


## Original Article

# Migraine Association with Alzheimer's Disease Risk: Evidence from the UK Biobank Cohort Study and Mendelian Randomization

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**ABSTRACT: Background:** Epidemiological studies on the association between migraine and Alzheimer's disease (AD) risk have yielded inconsistent conclusions. We aimed to characterize the phenotypic and genetic relationships between migraine and AD. **Methods:** To investigate the association between migraine and the risk of AD by analyzing data from a large sample of 404,318 individuals who were initially free from all-cause dementia or cognitive impairment, utilizing the UK Biobank dataset. We employed Cox regression modeling and propensity score matching techniques to examine the relationship between migraine and subsequent occurrences of AD. Additionally, the study utilized Mendelian randomization (MR) analysis to identify the genetic relationship between migraine and the risk of AD. **Results:** Migraine patients had a significantly increased risk of developing AD, compared to non-migraine patients (adjusted hazard ratio (HR) = 2.34, 95% confidence interval (CI) = 2.01–2.74,  $P < 0.001$ ). Moreover, the propensity scores matching analyses found that migraine patients had a significantly higher risk of developing AD compared to non-migraine patients (HR = 1.85, 95%CI = 1.68–2.05,  $P < 0.001$ ). Additionally, the MR suggested that significant causal effects of migraine on AD risks were observed [odds ratio (OR) = 2.315; 95% confidence interval (CI) = 1.029–5.234;  $P = 0.002$ ]. Moreover, no evidence supported the causal effects of AD on migraine (OR = 1.000; 95%CI = 0.999–1.006;  $P = 0.971$ ). **Conclusion:** The present study concludes that migraine patients, compared to a matched control group, exhibit an increased risk of developing AD. Moreover, migraine patients exhibit an increased predisposition of genetic susceptibility to AD. These findings hold significant clinical value for early intervention and treatment of migraines to reduce the risk of AD.

**RÉSUMÉ :** L'association de la migraine avec le risque de maladie d'Alzheimer : données probantes tirées de l'étude de cohorte de la UK Biobank (la biobanque du Royaume Uni) et analysées par répartition aléatoire mendélienne. **Contexte :** Des études épidémiologiques ont déjà porté sur l'association de la migraine avec le risque de maladie d'Alzheimer (MA), mais il s'en dégage des conclusions divergentes. Aussi l'étude ici décrite avait-elle pour but de caractériser les relations phénotypiques et génétiques entre la migraine et la MA. **Méthode :** Afin d'examiner l'association de la migraine avec le risque de MA, l'équipe de recherche a procédé à une analyse de données provenant de la UK Biobank, fondée sur un imposant échantillon de 404 318 sujets exempts, au départ, de toute cause de démence ou de troubles cognitifs. Les chercheurs ont aussi eu recours à la modélisation de régression de Cox et aux techniques d'appariement des scores de propension pour examiner la relation entre la migraine et la présence ultérieure de la MA. De plus, l'équipe s'est appuyée sur une analyse par répartition aléatoire mendélienne (RAM) afin d'établir une relation génétique entre la migraine et le risque de MA. **Résultats :** Les sujets migraineux avaient un risque significativement accru de MA, comparativement aux sujets non migraineux (rapport de risques instantanés [RRI] rajusté = 2,34; intervalle de confiance [IC] à 95 % = 2,01-0,74;  $p < 0,001$ ). En outre, d'après les analyses d'appariement des scores de propension, les participants ayant des migraines connaissaient un risque significativement plus grand de MA que les sujets qui en étaient exempts (RRI = 1,85; IC à 95 % = 1,68-2,05;  $p < 0,001$ ). De plus, un effet causal important de la migraine sur le risque de MA se serait dégagé de l'analyse par RAM (risque relatif approché [RRA] = 2,315; IC à 95 % = 1,029-5,234;  $p = 0,002$ ). Par contre, rien ne permet d'établir de lien causal entre la MA et la migraine (RRA = 1,000; IC à 95 % = 0,999-1,006;  $p = 0,971$ ). **Conclusion :** D'après les résultats de l'étude, les sujets qui souffrent de migraine connaissent un risque plus grand de MA que les témoins appariés qui en sont exempts. De plus, la migraine comporte une prédisposition accrue de susceptibilité génétique à la MA. Aussi faudrait-il accorder une grande valeur clinique aux interventions et aux traitements précoces de la migraine afin de réduire le risque de MA.

**Keywords:** migraine; Alzheimer's disease; risk; causal relationship; Mendelian randomization

(Received 5 January 2024; final revisions submitted 22 February 2024; date of acceptance 28 February 2024)

## Introduction

Alzheimer's disease (AD) stands as the primary contributor to dementia, marked by the accumulation of amyloid- $\beta$  (A $\beta$ ) peptides

and neurofibrillary tangles.<sup>1–3</sup> The protracted progression of AD elicits a substantial burden of disability, engendering significant economic pressures on society in its entirety, as well as the families

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**Cite this article:** Geng C and Chen C. Migraine Association with Alzheimer's Disease Risk: Evidence from the UK Biobank Cohort Study and Mendelian Randomization. *The Canadian Journal of Neurological Sciences*, <https://doi.org/10.1017/cjn.2024.35>

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directly impacted by this ailment.<sup>3,4</sup> It's worth noting that AD is a multifactorial and complex disease, and the lack of effective treatments makes it particularly important to explore modifiable risk factors for AD and develop effective prevention and treatment strategies.<sup>5</sup>

Migraine is the most prevalent disabling neurological disorder, affecting over 15% of the world's population, which characterized by recurrent headaches and can be classified into two subtypes based on symptoms, including migraine with aura and migraine without aura.<sup>6-9</sup> Headache is an important dementia risk.<sup>10,11</sup> Several epidemiological studies also had found that migraine may be related to the AD risk.<sup>12,13</sup> However, it is important to note that the conclusions have been inconsistent.<sup>14,15</sup> Establishing the link between migraine and AD may provide evidence and new strategies for interventions and delaying subsequent cognitive decline.

We hypothesized that patients with migraine may have a higher risk of developing AD compared to individuals without migraine. Due to previous studies exploring this association have been limited by small sample sizes, cross-sectional designs and confounding factors.<sup>16</sup> Importantly, these studies have not taken into account the causal relationship between migraine and AD in the context of genetic susceptibility.<sup>17-20</sup> Thus, novel research methodologies are necessary to attain a comprehensive understanding of the intricate association between these two conditions. Therefore, in this study, we sought to extensively dissect the genetic and phenotypic relationships between migraine and AD by using the UK Biobank and bidirectional Mendelian randomizations (MR) approach, which may provide new strategies for the treatment and clinical prevention of AD.

## Materials and methods

### Data source and study population

The UK Biobank indeed is a large population-based prospective cohort study that includes over 500,000 participants, who were initially recruited between 2006 and 2010 from 22 assessment centers.<sup>21</sup> Ethical approval was granted by the North West-Haydock Research Ethics Committee (REC reference:16/NW/0274).<sup>22</sup> All participants in the study provided informed consent and underwent a baseline screening process, during which individuals self-reporting cognitive impairment or those diagnosed with all-cause dementia through hospital records were excluded. Moreover, only participants who exhibited AD outcome during follow-up were considered for analysis, with those who developed AD before experiencing migraine symptoms being excluded. Additionally, individuals who did not report any headache symptoms at baseline or follow-up were included as control subjects. A schematic diagram representing the study design is presented in Figure 1.

### Migraine

The diagnosis of migraine is based on information derived from self-reported conditions, primary healthcare data, hospital admission records and death registry records. Migraine diagnosis is determined using ICD-10 codes, as well as reading codes (2nd edition and Clinical Terms Version 3).<sup>23</sup> Participants previously diagnosed with AD are excluded from the diagnosis of migraine.

### Ascertainment of AD

In the UK Biobank cohort study, AD was determined through algorithmic methods incorporating mortality register date,

hospital inpatient records, self-reported data.<sup>24,25</sup> The specific codes from the International Classification of Diseases–Tenth Revision (ICD-10) employed for defining AD can be found in Supplemental Table 1. The follow-up for all outcomes encompassed the period up to December 31, 2021.

### Covariates

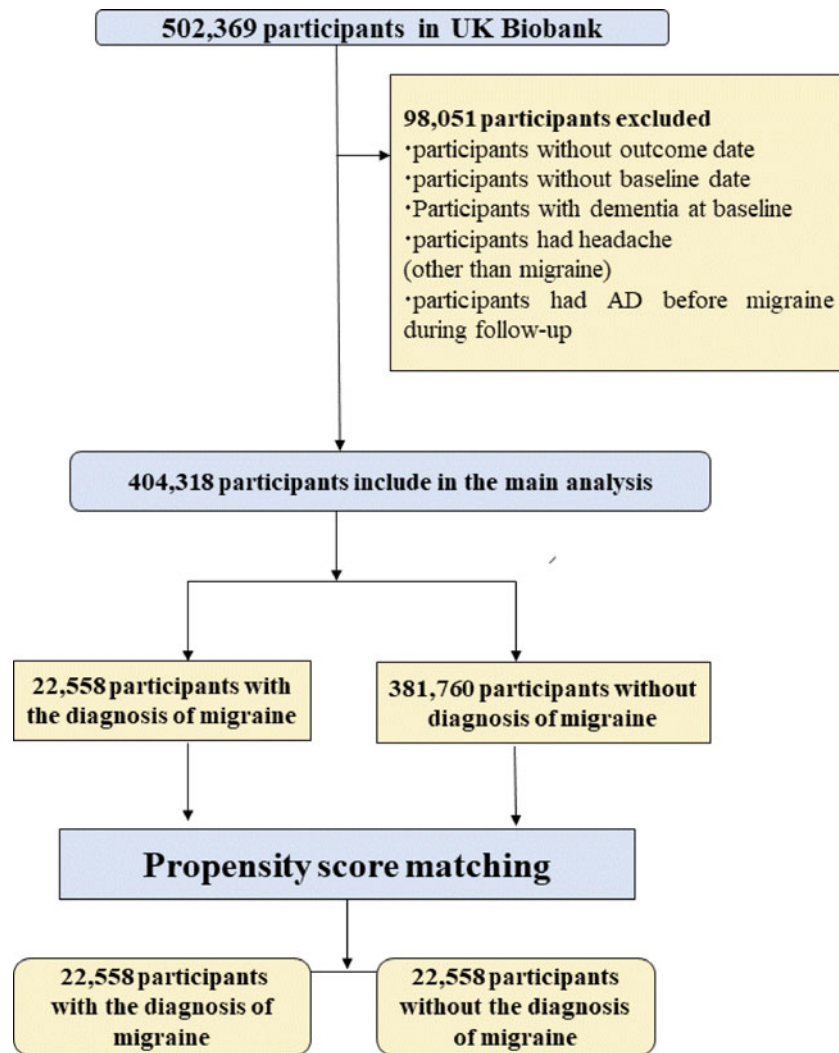
In this study, we adjusted for several potential confounding factors by including multiple covariates. Sociodemographic variables considered for adjustment included age, sex (female/male), race (white/nonwhite), education level (high school or below/college or above) and Townsend deprivation index (which reflects social deprivation status and was categorized into low/medium/high levels). The APOE  $\epsilon 4$  status was assessed using genetic database information, while tobacco use was self-reported by participants. Health conditions such as hypertension and diabetes were ascertained through self-reports and electronic medical records. Additionally, we considered various health-related factors including body mass index (BMI), hypertension, diabetes, stroke and coronary heart disease (CHD). The presence of CHD was identified through a 12-lead resting electrocardiogram recording coded according to the Minnesota system, and further confirmed by linkage to the HES database using the ICD-10 codes I20-I25. Similarly, for stroke, we utilized the same approach of linking our data to the HES database and identifying cases using the ICD-10 codes I60-I64. All of these factors were assessed at the baseline. Detailed definitions and assessments of covariates can be found in Supplemental Table 2.

### MR analysis

The bidirectional MR study was conducted to investigate the causal relationship between migraine and genetic susceptibility to AD. The overview of research was shown in Supplement Figure S1. The present study utilized a large-sample cohort of the European population, encompassing data obtained from a publicly available genome-wide association study (GWAS) dataset. The summary data on migraine was derived from the largest genome-wide meta-analysis, which comprised 102,084 migraine cases and 771,257 European ancestry controls.<sup>26</sup> For AD, summary data from the recent GWAS on AD from the Alzheimer's Disease and Dementia Consortium were utilized, which comprised 85,934 European ancestry cases and 401,577 controls.<sup>27</sup> The main analysis employed a random effects inverse variance weighted model as the primary criterion, with supplementary analyses using MR-Egger regression, weighted median and maximum likelihood estimation. Moreover, sensitivity analyses, including tests for heterogeneity and horizontal pleiotropy, were conducted using Cochran's Q, MR-Egger intercept and MR-PRESSO tests to ensure robustness of the conclusions. In addition, when migraine was used as the exposure and AD as the outcome, the measure of effect was odds ratio (OR) and its 95% CI; conversely, the effect measure was  $\beta$  and its 95% CI. The MR analysis was conducted using R version 4.2.1 and the "Two Sample MR" (version 0.5.6) and "MR-PRESSO" (version 1.0) packages in R software.<sup>28,29</sup> Significance was determined at a two-sided P-value less than 0.05.

### Statistical analyses

Baseline characteristics were compared using one-way analysis of variance and chi-square tests. Categorical variables were presented



**Figure 1.** Flowchart of participant selection for this study. AD = Alzheimer's disease.

as numbers and percentages, while continuous variables were presented as means and standard deviations.

The primary aim of our analysis was to investigate the association between migraine and incident AD. We employed Cox proportional hazard models to estimate hazard ratios (HRs) and confidence intervals (CIs) for migraine (positive vs. negative). Person-years from baseline to AD diagnosis, death or loss to follow-up, whichever occurred first, were used as the measure of time. The assumption of proportional hazards was assessed by including an exposure-time interaction term in the model.

Our analysis comprised several steps. In Model 1, we adjusted for covariates including year of birth, sex, race, smoking status, alcohol-drinking status and education level. Model 2 additionally considered the competing risk of mortality and included adjustments for year of birth, sex, race, education, BMI, current smoking, current drinking, hypertension, diabetes, coronary heart disease, stroke and APOE  $\epsilon 4$  status.

To validate our findings, subgroup analyses were performed based on factors such as sex (female/male), Townsend deprivation index (high/medium/low), education level (high school or below/college or above), smoking status (ever/never smoker), alcohol-drinking status (current/non-current drinker), BMI and APOE  $\epsilon 4$  status (carrier/non-carrier). Furthermore, we employed a propensity score methodology to select matched controls from the pool

of participants without migraine. This approach accounted for various demographic and health-related factors, including age, sex, race, education, BMI, current smoking, current alcohol consumption, hypertension, diabetes, coronary heart disease, stroke and APOE  $\epsilon 4$  status. Subsequently, within each of the four age-of-onset groups, we examined the association between migraine and AD by comparing the cases to their respective matched control subjects.

All statistical analyses were conducted using R 4.2.1, and a two-sided  $P$ -value  $< 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

Table 1 demonstrates the baseline characteristics of the study population, stratified by AD status. The population included 404,318 participants, and during the mean follow-up time of 12.31 years, for 22,558 migraine patients, with a mean age of 54.95 ( $\pm 0.05$ ) years, and a mean BMI of 27.43 ( $\pm 0.01$ ); for non-migraine individuals, with a mean age of 56.21 ( $\pm 0.01$ ) years, and a mean BMI of 27.24 ( $\pm 0.03$ ); During the mean follow-up time of 12.31 years. Additionally, we analyzed the differences in other baseline characteristics between migraine and non-migraine patients.

**Table 1.** Baseline characteristics of the study participants in the UK biobank

Characteristics	Migraine (N = 22,558)	Non-Migraine (N = 381,760)	p value
Age at migraine onset, year (mean [SD])	54.95 ± 0.05	56.21 ± 0.01	<0.001
Sex (%)			
Male	9,993 (44.34)	165,264 (43.29)	<0.001
Female	12,565 (55.66)	216,496 (56.71)	
White ethnicity (%)	18,520 (82.10)	333,086 (87.25)	<0.001
Education (%)			
High school and below	14,504 (64.6)	251,198 (65.8)	<0.001
Body mass index (mean [SD])	27.43 ± 0.01	27.24 ± 0.03	<0.001
College and above	7,940 (35.2)	149,649 (39.2)	<0.001
Townsend deprivation index			
Low	4,512 (20.0)	60,318 (15.8)	<0.001
Medium	11,595 (51.4)	214,929 (48.5)	<0.001
High	6,000 (26.6)	185,154 (36.7)	<0.001
Ever smoked (%)	8,014 (34.55)	148,544 (38.91)	<0.001
Currently drinking alcohol (%)	1,399 (6.21)	19,921 (5.22)	<0.001
APOE ε4 carrier (%)	5,121 (22.7)	82,460 (21.6)	<0.001
Hypertension	8,031 (35.6)	133,234 (34.9)	<0.001
Diabetes	3,654 (16.2)	68,335 (17.9)	<0.001
Coronary heart disease	2,549 (11.3)	47,720 (12.5)	<0.001
Stroke	722 (3.2)	12,979 (3.4)	<0.001

SD = standard deviation. Data are presented as n (%) and mean (SD). The p values are derived using Student's t test, Mann-Whitney U test or  $\chi^2$  test.

**Table 2.** Associations between migraine and incident AD among total participants (N = 404,318)

Outcome	Migraine vs Controls	p value <sup>a</sup>
Before using propensity score matching (N = 404,318)		
Model 1 <sup>a</sup>	2.47 (2.11–2.88)	<0.001
Model 2 <sup>b</sup>	2.34 (2.01–2.74)	<0.001
After using propensity score matching (N = 45,116)		
Model 1 <sup>a</sup>	2.02 (1.93–2.23)	<0.001
Model 2 <sup>b</sup>	1.85 (1.68–2.05)	<0.001

AD = Alzheimer's disease; CI = confidence intervals; HR = hazard ratio. Values are HR (95% CI), unless otherwise indicated.

<sup>a</sup> Adjusted for covariates including year of birth, sex, race and education.

<sup>b</sup> Adjusted for competing risk of deaths and covariates including year of birth, sex, race, education, BMI, current smoking, current drinking, hypertension, diabetes, coronary heart disease, stroke and ApoE4 carriers.

### Association between migraine and AD risk among patients with migraine

As shown in Table 2 and after adjusting for multiple factors, migraine patients had a significantly increased risk of developing AD compared to non-migraine patients, with a multivariable-adjusted hazard ratio (HR) of 2.34, 95% confidence interval (CI) of 2.01–2.74,  $P < 0.001$ ; Additionally, using propensity score matching, one control participant was randomly selected for each

migraine patient from the pool of subjects without migraine, we separately analyzed the association between migraine and AD in both the group of migraine patients and their matched control group participants. After propensity score matching, a total of 45,116 migraine participants and 45,116 matched control participants were included in this analysis. As shown in Table 2, after adjusting for multiple factors, migraine patients had a significantly higher risk of developing AD compared to non-migraine patients (HR = 1.85, 95%CI = 1.68–2.05,  $P < 0.001$ ).

### Causal relationship between migraine and AD

In the analysis of the causal relationship between migraine and AD. Initially, 59 SNPs were obtained as IVs after excluding palindromic SNPs and SNPs related to confounding factors. The F-statistic scores of all these selected SNPs were over 10, indicating that the strength of the instruments was robust. Using the IVW-based method, the MR analysis demonstrated significant correlation between genetically determined migraine and AD [odds ratio (OR) = 2.315; 95% confidence interval (CI) = 1.029–5.234;  $P = 0.002$ ] (Table 3 and Fig. 2a). In addition, there was no evidence of heterogeneity (MR-Egger regression:  $Q = 71.05$ ,  $p = 0.099$ ; IVW model:  $Q = 71.16$ ,  $p = 0.114$ ) and horizontal pleiotropy (MR-Egger intercept and MR-PRESSO tests, all  $p > 0.05$ ). Moreover, the leave-one-out sensitivity analysis further confirmed that no single SNP was driving the causal effect, indicating that this study is stable (Fig. 3a).

### Causal relationship between AD and migraine

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## Discussion

This study evaluated the association between migraine and AD using the UK Biobank cohort and found that migraine patients had a higher incidence of AD compared to non-migraine patients. Additionally, to the best of our knowledge, the present study firstly demonstrated that migraine patients performed an increased tendency toward genetic susceptibility to AD by using MR. Therefore, our findings had provided valuable insights into the potential causal relationship between these two conditions.

Several studies have shown associations between headache and dementia.<sup>11,30,31</sup> However, associations between migraine and AD development have been conflicting. The variability of outcomes

**Table 3.** The result of the MR study and reverse MR study

Exposure	Outcome	Method	SNP (n)	$\beta$	SE	p-value	OR (95CI%)
Migraine	AD	MR Egger	59	0.333	0.744	0.200	1.396 (0.312–3.242)
		Weighted median	59	0.172	0.799	0.007	1.188 (1.240–2.864)
		Inverse variance weighted	59	0.842	0.586	0.002	2.315 (1.029–5.234)
		Simple mode	59	0.213	0.773	0.075	1.237 (0.948–2.310)
		Weighted mode	59	0.277	0.316	0.016	1.320 (1.602–2.196)
AD	Migraine	MR Egger	58	0.001	0.004	0.795	1.001 (0.998–1.004)
		Weighted median	58	0.001	0.001	0.674	1.001 (0.999–1.003)
		Inverse variance weighted	58	0.000	0.001	0.971	1.000 (0.999–1.001)
		Simple mode	58	0.001	0.002	0.595	1.002 (0.999–1.006)
		Weighted mode	58	0.000	0.001	0.741	1.001 (0.999–1.003)

OR = odds ratio; CI = confidence interval; MR = Mendelian randomization; SNPs = single nucleotide polymorphisms; NA = not available; AD = Alzheimer's disease; SE = standard error.

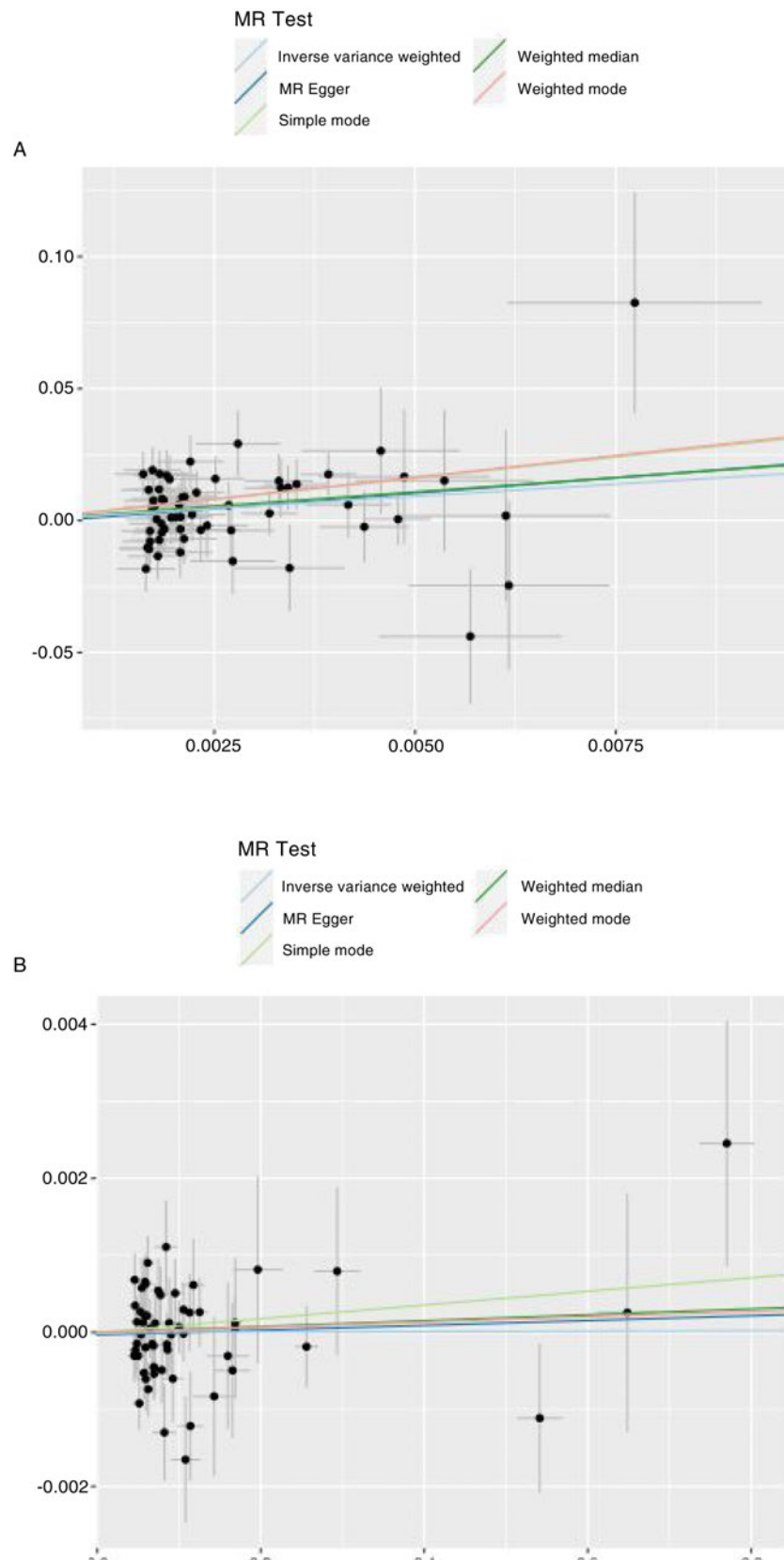
across different studies may be a contributing factor to the inconsistent results.<sup>13</sup> A meta-analysis including four case-control studies found a significant negative correlation between migraine and AD.<sup>32</sup> Conversely, other studies have shown that migraine significantly increases the risk of dementia,<sup>31,33</sup> but this effect may be limited to dementia subtypes, such as vascular dementia,<sup>10</sup> specific subgroups, such as women<sup>34</sup> or to broader headache disorders or non-migraine cases.<sup>35</sup> Additionally, prior cohort studies also confirmed that migraine patients may be associated with the higher risk of AD,<sup>36–39</sup> which was consistent with our finding. It is important to note that after controlling for all potential confounding factors using propensity score matching, migraine patients showed an increased risk of AD compared to matched non-migraine controls, which was the main innovation of the current study in controlling confounding factors, providing more robust conclusions. Therefore, it should be closely monitored and screen cognitive function changes in migraine patients in order to detect cognitive impairment early and enable timely intervention to prevent or at least delay the onset and progression of AD.

It is important to note that MR is a statistical technique employed in epidemiology and genetics to ascertain causal relationships between risk factors and outcomes.<sup>40,41</sup> MR is based on the principles of Mendelian genetics, which describe how genetic variations are randomly allocated during meiosis.<sup>42</sup> This method utilizes instrumental variables, particularly genetic variants such as single nucleotide polymorphisms (SNPs) associated with the relevant risk factor, to explore whether the selected risk factor has a causal impact on the outcome of interest.<sup>43</sup> In the absence of randomized controlled trials (RCTs), MR studies represent an alternative strategy for causal inference as genetic variations are randomly allocated during meiosis, thereby introducing an additional layer of data compared to observational studies.<sup>20,44</sup> Consequently, MR offers advantages over traditional observational research, reducing the risk of confounding and reverse causation, making it a preferred tool for investigating causal relationships in epidemiological research.<sup>45</sup> The bidirectional MR results of this study demonstrate an increased genetic susceptibility to AD in individuals with migraine, further reinforcing the evidence for migraine as a risk factor for AD and providing valuable insights for the development of novel prevention and treatment strategies for AD.

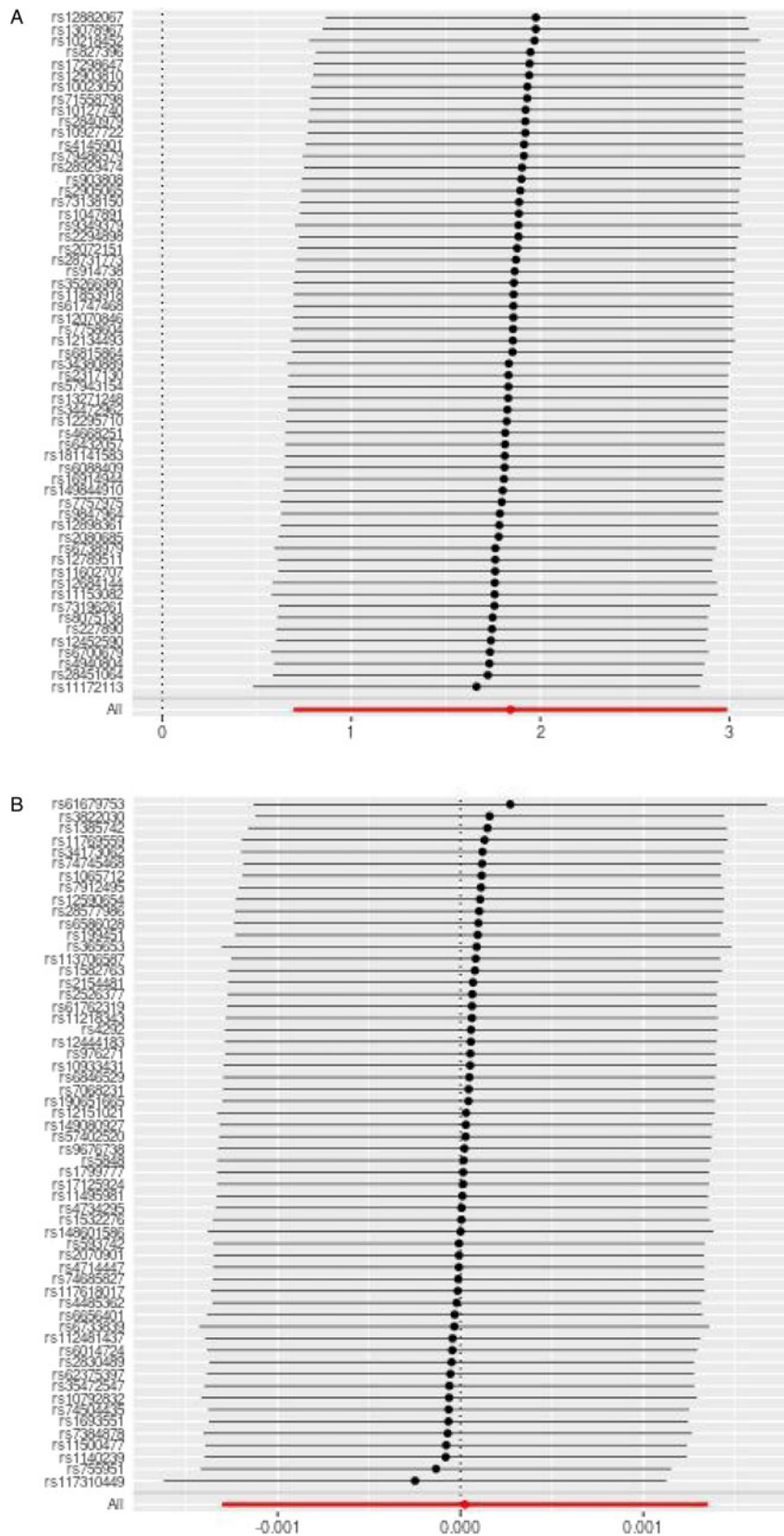
Several hypothetical mechanisms may underlie the link between migraine and AD risk. On the one hand, Oxidative stress and inflammatory responses have been identified as key risk factors for migraine attacks.<sup>46,47</sup> Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of glucocorticoids and HPA axis dysregulation.<sup>48</sup> Moreover, research evidence supports an association between HPA axis dysregulation and amyloid deposition, as well as synaptic plasticity disruption related to the progression of AD.<sup>49,50</sup> On the other hand, the association between migraine and AD may also be influenced by genetic factors. Individuals with familial AD due to presenilin-1 mutations are more likely to suffer from migraine or recurrent headaches.<sup>51</sup> Additionally, studies had found that chromosomes 1 and 19 are associated with both migraine and AD.<sup>52</sup> Further investigation of these or other genotypes may help to elucidate the association between migraine and AD, as well as identify high-risk individuals. However, the exact mechanisms still require more research to fully understand.

The strengths of our study are multifaceted. Firstly, the inclusion of a large-sample size enabled the precise identification of statistically significant associations between the onset of migraines and subsequent development of AD. Moreover, propensity score matching methodology was also employed, reducing confounding bias and ensuring the robustness of our findings. Additionally, the utilization of the UK Biobank algorithm-defined outcome provided a standardized and reliable approach to defining cases of AD, enhancing the validity of our results. Moreover, our use of MR analysis offered primary evidence for causative associations between migraines and AD. Overall, by diligently accounting for confounding variables through propensity score matching and leveraging precise data from a sizable sample, our study offers valuable insights into the relationship between migraines and subsequent AD.

However, our study has certain limitations. Firstly, its observational nature precludes the establishment of causal relationships. Moreover, the selection of the study population did not employ systematic sampling methods, potentially impacting the generalizability of our findings to other ethnic groups and the wider UK population. Therefore, caution must be exercised when extrapolating the results, as they may only apply to white individuals in the UK. Future investigations in diverse populations are necessary to validate our findings. Secondly,



**Figure 2.** Scatter plot of genetic correlation between migraine and AD using four MR methods. **A:** Evaluation the effect of migraine on AD **B:** Evaluation the effect of AD on migraine. MR = Mendelian randomization.



**Figure 3.** Leave-one-out analysis of the MR results between migraine and Alzheimer's disease (AD) using four MR methods. **A:** Evaluation the effect of migraine on AD **B:** Evaluation the effect of AD on migraine. MR = Mendelian randomization.

despite controlling for various potential confounders implicated in the pathogenesis of AD, residual confounding may persist due to unmeasured factors within the UK Biobank dataset. Thirdly, underdiagnosis and underreporting of AD in medical records could have introduced misclassification bias, affecting the estimation of associations. While the diagnostic accuracy of dementia is generally high, this limitation should not be overlooked. Additionally, we did not explore the potential of migraine medications in reducing the risk of AD, an important avenue for future research.

## Conclusion

In conclusion, the present study concludes that migraine patients, compared to a matched control group, exhibit an increased risk of developing AD. Moreover, migraine patients exhibit an increased predisposition of genetic susceptibility to AD. These findings hold significant clinical value for early intervention and treatment of migraines to reduce the risk of AD. However, further research is needed to synthesize our findings and elucidate the underlying pathological and physiological mechanisms between migraine and AD.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/cjn.2024.35>.

**Acknowledgements.** The author expresses his profound gratitude to the establishers and participants of the GWAS databases for their invaluable contributions, which facilitated the successful execution of this MR study.

**Data availability statement.** The authors acknowledge and appreciate the effort and involvement of the UK Biobank participants and staff in this study; Additionally, the datasets analyzed for this study can be found in the IEU Open GWAS project ([mrcieu.ac.uk](http://mrcieu.ac.uk)).

**Author contributions.** G-CF: Study concept, design, software and paper writing. C-C: Dissertation Revision. All authors read and approved the final manuscript.

**Funding statement.** None.

**Competing interests.** None.

**Ethics approval.** UK Biobank received ethical approval from the National Health Service North West Centre for Research Ethics Committee (Ref: 11/NW/0382); Additionally, the MR analysis used summary GWAS data publicly available from GWASs. All these GWAS summary data are publicly available, and all studies included were approved by relevant ethics committee. All participants signed written informed consent prior to participation.

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