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Migraine is a risk factor for dementia: a systematic review and meta-analysis of cohort studies

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Abstract

Background Migraine affects more than one billion people worldwide, and there is growing concern about the burden of migraine. Migraine affects cognitive function during an attack, but reports are inconsistent on whether the effect of migraine on cognitive function persists and increases the risk of developing dementia. This systematic review and meta-analysis aimed to examine whether migraine is a risk factor for dementia.

Methods We searched six databases and included cohort studies with participants without dementia and with migraine at baseline, the outcome of interest was the risk of dementia, expressed in adjusted hazard ratios and 95% confidence intervals. Subgroup analyses and meta-regression were used to explore the sources of heterogeneity.

Results A total of 11 cohort studies containing 6,964,353 participants were included. Migraine increased the risk of all-cause dementia (HR = 1.26; 95% CI = 1.09–1.46), AD (HR = 1.32; 95% CI = 1.26–1.38), and VaD (HR = 1.28; 95% CI = 1.24–1.32). Subgroup analyses revealed migraine with aura had an increased risk of all-cause dementia compared to migraine without aura. The pooled results showed that migraine significantly increase the risk of all-cause dementia in studies with high quality and studies with sample sizes more than 2000. The results of meta-regression analyses revealed that region, migraine type, diagnostic criteria for dementia, gender, Newcastle-Ottawa Scale score, sample size, controls and mean follow-up time were not significant sources of study heterogeneity.

Conclusions This meta-analysis suggest migraine as a risk factor for dementia. Due to significant heterogeneity between studies, residual confounding factors and bias, the results should be cautiously interpreted.

Keywords Migraine, Dementia, Alzheimer's disease, Vascular dementia, Meta-analysis

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Introduction

Migraine is a highly prevalent chronic neurological disorder characterized by reversible neurological and systemic symptoms along with episodes of moderate to severe headaches [1, 2]. It affects approximately one billion people worldwide, and ranks the second most prevalent contributor to disability-adjusted life years among individuals under 50 years old [3]. Studies have consistently demonstrated that during migraine episodes, patients may exhibit cognitive impairments to varying degrees across multiple domains, including processing speed, language skills, planning, executive function, attention, visual memory, and verbal memory [4–6]. The question of whether cognitive decline in migraine patients persists over time and potentially progresses to dementia has garnered significant attention in recent years. Neuroimaging studies have reported that migraineurs may have smaller hippocampal volumes and altered hippocampal connectivity with other brain regions [7–9]. As the hippocampus plays a crucial role in cognitive and memory processes, these findings suggest that patients with migraine may have a potential risk of dementia.

Globally, the age-standardized rate of dementia incidence was 95.0 (81.6–107.9) per 100,000, and showed an upward trend [10]. According to projected data, the number of people living with dementia will rise to 153 million by 2050 [11]. The Lancet Commission on Dementia identified that according to the characteristics of different groups, tailored and nuanced dementia prevention methods should be adopted [12], clarifying the risk for dementia in migraine patients is of great significance for the effective dementia prevention and treatment planning. Previous systematic reviews and meta-analyses on this topic have shown varied results [13, 14]. Our study provides an updated perspective by incorporating the latest available literature. Focusing on cohort studies that consider migraine as an exposure factor, we aimed to quantify the risk of dementia in patients with migraine, and offering new insights by conducting subgroup and sensitivity analysis.

Methods

This study was conducted following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The protocol of this study was registered in PROSPERO (CRD42024571444), and updated according to the research progress.

Data sources and search strategy

An electronic search of six databases (PubMed, Embase, EBSCO, Scopus, Web of science and Cochrane Library) was conducted, starting from the inception of each database to December 1, 2024. Medical Subject Headings (MeSH) terms and related free text terms/keywords ('migraine', 'dementia') were combined for search. The detailed search strategies for each database are shown in Supplementary Table 1.

Study selection

Two authors screened the studies independently, according to the inclusion and exclusion criteria, disagreement was resolved by a third author. Inclusion criteria: (1) population: general population; (2) exposure: migraine, diagnosed based on self-reported diagnosis or medical diagnosis of migraine according to the International Classification of Headache Disorders (ICHD) [16, 17] or International Classification of Diseases (ICD) criteria [18–21]; (3) control: no history of migraine or headache; (4) outcome: dementia, provided sufficient information for adjusted hazard ratios (HRs) and 95% confidence intervals (CIs); (5) study design: cohort studies; (6) written in English. Exclusion criteria: (1) animal studies, case reports, protocols without results, conference abstracts, duplicate articles; (2) no healthy controls; (3) the studies did not report a measure of risk association between migraine and dementia outcomes; (4) diagnosis of any kind of dementia at baseline (except removed these participants from the dementia risk analysis); (5) for studies that involved the same cohort and reported the same measures, we chose the study with the longest follow-up.

Data extraction and quality assessment

Two principal authors independently read the included literature and extracted relevant data. Cross-checks were performed, and disagreements were resolved by a third author. The information included first author name, year of publication, location, size of cohort, population demographics, mean follow-up (years), migraine diagnosis, migraine subtypes, AD diagnosis, number who develops AD, adjusted factors. The quality assessment utilized in this study followed recommendations from Cochrane for observational studies through application of Newcastle-Ottawa Scale (NOS) [22]. The total scores of NOS can range from 0 to 9, the scores of studies more than 7 indicated high quality [23].

Statistical analysis

The main outcome of interest was expressed in adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The heterogeneity between studies was assessed using Cochran's Q test and I^2 statistics. Random-effects models were applied when there was a considerable amount of heterogeneity ($P < 0.05$ for the Cochran's Q test or $I^2 > 50\%$) during meta-analysis. Otherwise, the fixed-effects model was chosen for analysis. Subgroup analyses by region, gender, migraine type, diagnostic criteria for dementia, NOS score, controls, sample size and mean follow-up were performed to identify potential sources

of heterogeneity. To explore whether the above variables influencing the conclusions of the analyses, meta-regression analysis was performed. Sensitivity analysis was used to evaluate the stability of the study. Publication bias investigation involved funnel plots alongside Begg's test, Egger's test. A slope coefficient $P < 0.05$ indicated significant asymmetry. All statistical analyses and visualizations were conducted using the meta package in Stata, Version 17.0 (Stata, College Station, TX, USA).

Results

The initial search of six databases (PubMed, Embase, EBSCO, Scopus, Web of science and Cochrane Library) yielded 8,449 articles. A total of 124 studies received full-text screening, after excluding 113 studies, 11 studies were finally included. Figure 1 displays the PRISMA flowchart for detailed research selection.

Study characteristics

Eleven cohort studies [24–34] including 6,691,588 controls and 272,765 migraine patients, fulfilled our inclusion criteria (three of the studies had overlap of cohorts, study with the largest cohort sizes was calculated). The publication data of the included articles were from 2014 to 2024, 6 studies were conducted in Europe [24, 26, 28, 30, 31, 33], 4 studies were conducted in East Asia [27, 29, 32, 34], and 1 [25] in USA. All of the studies included both genders. For control cohorts, 6 studies [24, 27–30, 32] compared cases to non-migraine controls, 3 studies utilized non-headache as the control group [25, 26, 31], and 1 study [33] included non-migraine, stroke, or epilepsy, and 1 study included non-primary headache disorders [34]. All studies used the appropriate diagnostic criteria to identify people with migraine, 7 studies [25–29, 31, 32] reported on migraine aura status. Of the 11 studies included, patients had no cognitive decline or dementia at baseline. Of the outcome indicators, 7 studies [25, 27, 28, 30, 31, 33, 34] reported all-caused dementia, 4 studies [24, 27, 29, 30] reported AD, 5 studies [26, 27, 30, 32, 34] reported VaD. All studies reported the effect measures using HR and all studies performed multivariate analyses, adjusted for at least age and sex, the majority of the studies adjusted for comorbidities, including hypertension, heart disease, stroke, hyperlipidemia and diabetes mellitus. The detailed study characteristics are shown in Table 1.

Methodological quality

Every cohort study had NOS scores of more than seven, indicating high quality. In the comparability domain, due to the use of matched controls, 5 studies [24, 27, 28, 30, 34] demonstrated a low risk of bias. In the outcome domain, 3 studies [24, 30, 33] had a risk of bias due to inadequate follow-up data (Table 2).

Meta analysis of the all-cause dementia risk in migraine

A total of 7 studies [25, 27, 28, 30, 31, 33, 34] that reported the risk of all-cause dementia in migraine patients were included in the calculation of pooled HR. Given the extremely high heterogeneity (I^2 = 84.5%) among the studies, a random-effects model was employed. According to the result, migraine substantially raised the chance of developing all-cause dementia (HR = 1.26; 95% CI = 1.09–1.46) (Fig. 2). Sensitivity analysis showed that, excluding none individual study altered the overall direction of effect (Supplementary Fig. 1.A). Funnel plot, Begg's test and Egger's test indicated no evidence of systematic asymmetry on examination (Supplementary Tables 2 and Fig. 2.A). Subgroup analysis on region showed that Asian migraine patients had an increased risk of all-cause dementia (HR = 1.59; 95% CI = 1.04–2.42, I^2 = 91.8%) (Table 3). Through subgroup analyses by the type of migraine, it was found that migraine with aura had an increased risk of all-cause dementia and reduced statistical heterogeneity (HR = 1.22; 95% CI = 1.03–1.44, I^2 = 38.6%), but migraine without aura was not (HR = 1.13; 95% CI = 0.94–1.37, I^2 = 74.9%). Subgroup analysis according to different diagnostic criteria for dementia showed that, migraine patients had an increased risk of all-cause dementia in studies that used ICD criteria (HR = 1.38; 95% CI = 1.18–1.62, I^2 = 82.2%). Heterogeneity between studies using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria decreased, but the risk of all-cause dementia was not significant (HR = 0.99; 95% CI = 0.83–1.18, I^2 = 23.8%). Subgroup analysis by gender showed that the result was only significant in women (HR = 1.28; 95% CI = 1.12–1.47, I^2 = 62.6%). Migraine significantly increased the risk of all-cause dementia in high quality studies (NOS score was 9) (HR = 1.51; 95% CI = 1.23–1.85, I^2 = 85.8%) and studies with sample sizes more than 2000 (HR = 1.29; 95% CI = 1.13–1.46, I^2 = 70.5%). The high risk of all-cause dementia in migraine groups was observed when the studies used non-migraine controls (HR = 1.29; 95% CI = 1.13–1.46, I^2 = 70.5%). The meta-regression analysis showed that region (P = 0.912), migraine type (P = 0.661), diagnostic criteria for dementia (P = 0.109), gender (P = 0.538), NOS score (P = 0.101), sample size (P = 0.819), controls (P = 0.819) and mean follow-up time (P = 0.427) were not significant sources of study heterogeneity.

Meta analysis of the Alzheimer's disease risk in migraine

Four studies [24, 27, 29, 30] reported the risk of AD. Meta-analysis showed that there was a notable difference in AD risk between individuals with migraine and the control group (HR = 1.48; 95% CI = 1.31–1.67). Substantial heterogeneity (I^2 = 90.9%) was observed across studies. Sensitivity analysis showed that the I^2 value decreased by 38.4% when the result of Geng [24] was not included.

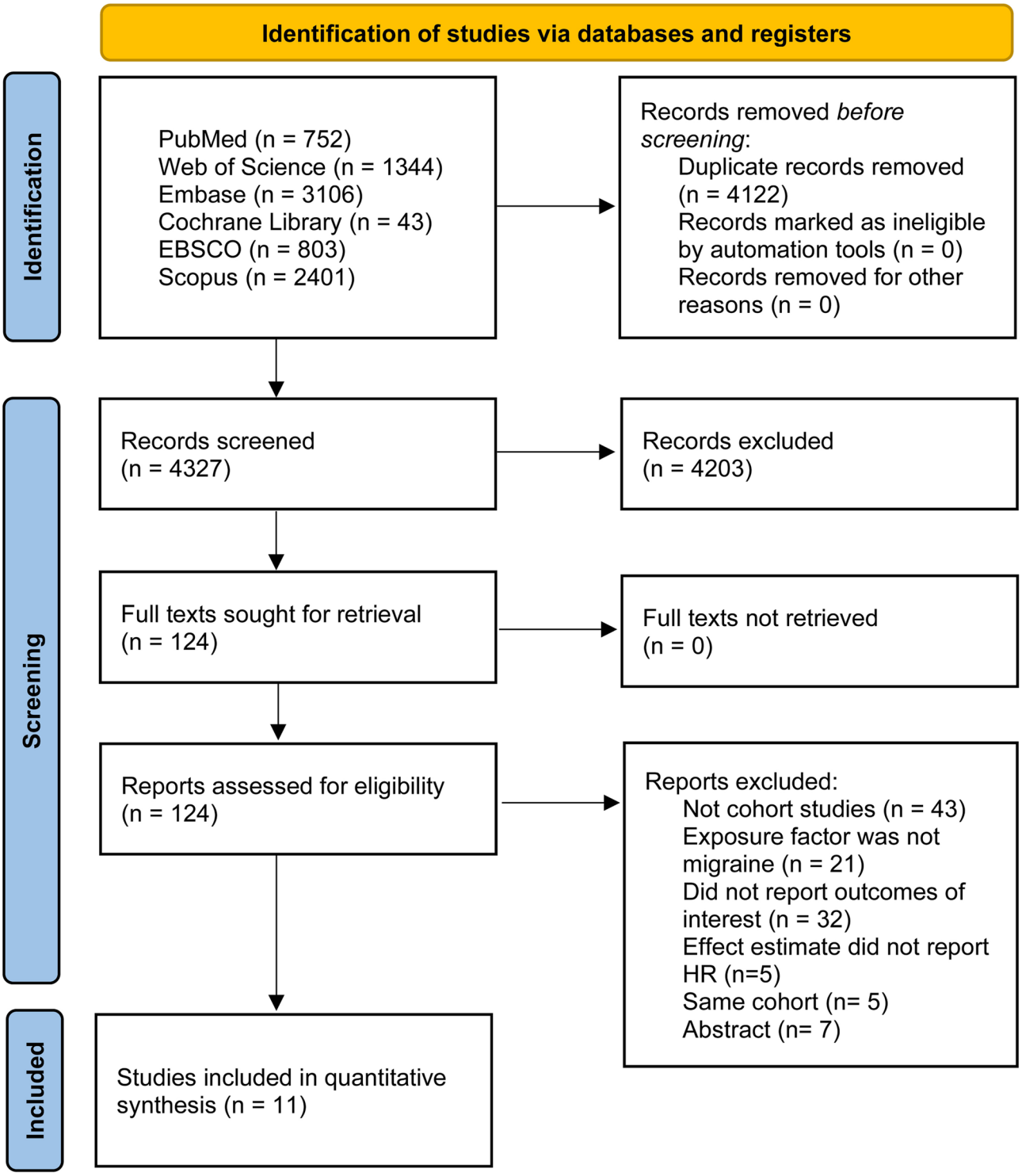

Fig. 1 Flow diagram of study selection

The study investigated the association between migraine and AD risk by analyzing data from a sample comprising 404,318 individuals, utilizing the UK Biobank dataset. Adults with migraines suffer from a significant burden of depression and/or anxiety [35], while study have found that people with depression have a higher chance of developing AD [36]. This study did not adjust for depression, hyperlipidemia, Parkinson's disease, resulting in a higher HR than the actual value. After removing this study as an outlier, migraine was still a risk factor for AD

Table 1 Characteristics of the included studies

Study	Year	Country	Database	migraine/control cohort size(female)	Controls description	Mean age (SD) (migraine/control)	Length of follow-up(years)	Mean follow-up (years)	Migraine diagnosis	Dementia diagnosis	Migraine subtypes	Dementia subtypes	Multivariable adjustment
Geng et al. [24]	2024	United Kingdom	UK Biobank cohort	22,558(12,565)/ 22,558(12,565)	Non-migraine	54.95(0.05)/ 54.95(0.05)	11–15	12.31	ICD-10	ICD-10	Migraine	AD	Year of birth, sex, race, education, BMI, current smoking, current drinking, hypertension, diabetes, coronary heart disease, stroke, and ApoE4 carriers
George et al. [25]	2020	America	Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)	1,397(1,088)/ 9,855(5,105)	Non-headache	58.3(5.5)/60.4(5.7)	20–25	21*	ICHD-III	DSM-V	Migraine, MO, MA	All-cause dementia	Age, race-center, APOE ε4, income, education, BMI, smoking status, hypertension, diabetes, prevalent coronary heart disease, drinking status, high-density lipoprotein cholesterol, and total cholesterol
Hagen et al. [26]	2014	Norway	Nord-Trøndelag Health Study	6,740/29,988(13,944)	Non-headache	NR/52.3(17.7)	1–16	8.6	ICHD-I	ICD-10	Migraine, MO, MA	VaD	Age, gender, education, total Hospital Anxiety and Depression Scale, and smoking
Hurh et al. [27]	2022	Korea	Korean National Health Insurance Service (NHIS) database	44,195(29,228)/ 44,195(29,228)	Non-migraine	55.3(9.4)	1–16	7.84	ICD-10	ICD-10	Migraine, MO, MA, unspecified	All-cause dementia, AD, VaD, mixed or other specified dementias, and unspecified dementia	Risk-set matching method (age, sex, socioeconomic status, comorbidities and lifestyle factors)
Islamoska et al. [28]	2022	Denmark	Denmark National register data	8,800(6,025)/ 281,414(216,589)	Non-migraine	50/50*	7–30	NR	ICD-8, ICD-10	ICD-8, ICD-10	Migraine, MO, MA, all other migraine diagnoses	All-cause dementia	Sex, country of origin, marital status, educational level, headache diagnoses, headache injuries, psychiatric morbidities, and Charlson Comorbidity Index
Kim et al. [29]	2023	Korea	Korean National Health Insurance Service (NHIS) database	212,836(153,766)/ 5,863,348(2,734,541)	Non-migraine	56.5(10.9)/ 54.0(10.3)	10	NR	ICD-10	ICD-10	Migraine, MO, MA, chronic migraine, episodic migraine	AD	Age, sex, comorbidities, eGFR, BMI, and lifestyle

Table 1 (continued)

Study	Year	Country	Database	migraine/control cohort size(female)	Controls description	Mean age (SD) (migraine/control)	Length of follow-up(years)	Mean follow-up (years)	Migraine diagnosis	Dementia diagnosis	Migraine subtypes	Dementia subtypes	Multivariable adjustment
Kostev et al. [30]	2019	United Kingdom	UK Disease Analyzer database	3,727(2,717)/ 3,727(2,717)	Non-migraine	67.7(5.8)/67.7(5.8)	10	NR	ICD-10	ICD-10	Migraine	All-cause dementia, AD, VaD, unspecified dementia	Age, sex, index year, diabetes mellitus, hyperlipidemia, coronary heart disease, stroke, mental and behavioral disorders, Parkinsons's disease and osteoporosis
Liang et al. [31]	2022	Sweden	Swedish National study on Aging and Care in Kungsholmen (SNAC-K)	267/229	Non-headache	73.6(10.86)	3–12	7.2	ICHD-II	DSM-IV	Migraine, MO, MA	All-cause dementia	Age, sex, education, smoking, alcohol consumption, physical activity, hypertension, diabetes, total cholesterol, heart disease, cerebrovascular disease, depression, APOE4 allele, and use of specific and non-specific antimigraine medications
Shin et al. [32]	2024	Korea	Korean National Health Insurance Service (NHIS) database	212,836(153,766)/ 5,863,348(2,734,541)	Non-migraine	56.49 (10.9)/ 53.98 (10.3)	10	9*	ICD-10	ICD-10, prescription records for anti-dementia medication	Migraine, MO, MA, chronic migraine, episodic migraine	VaD	Age, sex, comorbidities (hypertension, diabetes, dyslipidemia, myocardial infarction, congestive heart failure, and stroke), eGFR, BMI, and lifestyle (smoking status, drinking status, and regular exercise).

Table 1 (continued)

Study	Year	Country	Database	migraine/control cohort size(female)	Controls description	Mean age (SD) (migraine/control)	Length of follow-up(years)	Mean follow-up (years)	Migraine diagnosis	Dementia diagnosis	Migraine subtypes	Dementia subtypes	Multivariable adjustment
Tai et al. [33]	2024	United Kingdom	UK Biobank cohort	14,518/469,609	Non-migraine, stroke, or epilepsy	57.5(8.1)	5–14	12*	ICD-10, ICD-9	ICD-10, ICD-9	Migraine	All-cause dementia	Age, sex, education, socio-economic status, and assessment center.
Tzeng et al. [34]	2017	China	National Health Insurance Research Database (NHIRD)	1,922/10,860(7,389)	Non-primary headache disorders	NR	10	NR	ICD-9	ICD-9	Migraine	All-cause dementia, VaD, no VaD	Sex, age, region of residence, monthly income, comorbidities, urbanization level and insured premium

AD Alzheimer's disease; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; *DSM-V* Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; *ICD-8* Eighth Revision of International Classification of Diseases code; *ICD-9* Ninth Revision of International Classification of Diseases code; *ICD-10* Tenth Revision of International Classification of Diseases code; *ICHD-I* The International Classification of Headache Disorders, first edition; *ICHD-II* The International Classification of Headache Disorders, second edition; *ICHD-III* The International Classification of Headache Disorders, third edition; *MA* migraine with aura; *MO* migraine without aura; *VaD* vascular dementia

*Median value

(HR = 1.32; 95% CI = 1.26–1.38) (Fig. 3). Sensitivity analysis showed the result was reliable (Supplementary Fig. 1.B). Begg's test, Egger's test and funnel plot indicated no significant risk of publication bias (Supplementary Tables 2 and Fig. 2.B).

Meta analysis of the vascular dementia risk in migraine

A total of 5 studies [26, 27, 30, 32, 34] reported the VaD risk in migraine patients and the control group. There was no significant heterogeneity among the studies (I^2 = 27.6%), and a fixed-effect model was used. The result of meta-analysis demonstrated a significantly increased risk of VaD in migraine patients (HR = 1.28; 95% CI = 1.24–1.32) (Fig. 4). Sensitivity analysis showed that the result was reliable (Supplementary Fig. 1.C). Egger's test indicated the existence of publication bias in the included studies (P = 0.048) (Supplementary Tables 2 and Fig. 2.C).

Discussion

This systematic review and meta-analysis of 6,964,353 participants across 11 cohort studies confirms the positive correlation between migraine as a yes-no variable and an elevated risk for all-cause dementia, AD and VaD. According to our meta-analysis, the migraine group had a 1.26-fold higher risk of all-cause dementia compared to the control group. This finding was consistent with the meta-analysis of Gu (OR/RR = 1.30; 95% CI = 1.11–1.52) [14], Jiang (RR = 1.33; 95% CI = 1.16–1.53) [37], Cermelli (OR = 1.26; 95% CI = 1.13–1.40) [38] and Yuan (HR = 1.35; 95% CI = 1.19–1.52) [39]. The potential biological mechanisms underlying the increased risk of dementia in migraine patients include neuroinflammation and genetic predisposition. Mendelian randomization analysis demonstrated that migraine patients exhibit an increased predisposition of genetic susceptibility to dementia [24, 40]. Migraine attacks are associated with the activation and release of vasoactive neuropeptides such as calcitonin gene-related peptide, which may lead to neurogenic neuroinflammation and even neurodegeneration over time, thus potentially contributing to cognitive decline and dementia [41]. In the cortical spreading depression migraine model, abnormal activation of microglia and the neurogenic inflammation it mediates were observed [42], similar mechanisms may also play a role in the pathogenesis of dementia [43].

We observed some differences in the subgroup. A significant increased risk of all-cause dementia risk in Asian migraine patients was observed, whereas no significant difference was found in Europe. This may be explained by different ethnicities. Prevalence of disease varied depending on diagnostic classification system used, previous studies have reported differences in dementia prevalence between DSM-IV, DSM-V, ICD-9 and ICD-10 [44, 45]. In subgroup analysis, studies that diagnosed

Table 2 Methodological quality assessment results of the included studies

Author	Selection				Comparability	Outcome			Total scores
	Representativeness of the exposed cohort	Selection of the non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Geng et al. [24]	☆	☆	☆	☆	☆☆	☆	☆		8
George et al. [25]	☆	☆	☆	☆	☆	☆	☆	☆	8
Hagen et al. [26]	☆	☆	☆	☆	☆	☆	☆	☆	8
Hurh et al. [27]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Islamoska et al. [28]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kim et al. [29]	☆	☆	☆	☆	☆	☆	☆	☆	8
Kostev et al. [30]	☆	☆	☆	☆	☆☆	☆	☆		8
Liang et al. [31]	☆	☆	☆	☆	☆	☆	☆	☆	8
Shin et al. [32]	☆	☆	☆	☆	☆	☆	☆	☆	8
Tai et al.[33]	☆	☆	☆	☆	☆	☆	☆		7
Tzeng et al. [34]	☆	☆	☆	☆	☆☆	☆	☆	☆	9

dementia using ICD codes demonstrated a significant difference in all-cause dementia risk between migraine patients and those without migraine. It has been reported that the ICD-10 criteria have good stability, but the ICD-10 criteria are phrased in a way that leaves much to individual interpretation [46], and may affect dementia detection rates between specific populations. Only two studies used the DSM criteria, more studies are needed to examine the stability of the result. According to certain researches, women may be more susceptible to migraine and dementia than men [47, 48]. The results of subgroup analysis showed that women with migraine had a high risk of all-cause dementia, while this risk was not evident in men. Sex hormones may be responsible for the difference, Mendelian randomization study indicated that higher total testosterone levels, predicted genetically, might reduce the incidence of Alzheimer's disease [49]. The results of subgroup analysis for migraine type showed that dementia risk was higher for MA than for MO. The reduced statistical heterogeneity between the studies reporting aura-related migraine suggests that aura may aid in more accurate diagnosis of migraine. A cohort study conducted in Denmark reported that compared to the patient without aura, patients with aura had an increased risk of myocardial infarction and stroke [50]. The reasons for the high risk of various diseases in MA require more mechanism studies to explore. The dementia risk of migraine patients became significant with longer follow-up (≥ 10 years), some functional impairments over time may have an impact on the onset of dementia. For those that were not significant with less than 10 years follow-up, the magnitude of the effect consistently pointed towards risk increase. In addition, clinical features, study design, choose of covariables and statistical method might be the source of inconsistencies, more studies were essential to explore the dementia risk in migraine patients. Although the meta-regression analysis showed that region, migraine type, diagnostic criteria for dementia, gender, NOS score, sample size, controls and mean follow-up time had no independent effect on the risk of all-cause dementia in migraine patients, we observed differences among subgroups. The inconsistency between meta-regression and subgroup analysis results can be attributed to methodological distinctions, data distribution, potential interactions between covariates. In the case of the gender variable, within studies that have a higher proportion of women, there might be other confounding factors that mask the gender effect when analyzed at the study level. When directly comparing men and women within studies (subgroup analysis), these confounding factors may be controlled for, allowing the gender-specific effect to emerge. Another possible explanation for this discrepancy is that the meta-regression result might be influenced by the range of gender

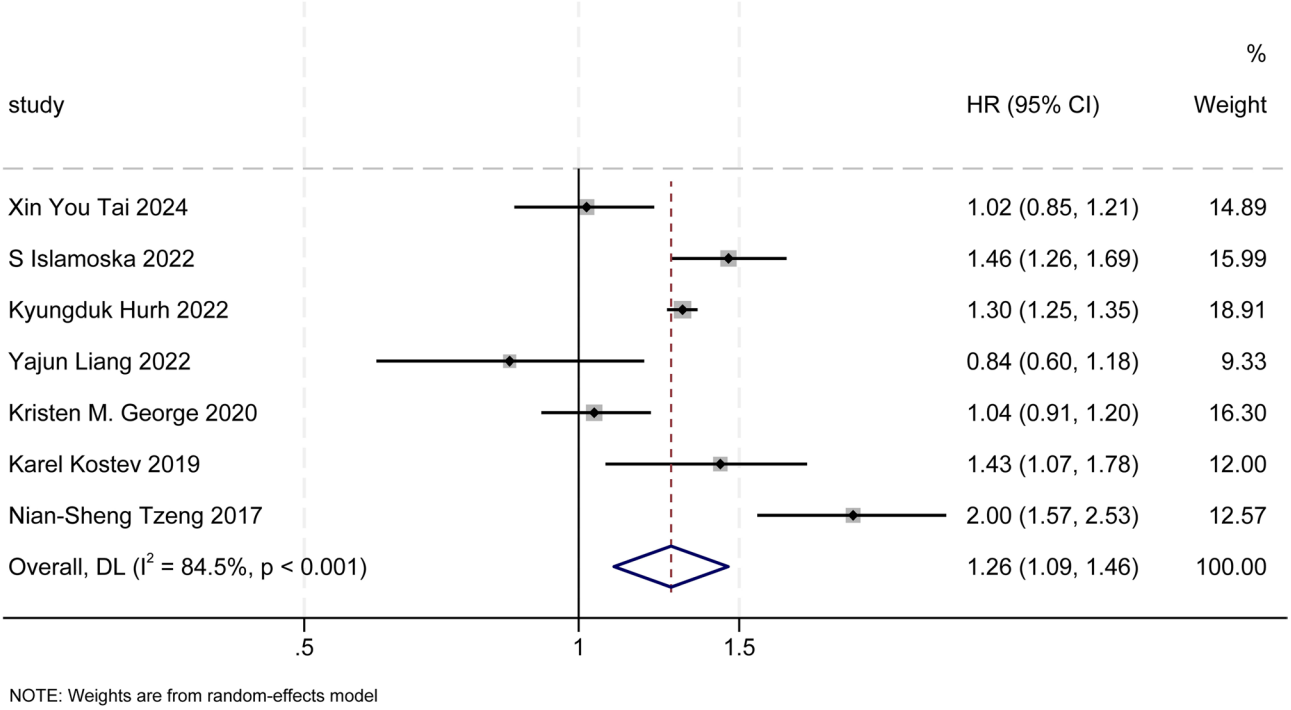

Fig. 2 Meta analysis of the all-cause dementia risk in migraine

Table 3 Subgroup analysis of the all-cause dementia risk in migraine

Study characteristic	Number of studies	Results from meta-analysis (HR 95% CI)	Heterogeneity
Study region			
Europe	4	1.18 (0.92–1.51)	I^2 = 81.0%, P = 0.001
Asia	2	1.59 (1.04–2.42)	I^2 = 91.8%, P<0.001
America	1	1.04 (0.91–1.19)	–
Migraine type			
Migraine without aura	4	1.13 (0.94–1.37)	I^2 = 74.9%, P = 0.008
Migraine with aura	4	1.22 (1.03–1.44)	I^2 = 38.6%, P = 0.181
Dementia diagnosis			
DSM	2	0.99 (0.83–1.18)	I^2 = 23.8%, P = 0.252
ICD	5	1.38 (1.18–1.62)	I^2 = 82.2%, P<0.001
Gender			
Men	3	1.14 (0.80–1.61)	I^2 = 81.4%, P = 0.005
Women	3	1.28 (1.12–1.47)	I^2 = 62.6%, P = 0.069
NOS score			
7	1	1.02 (0.85–1.22)	–
8	3	1.09 (0.84–1.41)	I^2 = 71.8%, P = 0.029
9	3	1.51 (1.23–1.85)	I^2 = 85.8%, P<0.001
Sample size			
<2000	3	1.21 (0.75–1.95)	I^2 = 92.3%, P<0.001
≥ 2000	4	1.29 (1.13–1.46)	I^2 = 70.5%, P = 0.017
Controls			
Non-migraine	4	1.29 (1.13–1.46)	I^2 = 70.5%, P = 0.017
Non-headache	3	1.21 (0.75–1.95)	I^2 = 92.3%, P<0.001
Mean follow-up (year)			
<10	2	1.08 (0.71–1.65)	I^2 = 84.2%, P = 0.012
≥ 10	5	1.33 (1.06–1.68)	I^2 = 87.5%, P<0.001

DSM Diagnostic and Statistical Manual of Mental Disorders; *ICD* International Classification of Diseases code

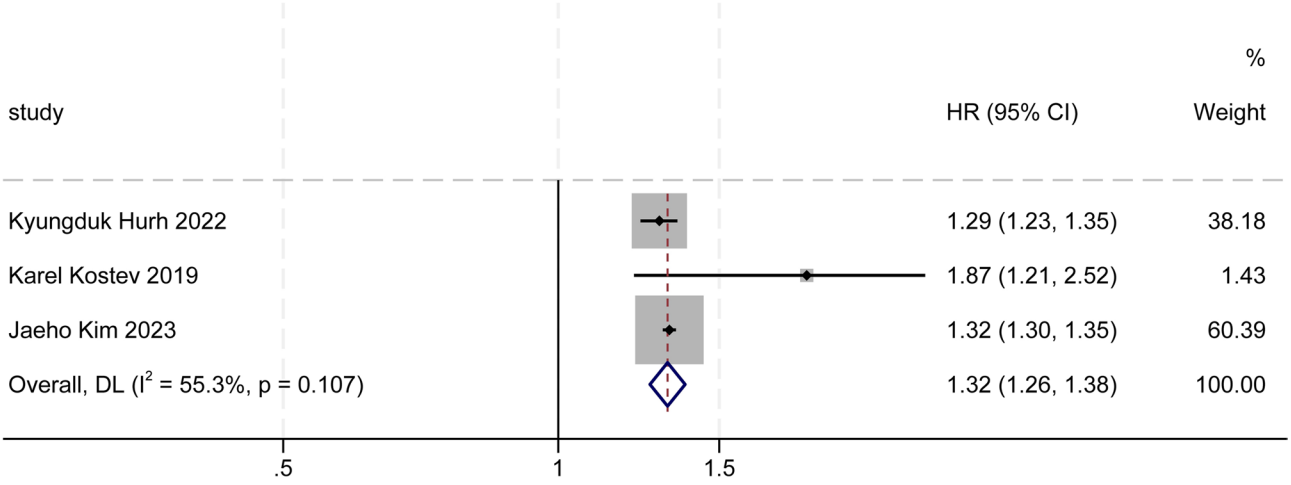

Fig. 3 Meta analysis of the Alzheimer's disease risk in migraine

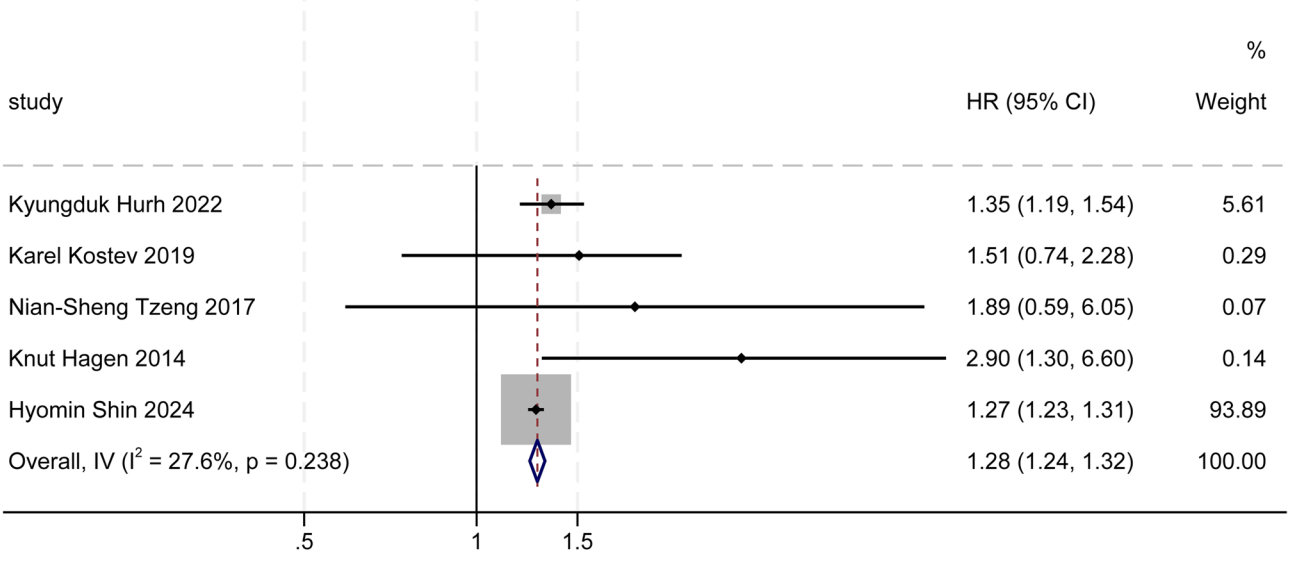

Fig. 4 Meta analysis of the vascular dementia risk in migraine

proportions across studies. If there's limited variation in gender distribution among the included studies, the meta-regression may lack the power to detect significance, even if it exists.

In this meta-analysis, we also demonstrated that patients with migraine had a high risk of AD and VaD. The risk of AD in migraine patients was consistent with previous review [13]. Although further research is needed to elucidate the pathological mechanisms linking migraine to Alzheimer's disease, current evidence indicates an association between the two. Based on GWAS summary statistics, a study used two-sample Mendelian randomization analysis to examine the genetic causal effect of migraine on Alzheimer's disease. The analysis demonstrated a significant association between genetically predicted migraine and an increased risk of AD, and identified thalamic atrophy as a potential mediator [51]. Migraine attacks can cause chronic repetitive pain, which may lead to the vulnerability of brain structures involved in pain processing and memory, such as the thalamus and hippocampus [52–54]. Over time, this could result in memory deterioration and an increased risk of AD. Additionally, brain insulin resistance may serve as a "metabolic bridge" between the two conditions. Brain insulin resistance is the metabolic alteration underlying the common pathophysiological changes between migraine and AD. In the long run, brain insulin resistance promotes a shift towards the amyloidogenic cascade and increases tau hyperphosphorylation, thereby driving the progression from migraine to AD [55].

A previous meta-analysis found no association between migraine and the risk of VaD (RR = 1.51; 95% CI = 0.77–2.96) [13]. That review included two studies of VaD, and one study had a small sample size (n = 679). By including 5 studies and more sample sizes, our study found the differences in dementia risk between migraine and non-migraine group. Migraine have been consistently linked with increased risk of ischemic stroke, hemorrhagic stroke and cardiovascular disease [56]. Stroke in migraine patients may be explained by genetic predisposition, aura-related electrophysiological processes (cortical spreading depolarization), and cerebral microembolim [57]. It is worth noting that in the cohort study observing the risk of VaD in patients with migraine, some confounding factors may not be accurately controlled. For example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) caused by NOTCH3 mutations usually presents with MA in the early stage of life, and ischemic stroke-induced cognitive decline often arise between 40 and 70 years [58]. Due to underdiagnosis and underreporting, accurate identification and exclusion of CADASIL are challenging. This may lead to an overestimation of the incidence of VaD among migraine patients.

Limitations

The study still has some limitations. First, most cohort studies recruited populations of European and Asian origin, leading to a potential population bias and thus limiting the generalizability of the findings. Excluding studies published in non-English languages may also introduce language bias. Second, the high heterogeneity among studies reported all-cause dementia might be caused by different methodological issues and clinical features, which lowered the quality of evidence. Third, the differences in adjusted HR values due to the different covariates adjusted in the included studies may have an impact on the results of this study. Some studies did not adjust for confounding factors, such as depression, sleep, hypertension, patent foramen ovale, rosacea, and these factors may all influence dementia risk in migraine patients [36, 59–62]. Fourth, the different anti-migraine drugs have different effects on cognition [63], we were unable to further evaluate the effect of anti-migraine drugs on dementia risk due to the lack of enough data for analysis. Fifth, one study employed a questionnaire adapted from diagnostic criteria to assess migraine status, and observed the dementia incidence during follow-up [25]. The questionnaire inherently possesses a degree of subjectivity. Inaccurate grouping increased sample heterogeneity, may have introduced misclassification bias, and obscured the true association between migraine and dementia risk. Sixth, the included studies did not distinguish between individuals with active migraine and those with a past history of migraine. We were unable to identify separate datasets specifically for these two populations. This limitation prevented us from analyzing whether the risk of dementia is specifically increased in patients with active migraine, thereby compromising the accuracy and generalizability of our results. This underscores the need for additional studies to better clarify the detailed relationship between migraine and dementia.

Conclusion

This systematic review and meta-analysis suggest migraine as a risk factor for dementia, migraine patients have higher incidence rates of all-cause dementia, AD and VaD. These findings may have clinical implications for the prevention of dementia, particularly for early diagnosis and intervention of cognitive decline in migraine. However, the results should be cautiously interpreted due to significant heterogeneity between studies, residual confounding factors, misclassification bias and publication bias. Despite limitations, our results suggest migraine may be one of the risk factors for dementia, and their relationship merits further exploration. Future studies should focus on controlling confounding factors and developing rigorous protocols to accurately understand the relationship between subtypes of migraine and dementia.

Abbreviations

AD	Alzheimer's disease
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CI	Confidence interval
HR	Hazard ratio
ICD	International Classification of Diseases
ICHD	International Classification of Headache Disorders
MeSH	Medical Subject Headings
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
VaD	Vascular dementia

Supplementary Information

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Supplementary Material 1.

Authors' contributions

WYZ: Study design, Data curation, Manuscript writing. YJZ: Data curation, Data analysis. JP: Supervision, Manuscript revision. QHF: Methodology, Manuscript revision. RQW: Software, Visualization. QWY: Data Curation. QYG: Data Curation. LKZ: Data Curation.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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