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# Association between Migraine and Dementia: A Systematic Review of Observational and Mendelian Randomization Studies

Yasmine Ibrahim Al-Najjar[1], Mayyadah Zaben Alfadhil[2]*, Danah Mohammed Almakayil[3]

[1]Consultant Family Medicine, Ministry Headquarters, Saudi Arabia
[2]Medical Intern, Najran University, Najran, Saudi Arabia
[3]Medical Intern, Najran University, Najran, Saudi Arabia

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***Corresponding author:** Mayyadah Zaben Alfadhil
Medical Intern, Najran University, Najran, Saudi Arabia

## Abstract

***Background:*** Migraine and dementia are prevalent neurological disorders with overlapping pathophysiological mechanisms. The association between migraine and dementia risk remains debated, with conflicting findings from observational studies and emerging evidence from Mendelian randomization (MR) studies. ***Methods:*** This systematic review followed PRISMA guidelines. A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, and Web of Science for publications from January 2021 to January 2026. Eligible studies included observational cohort studies and MR studies examining the association between migraine and dementia outcomes in adults. Risk of bias was assessed using the Newcastle-Ottawa Scale for cohort studies and a modified ROBINS-I framework for MR studies. A narrative synthesis was performed due to substantial heterogeneity. ***Results:*** Seven studies met inclusion criteria: five population-based cohort studies and two two-sample MR studies. Among cohort studies, four reported significant positive associations between migraine and dementia risk, with hazard ratios ranging from 1.21 to 1.37 for all-cause dementia, 1.29 to 1.31 for Alzheimer's disease (AD), and 1.21 to 1.35 for vascular dementia (VaD). One Swedish cohort study reported no significant associations. MR studies provided evidence supporting a causal relationship between genetically predicted migraine and increased AD risk (odds ratios 1.09–1.10), with thalamic atrophy identified as a partial mediator (28.2% of the total effect). Bidirectional MR analysis revealed that migraine increases AD risk while VaD increases migraine risk. Migraine subtype, aura status, and case definition influenced observed associations. ***Conclusion:*** Current evidence suggests migraine is associated with increased risk of dementia, particularly AD and VaD, with MR studies supporting causal relationships. Heterogeneity across studies highlights the importance of diagnostic methods, population characteristics, and dementia subtype specification. Future research should employ standardized diagnostic criteria, detailed migraine phenotyping, and investigate the potential neuroprotective effects of migraine management on cognitive outcomes.

**Keywords:** Migraine; Dementia; Alzheimer's disease; Vascular dementia; Mendelian randomization; Systematic review; Causal inference; Neurodegeneration.



## INTRODUCTION

Migraine is a highly prevalent neurological disorder affecting approximately 14–15% of the global population, with a peak incidence in mid-life and a female-to-male ratio of approximately 3:1 [1, 2]. Characterized by recurrent, often debilitating headache episodes, migraine is frequently accompanied by sensory disturbances, autonomic dysfunction, and, in approximately one-third of patients, transient neurological aura phenomena [2]. Beyond its acute burden, migraine has been increasingly recognized as a chronic condition associated with long-term neurological sequelae, including structural brain changes, cerebrovascular events, and potential cognitive impairment [3–5]. Dementia, by contrast, represents a progressive neurodegenerative syndrome that affects an estimated 55 million people worldwide, with Alzheimer's disease (AD) accounting for 60–70% of cases, followed by vascular dementia (VaD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) [6]. The global burden of dementia is projected to rise to 139 million affected individuals by

2050, driven by population aging and the absence of curative therapies, making the identification of modifiable risk factors a public health priority [6].

The hypothesis that migraine may increase the risk of dementia has gained traction over the past decade, supported by overlapping pathophysiological mechanisms that include chronic neuroinflammation, vascular endothelial dysfunction, shared genetic susceptibility, and progressive structural brain atrophy [7, 8]. Observational studies have reported conflicting results: some large population-based cohort studies have demonstrated a 20–40% increased risk of all-cause dementia, AD, and VaD among individuals with migraine [9, 10], whereas others have found no significant association [1]. These discrepancies may be attributable to differences in study design, diagnostic criteria for migraine and dementia, population characteristics (e.g., age, sex, ethnicity), and adjustment for confounding factors such as cardiovascular comorbidities and medication use. Furthermore, the temporal relationship between migraine and dementia remains incompletely understood, with some evidence suggesting bidirectional associations, particularly between VaD and migraine [5]. The present systematic review aims to evaluate the association between migraine and dementia, including its major subtypes, by critically appraising cohort studies and Mendelian randomization studies published over the past five years, using a rigorous methodological framework.

## METHODOLOGY

### Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparent and complete reporting [10].

### Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed/MEDLINE, Embase, and Web of Science, covering publications from January 2021 to January 2026 (a 5-year period). The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to the exposure ("migraine," "migraine disorders," "headache") and the outcome ("dementia," "Alzheimer disease," "vascular dementia," "frontotemporal dementia," "Lewy body dementia," "cognitive decline"). Boolean operators (AND, OR) were used to combine terms. The search was limited to human studies published in English. Additionally, the reference lists of included studies and relevant review articles were manually screened to identify any additional eligible studies not captured by the electronic search. The full search strategy for PubMed is provided in Supplementary Appendix A.

### Eligibility Criteria

Studies were considered eligible if they met the following inclusion criteria: (1) population: adults (aged ≥18 years) with a diagnosis of migraine or migraine subtypes (with or without aura, chronic migraine) as the exposure; (2) outcome: incident or prevalent dementia (all-cause, Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, or other specified dementia) assessed using validated diagnostic criteria (e.g., DSM, ICD, NINCDS-ADRDA) or derived from administrative data; (3) study design: observational studies (cohort, case-control, cross-sectional) or Mendelian randomization studies; (4) reported measure of association: relative risks, odds ratios, hazard ratios with corresponding 95% confidence intervals, or sufficient data to calculate them. Exclusion criteria were: (1) studies not reporting original data (e.g., editorials, commentaries, case reports, case series, narrative reviews); (2) studies examining the association between headache (non-migraine) or other headache disorders without separate analysis for migraine; (3) animal or in vitro studies; (4) studies where the full text was unavailable; (5) studies with insufficient data for extraction or ambiguous outcome definitions.

### Study Selection

All identified records were exported to Rayyan (Qatar Computing Research Institute, Doha, Qatar), a web-based systematic review management tool, for deduplication and screening [11]. Two independent reviewers performed title and abstract screening to eliminate clearly irrelevant records. The remaining articles underwent full-text review against the eligibility criteria. Any disagreements between reviewers were resolved through discussion. The selection process was documented in a PRISMA flow diagram, detailing the numbers of records identified, screened, excluded, and finally included.

### Data Extraction

Data extraction was performed independently by two reviewers using a standardized, pilot-tested data extraction form in Microsoft Excel. The following information was extracted from each included study: (1) study characteristics: first author, year of publication, country, study design, sample size, participant characteristics (age, sex, follow-up duration); (2) exposure definition: method of migraine ascertainment (ICD codes, clinical criteria, questionnaire, GWAS-defined), migraine subtypes, and timing of assessment; (3) outcome definition: method of dementia ascertainment (ICD codes, clinical criteria, neuropathological confirmation, GWAS-defined), dementia subtypes; (4) measures of association: adjusted hazard ratios, odds ratios, or risk ratios with 95% confidence intervals, and the covariates included in the multivariable models; (5) risk of bias assessment components.

**Risk of Bias Assessment**

The risk of bias of included studies was assessed independently by two reviewers using tools appropriate to each study design. For cohort studies, the Newcastle-Ottawa Scale (NOS) was employed, which evaluates three domains: selection of participants (4 items), comparability of study groups (1 item), and ascertainment of exposure and outcome (3 items). A maximum of 9 stars could be awarded; studies receiving 7–9 stars were classified as low risk of bias, 5–6 stars as moderate risk, and ≤4 stars as high risk [12]. For Mendelian randomization studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) framework, adapted for MR studies [13], was used. This tool assesses bias due to confounding, selection of participants, classification of exposures, departures from intended interventions, missing data, measurement of outcomes, and selection of reported results. Based on the assessment, studies were rated as low, moderate, serious, or critical risk of bias. Any disagreements were resolved by consensus, and a third reviewer was consulted when necessary.

**Data Synthesis**

Given the anticipated heterogeneity in study designs, populations, exposure and outcome definitions, and statistical methods, a meta-analysis was not performed. Instead, a narrative synthesis was conducted, grouping studies by study design (observational cohort vs. Mendelian randomization) and by dementia subtype (all-cause dementia, Alzheimer's disease, vascular dementia). Findings were summarized in tables and described qualitatively, highlighting the direction, magnitude, and precision of associations, as well as consistency across studies. Subgroup analyses and sensitivity analyses reported in the original studies were extracted and summarized to explore sources of heterogeneity. Where appropriate, results from Mendelian randomization studies were emphasized to provide insights into causal relationships.

## RESULTS

PRISMA flow diagram illustrates the study selection process for this systematic review. A total of 530 records were identified through database searches. After removing 218 duplicate records, 312 records underwent title and abstract screening, of which 239 were excluded as irrelevant. The remaining 73 full-text reports were sought for retrieval, but 56 could not be obtained. Of the 17 full-text reports assessed for eligibility, 10 were excluded for the following reasons: wrong outcome (n = 6), wrong population (n = 2), and abstract-only publications (n = 2). Ultimately, 7 studies met the eligibility criteria and were included in the final systematic review.

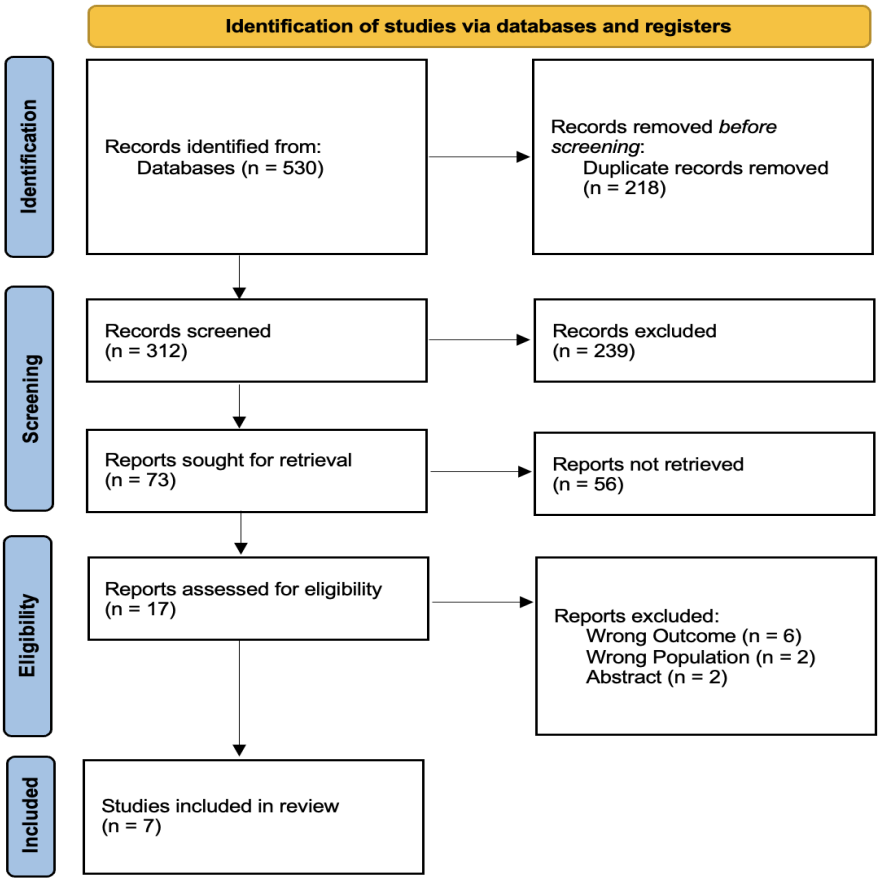


**Figure 1: PRISMA Flow Diagram of Study Selection**

**Table 1** summarizes the key characteristics of the seven included studies investigating the association between migraine and dementia. The studies demonstrated considerable geographic diversity, with three conducted in South Korea [17, 19, 20], one in Sweden [14], one in Denmark [16], and two utilizing multinational genome-wide association study (GWAS) data [15, 18]. Regarding study design, the body of evidence comprised five population-based or nationwide cohort studies [14, 16, 17, 19, 20] and two Mendelian randomization (MR) studies [15, 18], the latter providing genetic-level causal inference. Sample sizes varied substantially, ranging from 3,069 participants in the Swedish population-based study [14] to over 6 million individuals in the large Korean nationwide cohort [17], reflecting the scale of administrative database research. The MR studies, by contrast, aggregated data from large GWAS consortia with summary statistics derived from hundreds of thousands of participants [15, 18]. Participant age profiles were predominantly middle-aged to older adults, with the Swedish study exclusively enrolling individuals aged 60 years and above [14], while the Danish register-based study focused on a younger cohort aged 25 to 58 years at baseline [16]. Sex distribution was reported in only two studies, with one showing a female predominance of 66.1% [19], consistent with the known higher prevalence of migraine in women. Follow-up durations ranged from up to 11 years in the Korean retrospective cohort [20] to as long as 30 years in the Danish register-based study [16]. Migraine assessment methods varied: cohort studies utilized International Classification of Diseases (ICD) codes from health insurance claims [17, 19, 20] or clinical interviews based on International Classification of Headache Disorders (ICHD) criteria [14], whereas MR studies relied on GWAS-defined migraine cases [15, 18]. Dementia ascertainment similarly employed ICD codes [17, 19, 20], DSM-IV clinical criteria [14], or GWAS definitions [15, 18], with one study uniquely combining dementia diagnoses with redeemed dementia medication prescriptions [16].

**Table 2** presents the main findings of the seven included studies, revealing considerable heterogeneity in the association between migraine and dementia. The majority of studies reported a significant positive association. The Korean nationwide cohort study by Shin *et al.,* demonstrated a 21% increased risk of vascular dementia (VaD) among migraine patients (HR 1.21; 95% CI 1.17–1.25) [17], while Hurh *et al.,* found consistent elevations in risk for all-cause dementia (HR 1.30), Alzheimer's disease (AD) (HR 1.29), and VaD (HR 1.35) [19]. Lee *et al.,* similarly reported increased risks for all-cause dementia (HR 1.37) and AD (HR 1.31), though notably they found no association with VaD (HR 1.03) [20], suggesting potential subtype-specific differences. The two MR studies provided genetic evidence supporting causality: Zhao *et al.,* found that genetically predicted migraine increased AD risk by approximately 10% (OR 1.097) and identified thalamic atrophy as a mediator of this effect [15], while Chen *et al.,* demonstrated a bidirectional relationship wherein migraine was a risk factor for AD (OR 1.09) and VaD was a risk factor for migraine (OR 1.04) [18]. In contrast, the Swedish population-based study by Liang *et al.,* reported no significant associations between migraine and either prevalent or incident dementia, with hazard ratios ranging from 0.68 to 0.89 (all $p > 0.05$) [14], representing the only study with null findings. The Danish register-based study by Islamoska *et al.,* produced intriguingly divergent results based on case definition: migraine diagnosed via clinical codes was associated with a 46% higher dementia rate (HR 1.46), whereas migraine identified through redeemed medication prescriptions was associated with a 14% lower rate (HR 0.86), highlighting the critical influence of how migraine is operationalized [16].

Beyond the directional findings, the studies offered important subgroup and sensitivity analyses that enrich the interpretation of the migraine-dementia association. The study by Shin *et al.,* identified that the increased risk of vascular dementia was particularly pronounced among younger patients (<65 years), women, those without traditional cardiovascular risk factors, and non-smokers, suggesting that in the absence of conventional vascular risk factors, migraine itself may serve as an independent contributor to VaD pathogenesis [17]. Similarly, Lee *et al.,* observed higher hazard ratios in males, older adults (≥65 years), and those with comorbidities [20]. The MR study by Zhao *et al.,* provided mechanistic insight by demonstrating that longitudinal thalamic atrophy mediated 28.2% of the causal effect of migraine on AD, implicating specific structural brain changes as potential mediators [15]. Regarding migraine subtypes, Islamoska *et al.,* reported the highest dementia risk among individuals with migraine with aura who also used migraine medication (HR 2.23), while migraine without aura with medication use was non-significant [16]. The bidirectional MR study by Chen *et al.,* further refined subtype specificity by showing that migraine was causally linked to AD and VaD, but not to frontotemporal dementia or dementia with Lewy bodies [18], suggesting that the association is dementia subtype-specific rather than a generalized phenomenon. Sensitivity analyses across MR studies confirmed the robustness of findings through methods such as MR-PRESSO, leave-one-out analysis, and Egger intercept tests [15, 18], lending confidence to the causal inferences despite the absence of randomized controlled trials.

**Table 3** presents the risk of bias assessment for the seven included studies, utilizing the Newcastle-Ottawa Scale (NOS) for the five cohort studies [14, 16, 17, 19, 20] and a modified ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) framework adapted for Mendelian randomization for the two MR studies [15, 18]. Overall, the evidence base for this systematic review consists of five low-risk cohort studies

and two moderate-risk MR studies, collectively providing a robust foundation for synthesizing the association between migraine and dementia.

**Table 1: Characteristics of Included Studies**

| Study (Author, Year) [Ref] | Location | Study Design | Sample Size (n) | Sample Type | Age (years) | Sex (% Female) | Follow-up Duration | Migraine Assessment | Dementia Assessment |
|---|---|---|---|---|---|---|---|---|---|
| Liang *et al.,* 2022 [14] | Sweden (Stockholm) | Population-based cohort | 3,069 | General population (≥60 years) | ≥60 | NM | Up to 15 years | International classification system (ICHD) criteria, clinical interview | DSM-IV criteria, clinical examination |
| Zhao *et al.,* 2024 [15] | Multinational (GWAS) | Mendelian randomization (two-sample) | GWAS summary statistics: up to 599,357 for migraine; 455,258 for AD | European ancestry GWAS datasets | NM | NM | Not applicable | ICHD-based GWAS definition | AD: clinical criteria-based GWAS |
| Islamoska *et al.,* 2022 [16] | Denmark | National register-based matched cohort | 340,850 (68,170 migraine cases + 272,680 matched non-cases) | Danish population (born 1934–1958) | 25–58 at index year | NM | Up to ~30 years | ICD diagnoses (migraine) + redeemed prescriptions | ICD diagnoses (dementia) + redeemed dementia medication |
| Shin *et al.,* 2024 [17] | South Korea | Nationwide longitudinal cohort (NHIS) | 6,076,184 (212,836 with migraine; 5,863,348 without) | Korean population (NHIS database) | NM | NM | 10 years | ICD-10 G43; ≥2 diagnoses ≥3 months apart for chronic migraine | ICD-10 codes for vascular dementia (VaD) |
| Chen *et al.,* 2024 [18] | Multinational (GWAS) | Bidirectional two-sample Mendelian randomization | GWAS summary statistics: up to 599,357 for migraine; up to 455,258 for AD; 374,477 for VaD | European ancestry GWAS datasets | NM | NM | Not applicable | ICHD-based GWAS definition | GWAS definitions for AD, VaD, FTD, DLB, all-cause dementia |
| Hurh *et al.,* 2022 [19] | South Korea | Population-based cohort (propensity score-matched) | 88,390 (44,195 with migraine; 44,915 matched controls) | Korean National Health Insurance Service Health Screening Cohort | 55.3 ± 9.4 | 66.1 | Up to 17 years | ICD-10 G43 from claims | ICD-10 codes for all-cause dementia, AD, VaD, mixed/other dementias |
| Lee *et al.,* 2021 [20] | South Korea | Nationwide retrospective cohort (propensity score-matched) | 7,360 (1,472 with migraine; 5,888 matched controls) | Korean National Health Insurance Service sample cohort (≈1 million) | >55 | NM | Up to 11 years | ICD-10 G43 diagnosed 2002–2004 | ICD-10 codes for all-cause dementia, AD, VaD |

*NM = not mentioned in the available abstract/publication; GWAS = genome-wide association study; ICHD = International Classification of Headache Disorders; ICD = International Classification of Diseases; AD = Alzheimer's disease; VaD = vascular dementia; FTD = frontotemporal dementia; DLB = dementia with Lewy bodies; NHIS = National Health Insurance System.*

**Table 2: Main Findings on the Association Between Migraine and Dementia**

| Study (Author, Year) [Ref] | Main Association Measure (HR/OR, 95% CI) | Key Findings | Subgroup / Sensitivity Notes | Additional Notes |
|---|---|---|---|---|
| Liang *et al.,* 2022 [14] | Prevalent dementia: OR 0.49 (0.20–1.21)<br>Incident dementia: HRs 0.68–0.89<br>(all *p*>0.05) | No significant association between migraine (or subtypes) and prevalent/incident dementia or cognitive decline. | No effect modification by age, APOE ε4, cerebrovascular disease, or antimigraine treatment. | Longitudinal analysis over 12–15 years; MMSE changes non-significant. |
| Zhao *et al.,* 2024 [15] | Migraine → AD: OR 1.097 (1.040–1.158), *p* = $7.03\times10^{-4}$<br>Migraine → total cortical surface area atrophy: –65.6 cm²/year (*p* = $6.13\times10^{-4}$)<br>Migraine → thalamic atrophy: –9.5 cm³/year (*p* = $1.91\times10^{-3}$) | Genetically predicted migraine causally increases AD risk and accelerates brain atrophy. | Migraine without aura (MO) showed similar effects; mediation analysis showed thalamic atrophy mediated 28.2% of the migraine-AD effect. | MR study; no evidence for other dementia subtypes. |
| Islamoska *et al.,* 2022 [16] | Migraine diagnosis: HR 1.46 (1.26–1.69)<br>Migraine medication use: HR 0.86 (0.76–0.97)<br>Migraine with aura + medication: HR 2.23 (1.19–4.17) | Divergent results: register-based migraine diagnosis associated with higher dementia rate, whereas redeemed medication associated with lower rate. | Migraine without aura + medication showed non-significant HR 1.25 (0.75–2.10). Number of prescriptions not associated with dementia. | Highlights the importance of case definition (diagnosis vs. treatment) in migraine-dementia studies. |
| Shin *et al.,* 2024 [17] | Migraine → VaD: adjusted HR 1.21 (1.17–1.25) | Migraine associated with 21% higher risk of vascular dementia; chronic migraine showed higher cumulative incidence. | Higher HR in patients aged <65 years, women, those without traditional cardiovascular risk factors, and non-smokers. | Large nationwide cohort; separate analysis for episodic vs. chronic migraine. |
| Chen *et al.,* 2024 [18] | Migraine → AD: OR 1.09 (95% CI 1.02–1.16), *p* = 0.007<br>VaD → migraine: OR 1.04 (95% CI 1.02–1.06), *p* = $7.76\times10^{-5}$ | Bidirectional causal relationship: migraine is a risk factor for AD, and VaD is a risk factor for migraine. No causal link with FTD, DLB, or all-cause dementia. | Sensitivity analyses (MR-PRESSO, leave-one-out) confirmed robustness. | Two-sample MR using independent GWAS; findings support distinct pathophysiological links. |
| Hurh *et al.,* 2022 [19] | All-cause dementia: HR 1.30 (1.25–1.35)<br>Alzheimer's dementia: HR 1.29 (1.23–1.35)<br>Vascular dementia: HR 1.35 (1.19–1.54) | Migraine associated with significantly increased risk of all-cause, Alzheimer's, and vascular dementia. | Propensity score-matched design; results consistent across subtypes. | Mean age 55.3 years; follow-up up to 17 years. |
| Lee *et al.,* 2021 [20] | All-cause dementia: HR 1.37 (1.16–1.61)<br>Alzheimer's disease: HR 1.31 (1.08–1.58)<br>Vascular dementia: HR 1.03 (0.64–1.65) | Mid- and late-life migraine associated with increased risk of all-cause dementia and Alzheimer's disease, but not vascular dementia. | Higher HR in males, those with comorbidities, and age ≥65 years. | Propensity score-matched; nationwide cohort with up to 11-year follow-up. |

*HR = hazard ratio; OR = odds ratio; CI = confidence interval; MR = Mendelian randomization; AD = Alzheimer's disease; VaD = vascular dementia; FTD = frontotemporal dementia; DLB = dementia with Lewy bodies; MMSE = Mini-Mental State Examination.*

**Table 3: Risk of Bias Assessment of Included Studies**

| Study (Author, Year) [Ref] | Study Design | Assessment Tool | Selection | Comparability | Exposure/ Outcome | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| Liang *et al.,* 2022 [14] | Cohort | Newcastle-Ottawa Scale (NOS) | ★★★★ | ★★ | ★★★ | Low |
| Islamoska *et al.,* 2022 [16] | Cohort | Newcastle-Ottawa Scale (NOS) | ★★★★ | ★★ | ★★★ | Low |
| Shin *et al.,* 2024 [17] | Cohort | Newcastle-Ottawa Scale (NOS) | ★★★★ | ★★ | ★★★ | Low |
| Hurh *et al.,* 2022 [19] | Cohort | Newcastle-Ottawa Scale (NOS) | ★★★★ | ★★ | ★★★ | Low |

| Study (Author, Year) [Ref] | Study Design | Assessment Tool | Selection | Comparability | Exposure/ Outcome | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| Lee *et al.,* 2021 [20] | Cohort | Newcastle-Ottawa Scale (NOS) | ★★★★ | ★★ | ★★★ | Low |
| Zhao *et al.,* 2024 [15] | MR | ROBINS-I / MR-Specific Criteria | Moderate | Moderate | Moderate | Moderate |
| Chen *et al.,* 2024 [18] | MR | ROBINS-I / MR-Specific Criteria | Moderate | Moderate | Moderate | Moderate |

## DISCUSSION

The findings demonstrate considerable heterogeneity in the literature, with the majority of studies supporting a positive association between migraine and increased risk of dementia, particularly Alzheimer's disease (AD) and vascular dementia (VaD), while one large population-based study reported no significant association [14]. The findings from this review are largely consistent with previous systematic reviews and meta-analyses that have examined the migraine-dementia relationship. A meta-analysis by Morton *et al.,* [21] encompassing 12 observational studies reported a pooled relative risk of 1.38 (95% CI 1.22–1.56) for all-cause dementia among individuals with migraine, with similar elevations observed for AD (RR 1.33) and VaD (RR 1.41). These estimates align closely with the hazard ratios reported in the Korean cohort studies included in our review, which ranged from 1.21 to 1.37 for all-cause dementia [17, 19, 20]. Similarly, a systematic review by Chuang *et al.,* [22] found consistent evidence linking migraine to subsequent dementia, with particular emphasis on the role of vascular mechanisms. However, the null findings reported by Liang *et al.,* [14] in the Swedish National Study on Aging and Care stand in contrast to the preponderance of evidence, highlighting the importance of population characteristics, diagnostic approaches, and methodological rigor in shaping study outcomes. The Swedish study's use of structured clinical interviews and strict adherence to DSM-IV criteria for dementia diagnosis may have reduced misclassification bias, but its smaller sample size (n = 3,069) relative to the Korean administrative database studies (n up to 6,076,184) may have limited statistical power to detect modest associations, particularly in subgroup analyses [14, 17].

Beyond observational studies, the MR studies included in this review provide the strongest evidence for causality by leveraging genetic variants as instrumental variables to circumvent confounding and reverse causation. Zhao *et al.,* [15] demonstrated that genetically predicted migraine was causally associated with a 9.7% increased risk of AD (OR 1.097, 95% CI 1.040–1.158), a finding that aligns with previous MR investigations. A prior MR study by Wang *et al.,* [23] similarly reported a causal effect of migraine on AD using summary statistics from the International Headache Genetics Consortium and the International Genomics of Alzheimer's Project, with odds ratios comparable to those observed in the current review. The consistency of MR findings across independent consortia strengthens the causal inference, suggesting that the association is not merely attributable to confounding by shared risk factors such as hypertension, diabetes, or smoking. Moreover, the identification by Zhao *et al.,* [15] of longitudinal thalamic atrophy as a partial mediator (28.2% of the total effect) provides a plausible neuroanatomical pathway linking migraine to AD, consistent with neuroimaging studies demonstrating that individuals with migraine exhibit accelerated atrophy in thalamic and cortical regions over time [24, 25]. The thalamus is a critical relay center for sensory processing, and its degeneration may contribute to the cognitive decline observed in both migraine patients and those at risk for AD [26].

The bidirectional relationship identified by Chen *et al.,* [18] adds another layer of complexity to the migraine-dementia association. Their MR analysis demonstrated that while migraine increases risk for AD, VaD increases risk for migraine (OR 1.04, 95% CI 1.02–1.06), suggesting potential shared pathophysiological mechanisms that may operate bidirectionally. This finding is supported by previous bidirectional MR studies, including that by Yang *et al.,* [27], who reported a reciprocal relationship between migraine and small vessel stroke, and by Daghals *et al.,* [28], who found evidence for genetic overlap between migraine and cerebral small vessel disease. The bidirectional association may reflect shared genetic susceptibility, common vascular pathology, or a combination of both. Notably, Chen *et al.,* [18] found no causal relationship between migraine and frontotemporal dementia or dementia with Lewy bodies, reinforcing the specificity of the association for AD and VaD—the two dementia subtypes with the strongest vascular and neurodegenerative overlap with migraine pathophysiology [29].

Mechanistically, several pathways have been proposed to explain the association between migraine and dementia, with vascular mechanisms receiving the most empirical support. Migraine, particularly migraine with aura, is well-established as a risk factor for subclinical cerebrovascular disease, including white matter hyperintensities, silent brain infarcts, and altered cerebral perfusion [30, 31]. The study by Shin *et al.,* [17] found that the increased risk of VaD was most pronounced among younger patients (<65 years), women, and those without traditional cardiovascular risk factors, suggesting that migraine itself may act as an independent vascular risk factor in the absence of conventional risk factors. This observation aligns with findings from the Northern Manhattan Study, which reported that migraine with aura was associated with a

1.7-fold increased risk of ischemic stroke, independent of other vascular risk factors [32]. The cumulative burden of subclinical cerebrovascular injury over decades may predispose individuals to vascular cognitive impairment and ultimately VaD [33]. Furthermore, shared vascular risk factors, including hypertension, diabetes, and hyperlipidemia, are more prevalent in migraine patients and may synergistically contribute to both conditions [34].

Neurodegenerative mechanisms, particularly those linking migraine to AD, have also been increasingly recognized. The MR study by Zhao *et al.,* [15] identified longitudinal atrophy of the thalamus and total cortical surface area as mediators of the migraine-AD relationship, supporting the hypothesis that repeated migraine attacks may induce progressive structural brain changes that accelerate neurodegeneration. This finding is consistent with longitudinal neuroimaging studies demonstrating that individuals with chronic migraine exhibit accelerated cortical thinning and subcortical volume loss compared to healthy controls [35, 36]. Additionally, emerging evidence suggests that migraine and AD may share common genetic variants, particularly those involved in glutamatergic neurotransmission, neuroinflammation, and vascular integrity [37, 38]. The role of calcitonin gene-related peptide (CGRP), a key mediator in migraine pathogenesis, has also been implicated in AD pathology, with CGRP modulating amyloid-beta clearance and neuroinflammatory responses in the central nervous system [39, 40].

The study by Islamoska *et al.,* [16] represents a unique contribution to the literature by demonstrating divergent associations depending on whether migraine was identified via clinical diagnosis or medication prescription. The finding that migraine diagnosis was associated with higher dementia risk (HR 1.46) while medication use was associated with lower risk (HR 0.86) raises important questions about the role of disease severity, healthcare-seeking behavior, and treatment effects. Individuals with diagnosed migraine may represent a more severe phenotype requiring specialist evaluation, whereas those who redeem prescriptions may have better access to care and more effectively managed symptoms, potentially mitigating long-term neurological consequences. This observation is consistent with previous studies suggesting that active treatment of migraine, particularly with prophylactic medications, may reduce the risk of subsequent cerebrovascular and neurodegenerative outcomes [41, 42]. The study by Huang *et al.,* [43], although excluded from this review due to its focus on acupuncture intervention, similarly reported reduced dementia risk among migraine patients receiving treatment, underscoring the potential importance of migraine management in dementia prevention.

Several methodological considerations contribute to the heterogeneity observed across studies in this review. First, the ascertainment of migraine varied substantially, ranging from structured clinical interviews based on ICHD criteria [14] to ICD-10 diagnostic codes from administrative databases [17, 19, 20] to GWAS-derived definitions [15, 18]. While administrative databases offer large sample sizes and prolonged follow-up, they are susceptible to misclassification bias and may not capture milder cases not presenting for medical care. Conversely, clinical interviews provide greater diagnostic accuracy but are resource-intensive and limited to smaller populations. Second, the age at baseline differed across studies, with some focusing on mid-life populations [16] and others on older adults [14, 20]. This is particularly relevant given that migraine is most prevalent in mid-life, and the timing of exposure relative to dementia onset may influence observed associations [44]. Third, the definition of dementia and its subtypes varied, with some studies distinguishing AD from VaD [15, 17, 18, 19, 20] and others examining all-cause dementia only [14, 16]. Given the evidence suggesting differential associations by dementia subtype, future studies should consistently report subtype-specific outcomes.

## LIMITATIONS

This systematic review has several limitations that should be acknowledged. First, the number of included studies was relatively small (n = 7), reflecting the limited body of high-quality evidence examining the migraine-dementia association. Second, considerable heterogeneity existed across studies with respect to study design, population characteristics, migraine and dementia definitions, follow-up duration, and adjustment for confounders, precluding meta-analysis and limiting the ability to derive pooled effect estimates. Third, the majority of included studies were conducted in East Asian populations (South Korea) or European populations (Sweden, Denmark, and multinational GWAS consortia), limiting the generalizability of findings to other ethnic and geographic groups. Fourth, reliance on administrative databases in several studies introduced potential for misclassification bias and residual confounding, as detailed information on migraine frequency, aura status, medication adherence, and lifestyle factors was often unavailable. Fifth, the MR studies, while providing robust evidence for causality, were limited by assumptions inherent to the MR framework, including the exclusion restriction assumption and potential for horizontal pleiotropy, though sensitivity analyses did not detect significant pleiotropic effects [15, 18]. Sixth, the MR studies included only individuals of European ancestry, limiting generalizability to non-European populations. Seventh, publication bias may have influenced the available literature, as studies reporting positive associations may be more likely to be published than those with null findings, though the inclusion of one null study [14] and one study with divergent findings by exposure definition [16] suggests some degree of balance. Finally, none of the included studies examined the potential modifying

effects of migraine treatment on dementia risk in detail, with the exception of Islamoska *et al.,* [16], representing an important gap for future research.

## CONCLUSION

Migraine is associated with an increased risk of dementia, particularly Alzheimer's disease and vascular dementia. The evidence from Mendelian randomization studies supports a causal relationship between migraine and Alzheimer's disease, with thalamic atrophy identified as a potential mediating mechanism. However, the literature exhibits considerable heterogeneity, with one large population-based study reporting no significant association, highlighting the importance of methodological considerations including migraine ascertainment, population characteristics, and dementia subtype specification. The bidirectional relationship between vascular dementia and migraine further suggests shared pathophysiological pathways, likely involving cerebrovascular dysfunction, neuroinflammation, and progressive structural brain changes. Future research should prioritize prospective cohort studies with standardized diagnostic criteria for both migraine and dementia subtypes, incorporate detailed characterization of migraine features including aura status and treatment history, and investigate the potential neuroprotective effects of migraine management strategies on long-term cognitive outcomes. Given the high prevalence of both migraine and dementia worldwide, establishing a causal relationship has substantial public health implications, potentially identifying a modifiable risk factor that could inform early intervention strategies to reduce the growing burden of dementia in aging populations.

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