study in which WMHs were assessed at baseline (Xie et al., 2018). In terms of time of data acquisition, studies can be divided into prospective (n = 22) and retrospective (n = 5) design. Overall, the 30 studies included a total of 3,502 migraineurs (median sample size n = 91.5; minimum n = 50; maximum n = 334) with a mean age of 37.2 years. Apart from three studies that did not report migraine subtypes distribution in participants, there were 1172 individuals with aura and 2129 without aura. The average age in the included studies ranged from 28.4 to 57.7 years, while the proportion of females ranged from 66.7 % to 100.0 %. WMHs were assessed by 3.0 T MRI in 11 studies and 1.5 T MRI in 19 studies. According to the quality assessment, the overall mean score on the JBI checklist was six (range = 4–9, standard deviation = 1.12). Approximately half of the studies (16/30) were of high quality (Supplementary Table 3).

3.3. WMH prevalence rate

The prevalence of WMHs ranged from 9.9 % to 78.4 % in the 30 studies (median = 42.5 %). The random effects model showed a pooled prevalence rate of 44 % (95 % confidence interval [CI] = 38 %–50 %, I^2 = 92 %, 30 studies) with heterogeneity across studies (Fig. 3). When the analysis was restricted to the studies that excluded patients with vascular risk factors, especially hypertension, the pooled prevalence rate was 47.0 % (95 % CI = 40.0 %–55.0 %, I^2 = 86 %, 17 studies). The *meta*-regression model suggested that age was significantly associated with the prevalence (P = 0.02). There was no significant effect of geographical region, study design, diagnostic criteria, sample size, sex, MRI field strength, or quality score on the prevalence of WMHs (Table 1). Subgroup analyses also revealed that the prevalence did not differ significantly between the groups stratified by the aforementioned variables (Fig. 4). Publication bias was not observed in the funnel plot (Fig. 5) or Egger's test (P = 0.92). The distribution of WMHs locations by cerebral lobes is as follows: most frequently in the frontal lobes (92.0 %, 95 % CI = 87.0 %–95.0 %, I^2 = 0 %, 5 studies), less commonly in the parietal lobes (31.0 %, 95 % CI = 25.0 %–39.0 %, I^2 = 4 %, 5 studies) followed by the temporal lobes (10.0 %, 95 % CI = 6.0 %–16.0 %, I^2 = 0 %, 5 studies) and occipital lobes (4.0 %, 95 % CI = 1.0 %–13.0 %, I^2 = 46 %, 5 studies). WMHs mostly located in subcortical area (93.0 %, 95 %
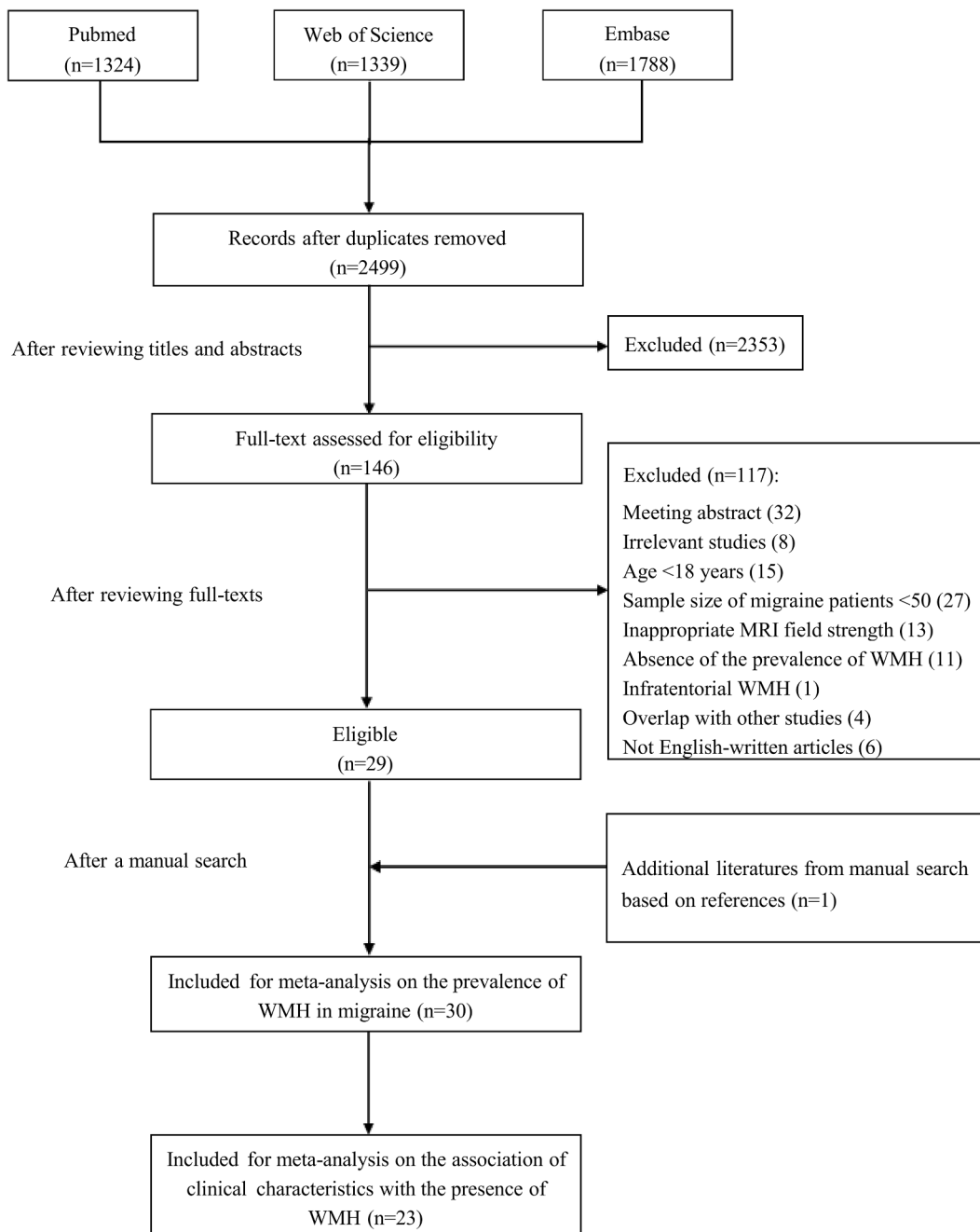
Fig. 2. Flowchart presenting the selection of eligible articles.

CI = 89.0 %–96.0 %, I^2 = 30 %, 5 studies), uncommon in juxtacortical (21.0 %, 95 % CI = 9.0 %–44.0 %, I^2 = 89 %, 5 studies), periventricular (12.0 %, 95 % CI = 7.0 %–20.0 %, I^2 = 45 %, 5 studies), and infra-tentorial (3.0 %, 95 % CI = 0.0 %–17.0 %, I^2 = 0 %, 6 studies) areas.

The prevalence of WMHs in migraine with aura ranged from 25 % to 83.3 % (median = 44.4 %), and the prevalence of WMHs in migraine without aura ranged from 18.8 % to 78.4 % (median = 37.2 %). The pooled prevalence rates of WMHs in migraine with and without aura were 45 % (95 % CI = 38 %–52 %, I^2 = 77 %, 19 studies; Supplementary Fig. 1) and 38 % (95 % CI = 32 %–44 %, I^2 = 83 %, 20 studies; Supplementary Fig. 2), respectively. Migraine status was associated with an increased WMHs prevalence rate when migraineurs were compared with controls (OR 4.32, 95 % CI = 2.56–7.28, I^2 = 67 %, 10 studies; Fig. 6), both in those with (OR 6.04, 95 % CI = 2.81–13.01, I^2 = 69 %, 6 studies; Supplementary Fig. 3) and without aura (OR 4.03, 95 % CI = 2.67–6.07,

I^2 = 23 %, 6 studies; Supplementary Fig. 4).

3.4. Association of clinical characteristics with WMH

Table 2 shows the associations between clinical characteristics and WMHs in patients with migraine. The migraineurs with WMHs were older (MD 6.28, 95 % CI = 4.57–7.98, I^2 = 64 %, 13 studies). No onset age and sex distribution differences were identified between migraineurs with and without WMHs.

Regarding pain characteristics, the aura was associated with a higher risk of WMHs (OR 1.43, 95 % CI = 1.03–1.98, I^2 = 64 %, 18 studies). Disease duration was another factor related to WMHs; migraineurs with WMHs were reported to have longer disease duration than those without WMHs (MD 3.90, 95 % CI = 2.41–5.40, I^2 = 64 %, 13 studies). Compared to episodic migraine, the risk of WMHs did not increase in

Table 2

Overview of analyses on the associations of clinical characteristics and WMHs in migraine patients.

Variables	No. of studies	Pooled estimates (95 % CI)	I^2	p for Cochran Q
Demographics				
Age (years)	13	MD = 6.28 (4.57–7.98)	64 %	<0.01
Onset age (years)	3	MD = − 0.18 (−2.99–2.64)	69 %	0.04
Female sex	12	OR = 0.98 (0.70–1.37)	27 %	0.18
Pain characteristics				
Aura	18	OR = 1.43 (1.03–1.98)	64 %	<0.01
Disease duration (years)	13	MD = 3.90 (2.41–5.40)	64 %	<0.01
Chronic migraine	4	OR = 1.69 (0.74–3.82)	54 %	0.09
Attack frequency (/month)	10	MD = 0.04 (−0.58–0.65)	84 %	<0.01
Attack duration (hours)	6	MD = 5.81 (−5.11–16.73)	89 %	<0.01
Painful days (/month)	2	MD = 1.05 (−0.20–2.31)	0 %	0.94
Aura frequency (/month)	1	MD = 0.20 (−1.89–2.29)	NA	NA
Aura duration (minutes)	1	MD = − 11.30 (−25.99–3.39)	NA	NA
Pain severity	7	MD = 0.26 (−0.19–0.71)	76 %	<0.01
Degree of disability	4	MD = 9.57 (−1.67–20.81)	96 %	<0.01
Family history of migraine	6	OR = 0.81 (0.52–1.25)	0 %	0.71
Vascular risk factors				
Hypertension	4	OR = 2.95 (1.23–7.11)	31 %	0.23
Diabetes mellitus	4	OR = 3.39 (1.34–8.57)	0 %	0.91
Hyperlipidemia	4	OR = 1.72 (0.80–3.71)	37 %	0.19
Smoking	7	OR = 0.89 (0.57–1.40)	0 %	1.00
Body mass index	4	MD = 0.77 (−0.15–1.70)	41 %	0.17
Oral contraceptive use	3	OR = 1.35 (0.50–3.62)	0 %	0.71
Right-to-left shunt	4	OR = 1.74 (1.03–2.93)	56 %	0.08

CI, confidence interval; MD, mean difference; NA, not applicable; OR, odds ratio; WMHs, white matter hyperintensities.

patients with chronic migraine. We did not find any associations between WMHs and most migraine-related characteristics, including migraine attack frequency and duration, painful days, aura frequency and duration, pain severity, degree of disability, or family history of migraine.

Vascular risk factors are well known to be associated with WMHs in the general population. Therefore, these factors were considered. Our *meta*-analysis reported a 3-fold higher prevalence of hypertension (OR 2.95, 95 % CI = 1.23–7.11, I^2 = 31 %, 4 studies) and diabetes mellitus (OR 3.39, 95 % CI = 1.34–8.57, I^2 = 0 %, 4 studies) in migraineurs with WMHs than in those without WMHs with low heterogeneity across studies. The pooled results showed higher odds of right-to-left shunt in migraineurs with WMHs than in those without WMHs (OR 1.74, 95 % CI = 1.03–2.93, I^2 = 56 %, 4 studies). The presence of WMHs in migraine was not associated with hyperlipidemia, smoking, body mass, or oral contraceptive use.

4. Discussion

In the present systematic review and *meta*-analysis, an overall WMHs prevalence of 44 % was reported in the migraine population. The estimated prevalence of WMHs in migraine with and without aura was 45 % and 38 %, respectively. In addition, an approximately fourfold increase in the likelihood of WMHs in migraineurs was documented compared to that in non-migraine controls. The frontal and parietal lobes were common locations of WMHs. We found the associations of increased age, aura, and longer disease duration with a higher prevalence rate of WMHs. Most pain characteristics were unrelated to WMHs. Comorbidities, including hypertension, diabetes mellitus and right-to-left shunt, increased the risk of WMHs in migraineurs.

Despite the great heterogeneity across studies, a prevalence of 44 % suggests that WMHs are quite common in migraineurs. In contrast, the prevalence of WMHs was only 5.3 % in 243 healthy subjects whose mean age was 37.0 years (Hopkins et al., 2006). A *meta*-analysis by Bashir et al. reported that migraine with aura was associated with a 1.68-fold increased risk of WMHs compared with controls (OR 1.68, 95 % CI = 1.07–2.65), whereas migraine without aura marginally increased the risk of WMHs (OR 1.34, 95 % CI = 0.96–1.87) (Bashir et al., 2013). Our findings are partially in line with those of Bashir et al. However, our study showed a 6- and 4-fold increased risk of WMHs in migraine with and without aura, respectively. The difference is attributed to the fact that our *meta*-analysis included more literature (6 versus 4) and was restricted to studies with a number of migraine subjects greater than 50 to reduce bias. The result in our study is more representative of the broad population. When we excluded the studies whose patients had vascular risk factors, no significant change in the prevalence of WMHs was observed. This may be due to low prevalence and short disease duration of vascular risk factors in young migraine population.

The pathophysiological mechanisms of WMHs attributed to migraine remain unclear. Several putative explanations have been proposed for this phenomenon. Firstly, compromised cerebral blood flow is associated with WMH formation (Wardlaw et al., 2019). Reduced resting cerebral blood flow was observed in migraineurs with aura with a high WMHs load during the interictal period (Zhang et al., 2017). Cerebrovascular reactivity is a better indicator of the adequacy of tissue level cerebral blood flow. According to a transcranial Doppler study, reduced cerebrovascular reactivity is associated with an increased number of WMHs in migraineurs (Lee et al., 2019). Although causality could not be established in these cross-sectional studies, longitudinal studies have confirmed that reduced cerebral blood flow and cerebrovascular reactivity precede WMHs development in the non-migraine population (Promjunyakul et al., 2018; Sam et al., 2016). Secondly, a number of studies have shown increased inflammatory biomarkers levels (e.g., interleukin-6, tumor necrosis factor-α) in both serum and cerebral spinal fluid in migraineurs (Yamanaka et al., 2021). Neutrophil to lymphocyte ratio and monocyte to high-density lipoprotein cholesterol ratio, which are easily available biomarkers of inflammatory status, were higher in migraineurs with WMHs than in those without WMHs (Morkavuk et al., 2020; Ulusoy, 2020). Not only migraine but also WMHs are affected by neuroinflammation in their pathogenesis process. Thus, neuroinflammation cannot be neglected in the formation of WMHs in migraineurs. Thirdly, accumulating evidence indicates that migraineurs have abnormal platelet activation and aggregation (Danese et al., 2014), hypercoagulability (Tietjen and Collins, 2018), and microembolism (Donmez-Demir et al., 2018), which could be potential causes of WMHs formation. Fourthly, impaired glymphatic clearance function is related to WMHs in patients with cerebral small vessel disease (Xu et al., 2022; Zhang et al., 2021). However, the current evidence does not find glymphatic dysfunction in migraineurs compared to healthy controls (Lee et al., 2022). Finally, blood–brain barrier damage is a fundamental disease mechanism in WMHs (Wardlaw et al., 2019). There is no direct evidence exploring the relationship between WMHs and blood–brain barrier permeability in migraine populations. Two studies showed intact

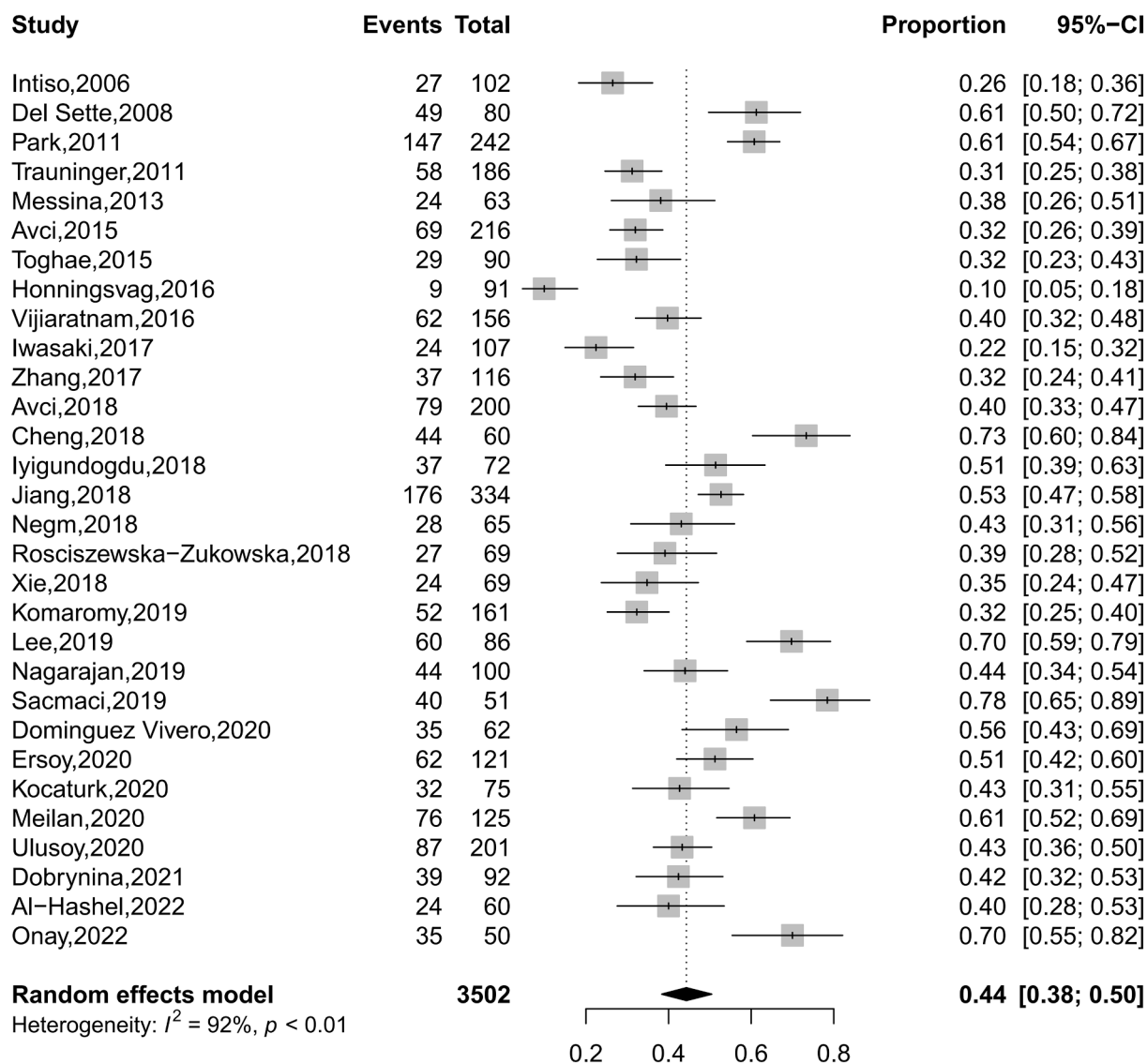| Study	Events	Total		Proportion	95%–CI
Intiso,2006	27	102		0.26	[0.18; 0.36]
Del Sette,2008	49	80		0.61	[0.50; 0.72]
Park,2011	147	242		0.61	[0.54; 0.67]
Trauninger,2011	58	186		0.31	[0.25; 0.38]
Messina,2013	24	63		0.38	[0.26; 0.51]
Avci,2015	69	216		0.32	[0.26; 0.39]
Toghae,2015	29	90		0.32	[0.23; 0.43]
Honningsvag,2016	9	91		0.10	[0.05; 0.18]
Vijiaratnam,2016	62	156		0.40	[0.32; 0.48]
Iwasaki,2017	24	107		0.22	[0.15; 0.32]
Zhang,2017	37	116		0.32	[0.24; 0.41]
Avci,2018	79	200		0.40	[0.33; 0.47]
Cheng,2018	44	60		0.73	[0.60; 0.84]
Iyigundogdu,2018	37	72		0.51	[0.39; 0.63]
Jiang,2018	176	334		0.53	[0.47; 0.58]
Negm,2018	28	65		0.43	[0.31; 0.56]
Rosciszewska–Zukowska,2018	27	69		0.39	[0.28; 0.52]
Xie,2018	24	69		0.35	[0.24; 0.47]
Komaromy,2019	52	161		0.32	[0.25; 0.40]
Lee,2019	60	86		0.70	[0.59; 0.79]
Nagarajan,2019	44	100		0.44	[0.34; 0.54]
Sacmaci,2019	40	51		0.78	[0.65; 0.89]
Dominguez Vivero,2020	35	62		0.56	[0.43; 0.69]
Ersoy,2020	62	121		0.51	[0.42; 0.60]
Kocaturk,2020	32	75		0.43	[0.31; 0.55]
Meilan,2020	76	125		0.61	[0.52; 0.69]
Ulusoy,2020	87	201		0.43	[0.36; 0.50]
Dobrynina,2021	39	92		0.42	[0.32; 0.53]
Al–Hashel,2022	24	60		0.40	[0.28; 0.53]
Onay,2022	35	50		0.70	[0.55; 0.82]
Random effects model		**3502**		**0.44**	**[0.38; 0.50]**
Heterogeneity: $I^2 = 92\%$, $p < 0.01$					

Fig. 3. The pooled analysis on the prevalence of white matter hyperintensities in migraineurs.

blood–brain barrier permeability during migraine attack, whether with or without aura, compared to the headache-free period in migraineurs (Amin et al., 2017; Hougaard et al., 2017).

Our study found that older age was an important risk factor for WMHs, which is consistent with previous findings in non-migraine populations (Zhuang et al., 2018). A *meta*-analysis containing 10 studies revealed increased blood–brain barrier permeability in older healthy subjects versus younger healthy subjects (Farrall and Wardlaw, 2009). Aura is another important risk factor for WMHs. Cortical spreading depression has been recognized as a specific electrophysiological event underlying aura, which distinguishes migraine with aura from migraine without aura (Eikermann-Haerter and Ayata, 2010). Endothelial dysfunction, decreased cerebral blood flow, and damage to the neurovascular unit are caused by cortical spreading depression (Yemisci and Eikermann-Haerter, 2019). Although the result implied that the association between disease duration and WMHs, it could result from the confounding effect of age. A few studies have reported that chronic migraine (Al-Hashel et al., 2022; Toghae et al., 2015), migraine attack frequency (Al-Hashel et al., 2022; Trauninger et al., 2011) and duration (Iyigundogdu et al., 2018; Ulusoy, 2020), pain severity (Ulusoy, 2020), and degree of disability (Al-Hashel et al., 2022; Ersoy et al., 2020; Ulusoy, 2020) were associated with WMHs, but these associations

were not found in other studies. After pooling the relative studies, the aforementioned variables were not related to WMHs in our *meta*-analysis. A prospective longitudinal study found no association of migraine attack frequency and duration with progression of WMHs (Palm-Meinders et al., 2012). As previous studies found compromised cerebral blood flow and elevated inflammatory biomarkers levels in migraineurs during the interictal period (Lee et al., 2019; Yamanaka et al., 2021; Zhang et al., 2017), this implies that cerebral small vessel damage is chronic and persistent in migraine, not confined to the ictal period.

Besides the pathogenesis of migraine affects WMH, comorbid hypertension and diabetes mellitus are likely to result in WMHs. Hypertension was reported to be associated with increased WMHs volume and count in a large population-based sample (n = 2367) (Habes et al., 2016). Among the numerous etiopathologies of cerebral small vessel diseases, hypertension is an important cause of type I small vessel diseases, which are also known as hypertensive small vessel diseases (Pantoni, 2010). Neuroimaging findings show that type 2 diabetes mellitus is related to a larger WMHs volume and reduced white matter integrity (Wang et al., 2020). Blood pressure and glycemic control, which may reduce the risk of WMHs, are necessary for migraineurs (de Havenon et al., 2019). There were no associations of hyperlipidemia, smoking and body mass index with WMHs in our findings. The reason
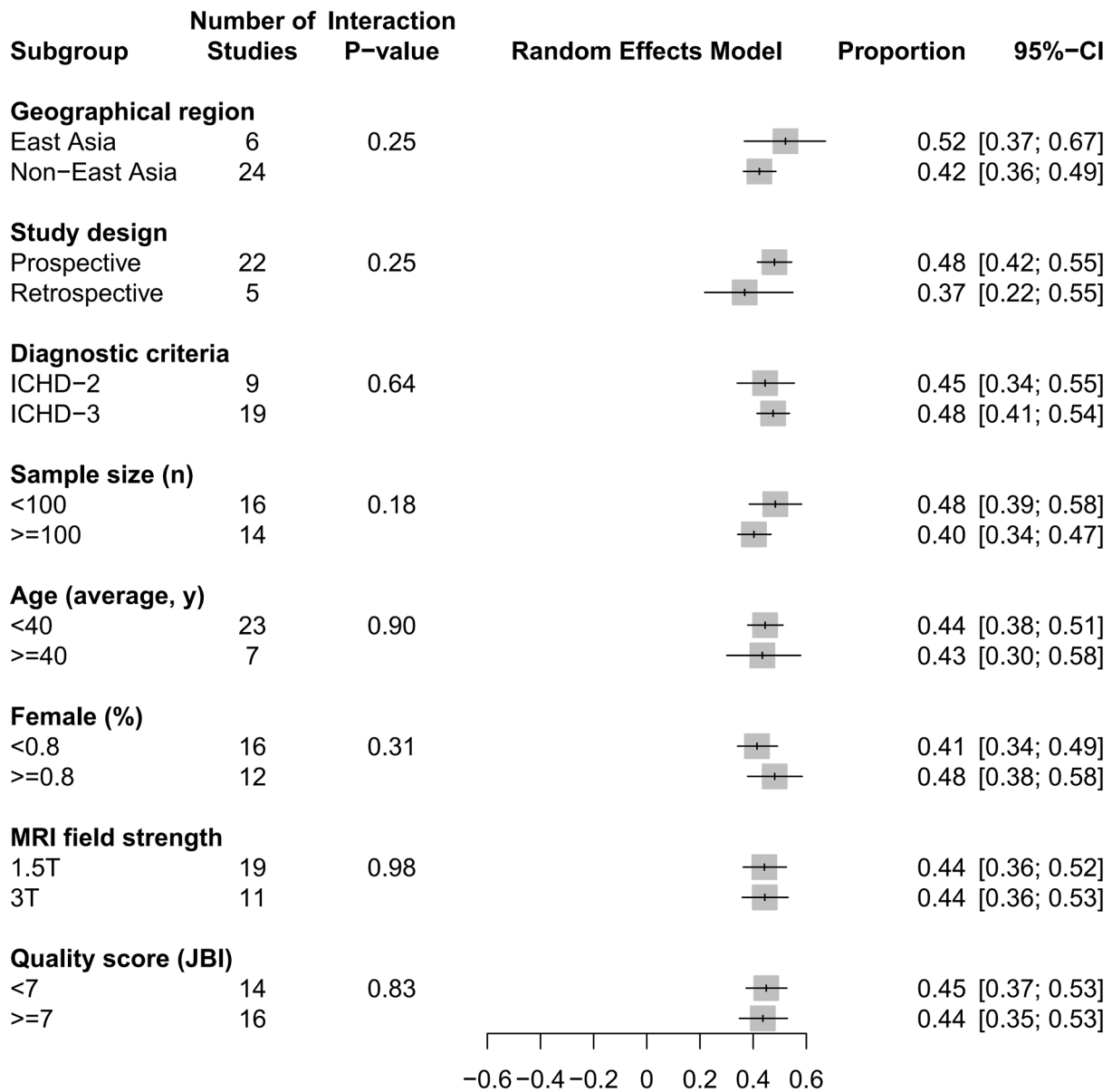
Subgroup	Number of Studies	Interaction P-value	Random Effects Model	Proportion	95%-CI
Geographical region					
East Asia	6	0.25		0.52	[0.37; 0.67]
Non-East Asia	24			0.42	[0.36; 0.49]
Study design					
Prospective	22	0.25		0.48	[0.42; 0.55]
Retrospective	5			0.37	[0.22; 0.55]
Diagnostic criteria					
ICHD-2	9	0.64		0.45	[0.34; 0.55]
ICHD-3	19			0.48	[0.41; 0.54]
Sample size (n)					
<100	16	0.18		0.48	[0.39; 0.58]
>=100	14			0.40	[0.34; 0.47]
Age (average, y)					
<40	23	0.90		0.44	[0.38; 0.51]
>=40	7			0.43	[0.30; 0.58]
Female (%)					
<0.8	16	0.31		0.41	[0.34; 0.49]
>=0.8	12			0.48	[0.38; 0.58]
MRI field strength					
1.5T	19	0.98		0.44	[0.36; 0.52]
3T	11			0.44	[0.36; 0.53]
Quality score (JBI)					
<7	14	0.83		0.45	[0.37; 0.53]
>=7	16			0.44	[0.35; 0.53]

-0.6 -0.4 -0.2 0 0.2 0.4 0.6

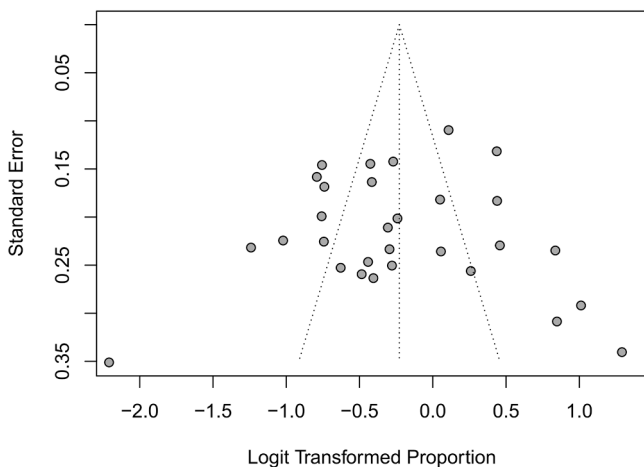**Fig. 4.** The prevalence of white matter hyperintensities in migraineurs in subgroup analyses.

Fig. 5. Funnel plot for the prevalence of white matter hyperintensities in patients with migraine.

for these negative results in migraineurs is unclear. A possible explanation is that the migraine subjects are young, and the duration of hyperlipidemia, smoking and obesity is relatively short. Right-to-left shunt may trigger a migraine attack with aura due to serotonin and microemboli bypassing the pulmonary circulation filter (Liu et al., 2020). A multi-center cross sectional study reported an increased prevalence of right-to-left shunt, especially large shunt, in migraineurs compared with healthy controls, but there was no difference between small and moderate shunts (Wang et al., 2018). Further studies should explore whether treating large shunt prevents the progression of WMHs.

The anatomic distribution of the WMHs across the included studies was similar. For every 10 migraineurs with WMHs, nine had frontal WMHs and three had parietal WMHs. By contrast, temporal, occipital, and infratentorial WMHs are uncommon. One potential explanation is that the branches of the anterior and middle cerebral arteries are vulnerable vascular regions. Subcortical WMHs are very common while juxtacortical and periventricular WMHs are less common. The deep white matter is supplied by deep perforating arteries branching and lacks collateral circulation. Therefore, ischemia-hypoperfusion damage first occurs in the deep white matter thereby causing subcortical WMHs
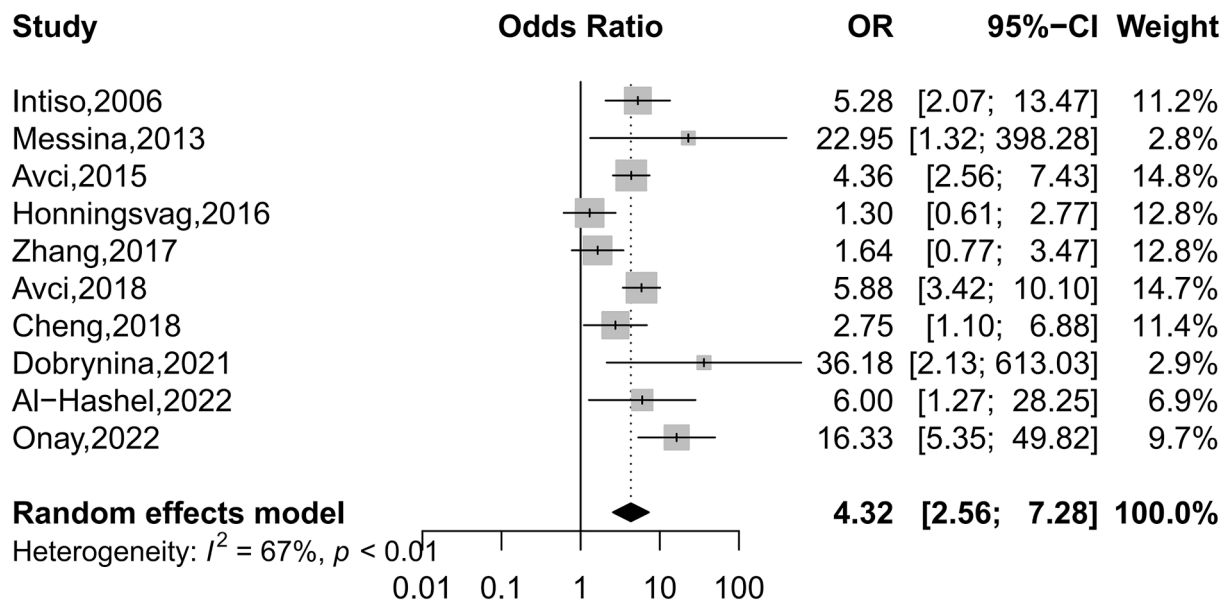
Study

Fig. 6. Forest plot depicting the risk of white matter hyperintensities in migraineurs compared with non-migraine controls.

([Cai et al., 2022](#)). Little is known about the laterality of WMHs in migraine. Regional WMHs asymmetry is associated with cognition and functional status. Patients with Alzheimer's disease with greater left-dominant WMHs asymmetry have poorer cognitive performance ([Low et al., 2019](#)). Community population with greater right-dominant WMHs asymmetry have lower baseline functional status and those with greater left-dominant WMHs asymmetry have accelerated functional decline ([Dhamoon et al., 2017](#)). Whether there is laterality and its impact on migraineurs deserve further exploration.

Evidences suggest that persons with an extensive WMHs burden have an increased risk of stroke and dementia in the future ([Debette et al., 2019](#)). This may explain the increased risk of stroke and dementia in patients with migraine. Considering that the presence of WMHs precedes stroke and dementia, it is plausible that preventing the formation and progression of WMHs could thereby reduce the risk of stroke and dementia in patients with migraine. Thus, it is necessary to explore potential means to prevent WMHs happening, e.g., therapeutic and prophylactic drugs for migraine targeting neurovascular mechanisms. In a study conducted in patients with chronic migraine, those with medication overuse had a lower WMHs burden than individuals without medication overuse ([Zheng et al., 2014](#)). This observation provides insights into the potential role of non-steroidal anti-inflammatory drugs in protecting against the development of WMHs. However, it should be noted that long-term use of non-steroidal anti-inflammatory drugs can affect cognitive function ([Wang et al., 2015](#)).

Some limitations should be acknowledged in our study. First, we did not attempt to identify unpublished studies and only included studies published in English. Therefore, some studies may have been overlooked. Second, the heterogeneity across studies of *meta*-analysis is difficult to avoid. Potential sources of the heterogeneity include inter-study differences in the target population, study design, assessment of WMHs, and statistical approaches. With that in mind, we analyzed the data using a random-effect model and explored the heterogeneity by *meta*-regression. Third, the included studies provided univariate analysis results of the clinical characteristics in migraineurs stratified by the presence of WMHs. Thus, the associations between the clinical characteristics and WMHs found in our study may not be independent. For instance, the association between disease duration and WMHs may result from confounding by age. Fourth, only one study on aura frequency and duration was included in our study, reporting negative results. However, a small longitudinal study reported the correlation of

aura frequency and duration with the number of new WMHs ([Dinia et al., 2013](#)). Thus, the evidence on aura characteristics and WMHs remains weak.

5. Conclusion

The overall evidence suggests that the prevalence of WMHs in migraineurs (44 %) is significantly higher than that in healthy controls, which may offer important insights into the early stage of stroke and dementia in migraine. Increased age, aura, hypertension, diabetes mellitus, and right-to-left shunt indicate a higher risk of WMHs in migraineurs. It is necessary to clarify the exact pathogenesis of WMHs in migraine and identify potential treatments to prevent WMHs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103312.

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