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REVIEW

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Association between proton pump inhibitor use and migraine: a systematic review and meta-analysis

Prakasini Satapathy[1,2*†], Mahalaqua Nazli Khatib[3*†], Nasir Vadia[4], Soumya V. Menon[5], Kattela Chennakesavulu[6], Rajashree Panigrahi[7], Muhammed Shabil[8,9], Mahendra Singh[10,11], Sanjit Sah[12,13,14], Doddolla Lingamaiah[15,16†], Khang Wen Goh[2,17], Edward Mawejje[18*] and Ganesh Bushi[19,20*]

Abstract

Background Migraine is a common neurological disorder with potential pharmacological triggers. Proton pump inhibitors (PPIs), commonly prescribed for managing gastroesophageal reflux disease and other acid-related gastrointestinal disorders, have been linked to headaches. However, their association with migraine remains unclear. This systematic review and meta-analysis assessed the association between PPI use and the incidence of migraine.

Method A systematic search of PubMed, Embase, and Web of Science was conducted in accordance with the PRISMA framework and registered with PROSPERO (ID: CRD42025644604) to enhance transparency. The search, conducted up to January 2024, included studies focusing on the association between migraine and PPI use. Data screening and extraction were performed using Nested Knowledge software. Meta-analyses were conducted in R software, with heterogeneity assessed through the I^2 statistic. Pooled adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Sensitivity analyses were also performed to assess the robustness of the results. Gender and migraine subtype were considered in subgroup analyses. Additionally, the GRADE approach was applied to assess the certainty of the evidence across the pooled outcomes.

Results Five studies involving over 1.5 million participants met the inclusion criteria. The overall pooled adjusted odds ratio (aOR) was 2.508 (95% CI, 0.790–7.969; $I^2 = 91.2\%$). However, there was a significant association in males (aOR, 3.875; 95% CI, 2.413–6.222; $I^2 = 0\%$) but not in females (aOR, 2.475; 95% CI, 0.563–10.890; $I^2 = 91.1\%$). No significant differences were found between migraine types: with aura (aOR, 2.079; 95% CI, 0.945–4.576; $I^2 = 25.4\%$) and

†Prakasini Satapathy, Mahalaqua Nazli Khatib and Doddolla Lingamaiah contributed equally as first authors.

*Correspondence:
Prakasini Satapathy
prakasini.satapathy@gmail.com
Mahalaqua Nazli Khatib
nazlikhatib@dmiher.edu.in
Edward Mawejje
emawejje62@gmail.com
Ganesh Bushi
ganeshbushi313@gmail.com

Full list of author information is available at the end of the article

without aura (aOR, 2.524; 95% CI, 0.807–7.896; $I^2 = 96.5\%$). The GRADE assessment indicated a very low certainty of the evidence.

Conclusion This review found no significant overall association between PPI use and migraine. However, a significant association was observed in males but not in females. Further research is needed to clarify this association and explore the underlying causality mechanisms, and migraine subtypes, particularly why the association appears more pronounced in males.

Clinical trial number Not applicable.

Keywords Migraine, Proton pump inhibitors, Systematic review, Meta-analysis

Introduction

Migraine is a prevalent neurological disorder affecting approximately 14–15% of the global population annually, with a higher incidence among women [1, 2]. Characterized by recurrent, pulsatile headaches, often accompanied by nausea, photophobia, and phonophobia [3]. The etiology of migraine involves a complex interplay of genetic, environmental, and neurological factors [4]. According to the International Classification of Diseases, 11th Revision (ICD-11), migraine is categorized under code 8A80, subdivided into migraine with aura, migraine without aura and chronic migraine [5, 6]. These classifications emphasize variations in frequency, duration, and symptomatology of the attacks. The pathophysiology of migraine is characterized by the activation of the trigeminovascular system, which triggers neurogenic inflammation, cortical spreading depression, and changes in cerebral blood flow, contributing to the typical migraine symptoms [7, 8]. Despite its well-understood clinical features and pathophysiological mechanisms, the precise triggers of migraine remain highly individualized, with pharmacological agents increasingly recognized as potential contributors to the onset or exacerbation of attacks.

Proton pump inhibitors (PPIs) are medications predominantly prescribed to suppress gastric acid production, thus managing peptic ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome [9]. These drugs function by irreversibly binding to and inhibiting the H+/K + ATPase enzyme system at the secretory surface of gastric parietal cells. This inhibition blocks the final step in acid production, thereby reducing gastric acidity [10]. While PPIs are deemed safe for short-term use, their prolonged usage has been implicated in various adverse effects, ranging from minor gastrointestinal disturbances to serious complications such as renal dysfunction and electrolyte imbalances [11]. More recently, neurological side effects like headaches have been reported, suggesting potential neurophysiological impacts that might exacerbate or trigger migraine episodes in susceptible individuals [12]. This may be due to influenced by its effects on neurotransmitter systems, particularly serotonin, which plays a crucial role in migraine pathogenesis [13]. Additionally, changes in gastric pH from PPI use could impact serotonin activity and potentially alter gut microbiota [14–16]. This alteration might influence the gut-brain axis, triggering migraines through disrupted gastric signaling and changes in nutrient absorption [17–19].

Although some observational studies suggest a possible association between PPI use and increased migraine episodes, the scientific evidence remains inconclusive due to inconsistencies in previous research. Some studies show a significant relationship, while others report no significant association [11, 13, 20]. The variability in study outcomes includes differences in effect sizes. These inconsistencies highlight the need for further investigation. The widespread use of PPIs and the significant health burden posed by migraines underscore the importance of understanding this potential relationship. By conducting this systematic review and meta-analysis, we aimed to synthesize the existing literature and assess the relationship between PPI usage and migraine. This synthesis aims to provide more definitive insights that can aid in refining clinical decision-making and guide future pharmacological research.

Methods

This systematic review and meta-analysis followed the PRISMA guidelines (Table S1) [21]. Furthermore, the review protocol was preregistered with PROSPERO (CRD42025644604).

Eligibility criteria

Studies eligible for inclusion had to meet the following criteria: The population included individuals using proton pump inhibitors (PPIs), with studies involving combined medication use (e.g., PPIs with H2 receptor antagonists or other medications) excluded unless the effects of PPIs were clearly separated. The primary exposure was PPI use, including omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. Eligible studies needed to assess the incidence of migraine, with a comparison group of non-PPI users. Eligible study designs included clinical trials (randomized or non-randomized), cohort studies, case-control studies, case-crossover studies, and

cross-sectional studies investigating the PPI-migraine association. Studies were excluded if they did not assess migraine, focused on unrelated outcomes, or lacked a clear methodology to assess the relationship between PPI use and migraine. Additionally, letters to the editor, commentaries, case reports, case series, abstracts, and review articles were excluded due to the lack of primary data (Table S2).

Search strategy

A thorough search strategy was employed to identify relevant studies examining the association of migraine with PPI use. We conducted searches in three major electronic databases: PubMed, Embase, and Web of Science. The search terms used included "Migraine Disorders" OR "Migraine Headache" OR "Migraine" OR "Chronic Migraine," combined with "Proton Pump Inhibitors" OR "Proton Pump Inhibitor" OR specific PPI medications (e.g., omeprazole, esomeprazole, lansoprazole). The search was limited to studies published in English up until January 2024 due to the linguistic capabilities of our team and the predominance of relevant literature published in English. While this restriction may limit the inclusion of studies in other languages, it was necessary to maintain consistency and feasibility in the review process. The complete search strategy for each database is provided in Table S3.

Screening

The Nested Knowledge, a semi-automatic software, was used to assist in the screening and data extraction process. After importing the search results from each database, it automatically removed any duplicate records. Following deduplication, two independent reviewers manually screened the titles and abstracts of the remaining records to identify relevant studies based on the predefined edibility criteria [22–24]. Full texts of potentially eligible studies were then retrieved manually for a more thorough assessment. Any disagreements between the reviewers regarding study inclusion were resolved through discussion or by consulting a third reviewer.

Data extraction

Once the final set of eligible studies was determined, data extraction was performed using a pre-defined data sheet that included details on study characteristics (such as author, publication year, and study design), participant demographics, PPI usage (including drug type, dosage, and duration), and outcomes associated with migraine occurrence. After data confirmation, the tagging function in the Nested Knowledge system was used to extract data by two independent reviewers to ensure accuracy. A third reviewer was involved to resolve conflicts and minimize errors, ensuring the robustness of the data for subsequent analysis.

Quality assessment

The included studies were evaluated for methodological quality using different versions of the Newcastle-Ottawa Scale (NOS) appropriate for case-control, cohort, and cross-sectional studies [25]. The assessment focused on risk of bias related to participant selection, the comparability of study groups, and outcome assessment. Two reviewers independently rated each study, and any disagreements were resolved through consultation with a third reviewer. Based on the quality assessment scores, studies were categorized as having low, moderate, or high risk of bias (Table S4-S6).

Evidence synthesis

The meta-analysis was conducted using R software (version 4.4) to assess the overall impact of PPI use on migraine [26]. Both random-effects and fixed-effects models were applied. The random-effects model was selected due to the high statistical heterogeneity observed across studies, indicating variability in study outcomes beyond chance [27]. The fixed-effects model was also used to evaluate the results under the assumption that all studies estimate the same effect. Pooled adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated to assess the relationship between PPI use and migraine. Statistical heterogeneity was evaluated using the I^2 statistic [28]. Subgroup analyses were performed based on factors such as gender and migraine subtype. Sensitivity analyses were conducted using a leave-one-out approach, excluding studies with a high risk of bias to test the robustness of the findings. A methodological limitation of this analysis was the inability to assess publication bias due to the inclusion of fewer than 10 studies. Consequently, funnel plots and Egger's test were not conducted. Additionally, meta-regression was not applied due to the limited number of studies included [29].

Certainty of evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach was used to assess factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias, leading to downgrading or Upgrading the evidence [30].

Results

Literature search

The literature search yielded a total of 583 records from databases. After removing 12 duplicates, 571 records remained for screening. Of these, 42 reports were available for full-text retrieval after 529 items were eliminated based on title and abstract. After evaluating each of the

42 full-text papers for eligibility, 37 were disqualified for the following reasons: no results of interest [20], no population of interest [7], editorial or opinion pieces [2], and reviews [8]. Consequently, 5 papers met the inclusion criteria. For further details, please refer to the PRISMA diagram (Fig. 1).

Summary characteristics of studies

The final analysis included five studies, representing diverse populations across different countries. Two studies were from the US, while Taiwan, Korea, and the UK each contributed one study. The population sizes ranged from 44,000 to over 700,000. The study designs included one case-control study, one case-crossover study, one cross-sectional study, and two cohort studies. The majority of the studies used ICD criteria for diagnosis. Study periods ranged from 1998 to 2015, and the mean age of participants varied from 40 to 58 years. The proportion of male participants ranged from 22.6 to 52%. Study periods, data sources, population characteristics, exposure and non-exposure groups, follow-up duration, and adjusted variables (Table 1).

Meta-analysis

Association of PPI use and migraine

The meta-analysis, based on three studies estimated the pooled aOR using a random-effects model. The pooled aOR for all studies was 2.508 (95% CI: 0.790 to 7.969), with substantial heterogeneity (I^2 = 91.2%), suggesting a non-significant increase in the odds of migraine (Fig. 2). We also performed the pooled aOR using a fixed-effects model, which resulted in a pooled aOR of 2.257 (95% CI: 1.769 to 2.880) (Figure S1). To determine the robustness of these findings, a leave-one-out sensitivity analysis of the random-effects model was conducted. This analysis showed that excluding the study by Slavin et al. 2024 or Kang et al. 2022 resulted in significant findings: 4.651 (95% CI: 3.166 to 6.833) and 1.390 (95% CI: 1.014 to 1.904), respectively, with 0% heterogeneity. In contrast, omitting the study by Pisanu et al. 2021 increased the heterogeneity to 95.6% (Figure S2).

Gender-specific association between use of PPI and migraine

Based on two studies, the meta-analysis assessed the association between PPI use and migraine within gender subgroups (Fig. 3). For males, the pooled aOR was 3.875

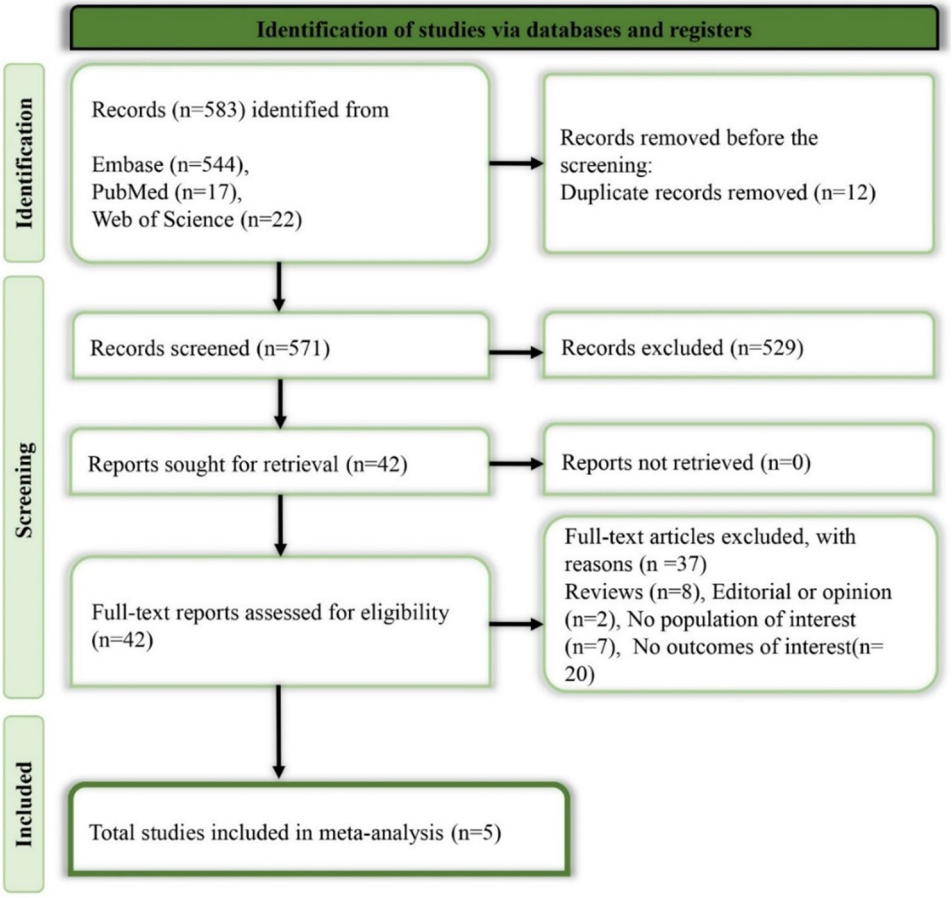

Fig. 1 PRISMA flow chart showing the studies selection process

Table 1 Summary characteristics of included studies

Study ID	Country	Study design	Male %	Mean age	Sample size	Study period	Diagnosis criteria	Data source and population characteristics	Exposure and non-exposure groups	Follow-up duration	Adjusted variables	Key findings
Pisanu,2021 [38]	UK	Retrospective cohort study	Case-22.6 Control-46.6	57	468,280	2006–2010	ICD-10 criteria	Data from UKB	Exposure group: Participants treated with PPIs Non-exposure group: Participants not treated with PPIs	Avg. follow-up of 10.06 years	Gender, age, BMI, comorbidities, med intake, dose intake	Migraines more common in PPI-treated participants, especially among men and those with slower PPI metabolism CYP2C19 phenotypes.
Liang,2015 [13]	Taiwan	Case-crossover design	41.2	41.9	314,210	1998–2010	ICD-9 criteria	Data from Taiwan NHIRD (1995–2010)	Patients with PPI prescriptions during case periods	NA	Age, sex, income, region, BP, BG, cholesterol, weight, smoking, alcohol consumption, GERD treatment, treatment duration, co-medications	PPI use linked to a higher risk of acute headache, varying risks by gender and specific PPI.
Kang,2022 [20]	Korea	Case-control study	33.6	58.6	44,168	2002–2015	ICD-10 criteria	Data from KNHIS-HSC	Exposure group: Participants with PPI use history within 30–365 days prior to migraine diagnosis Non-exposure group: No PPI use in the specified timeframe	Data from 2002 to 2015	Age, sex, income, region, BP, BG, cholesterol, weight, smoking, alcohol consumption, GERD treatment, treatment duration, co-medications	Potential association between prior PPI use and onset of migraines, with or without aura, in the Korean population.
Makunts,2019 [31]	US	Retrospective cohort study	28.52	58.3	732,696	1999–2012	NA	Data from FDA AERS	Exposure group: Patients using PPIs as monotherapy Non-exposure: Patients using H2RAs as monotherapy	Post-marketing analysis from Jan 2004 to Mar 2018	Age, sex, race, poverty, BMI, caffeine intake, alcohol intake, HEI-2010	Significant link between PPI monotherapy and neurological or neurosensory ADRs.
Slavin,2024 [39]	US	Cross-sectional study	52	40–60 (maximum)	11,818	1999–2004	Self-reported data from NHANES	Data from NHANES	Exposure group: Participants using acid-suppression therapy including PPIs, H2RAs Non-exposure group: Participants not using any acid-suppression therapy.	Cross-sectional analysis; data from 1999 to 2004	Age, sex, race, poverty, BMI, caffeine intake, alcohol intake, HEI-2010	Positive association between migraines or severe headaches and use of acid-suppressing medications, including PPIs, H2RAs, and antacids.

Abbreviations: US: United States, UKB: UK Biobank, PPIs: Proton Pump Inhibitors, NHIRD: National Health Insurance Research Database, BP: Blood Pressure, BG: Blood Glucose, GERD: Gastroesophageal Reflux Disease, KNHIS-HSC: Korean National Health Insurance Service-Health Screening Cohort, NA: Not Available, FDA AERS: FDA Adverse Event Reporting System, H2RAs: Histamine-2 Receptor Antagonists, NHANES: National Health and Nutrition Examination Survey, HEI-2010: Healthy Eating Index 2010

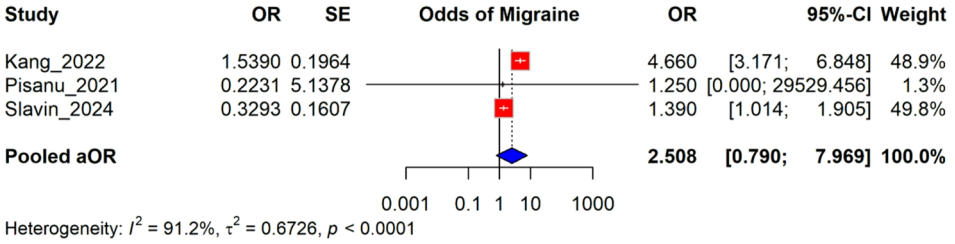

Fig. 2 Forest plot illustrating the association between PPI use and migraine

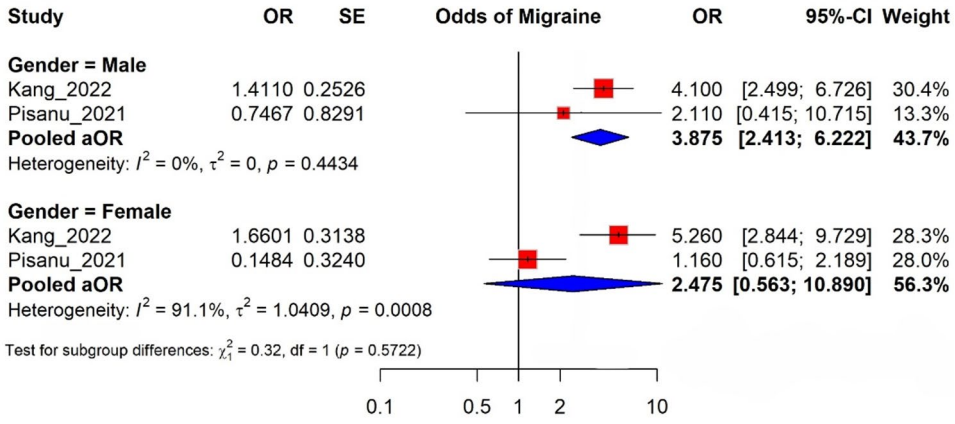

Fig. 3 Forest plot illustrating the gender-specific association between use of PPI and migraine

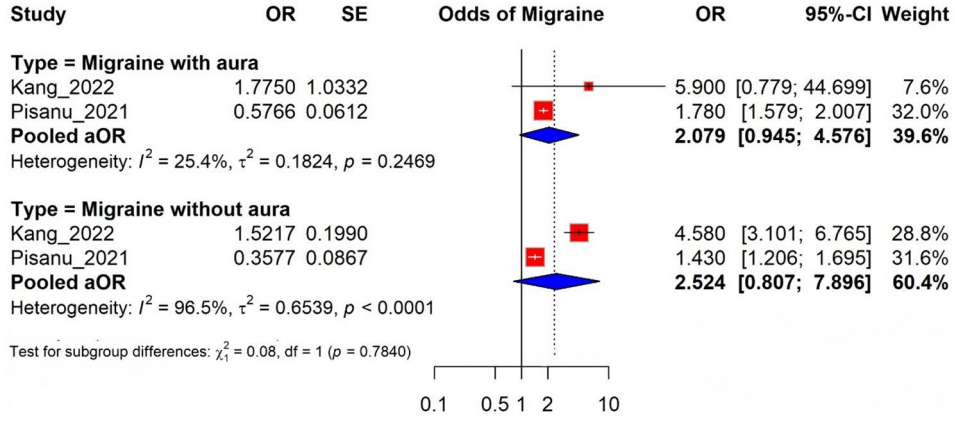

Fig. 4 Forest plot illustrating the association between use of PPI and migraine subtypes

(95% CI: 2.413–6.222), indicating a significant increase, with no significant heterogeneity (I^2 = 0%). For females, the pooled aOR was 2.475 (95% CI: 0.563–10.890), with a high degree of heterogeneity (I^2 = 91.1%). The higher heterogeneity in the female subgroup may be attributed to differences in study design, as the studies included in this analysis were methodologically diverse. Specifically, the study by Pisanu (2021) was a retrospective cohort study, while the study by Kang (2022) was a case-control study. While PPI use may also increase migraine risk in females, the evidence remains less consistent. The subgroup analysis did not show significant differences between males and females (p-value = 0.57), indicating that the association between PPI use and migraine was not significantly different between the genders. Further investigation into the factors contributing to the high heterogeneity in the female subgroup is warranted.

Association between use of PPI and migraine subtypes

Based on two studies, the meta-analysis evaluated the association between PPI use and migraine based on migraine type (with aura vs. without aura) (Fig. 4). For migraine with aura, the pooled aOR was 2.079 (95% CI: 0.945; 4.576), indicating a modest but non-significant

Table 2 GRADE approach depicting the certainty of the evidence

Certainty assessment							Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)		
Association between PPI use and migraine										
3	Non-randomized studies	serious	serious	not serious	serious	none	**OR 2.508** (0.790 to 7.969)	- **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL

increase, with low heterogeneity (I^2 = 25.4%). For migraine without aura, the pooled aOR was 2.524 (95% CI: 0.807; 7.896), with significant heterogeneity (I^2 = 96.5%), highlighting substantial variation across studies. However, these results are based on only two studies, so they may not be entirely reliable. The findings for both types of migraine suggest a non-significant association between PPI use and increased odds of migraine, but the evidence remains inconsistent. The subgroup analysis did not show a significant difference between the two migraine types (p-value = 0.78).

Qualitative synthesis

Two studies were qualitatively synthesized due to methodological differences, including differences in control groups and the short-term timeframes used. Makunts et al. (2019) assessed a short-term timeframe, while Liang et al. (2015) used a different control group. These differences made pooling the data inappropriate for meta-analysis. Liang et al. 2015 [13] reported a slight but significant increase odds of migraine with PPI use (aOR 1.01, 95% CI: 1.00–1.02) in a Taiwanese cohort of 314,210 individuals using a case-crossover design. In contrast, Makunts et al. 2019 [31] found a more pronounced association (OR 3.27, 95% CI: 2.90–3.69) using ADR data from a U.S. cohort of 732,696 individuals, comparing PPI users to those on H2 receptor antagonists. These differences highlight the need for cautious interpretation due to variations in control groups and diagnostic methods.

GRADE approach

The certainty of the evidence for Migraine outcomes was rated as very low due to serious concerns about risk of bias, inconsistency and imprecision across studies. Specifically, the studies were non-randomized, displayed significant variability in outcomes (serious inconsistency), and had wide confidence intervals (serious imprecision). Consequently, the evidence supporting the link between PPI use and increased odds of migraine is considered very low in certainty but critical in importance, as indicated in the Table 2.

Publication bias

Due to the small number of studies (fewer than 10) included, we are unable to perform a publication bias assessment.

Discussion

This systematic review is the first to explore the association between PPI use and migraine. While clinical reports have suggested a potential link between PPIs and headaches, our findings provide a more structured evaluation of the available evidence. The pooled analysis, which included five studies encompassing more than 1.5 million individuals, indicated non-significant increase in migraine among PPI users. Subgroup analyses further explored this association based on gender and migraine subtype, revealing variations in estimates. Despite these insights, substantial heterogeneity across studies suggests that further research is needed to establish a more definitive causal relationship.

The primary meta-analysis yielded a pooled aOR of 2.508 (95% CI: 0.790–7.969), suggesting a non-significant increase in migraine risk among PPI users. This may be influenced by the effect of PPIs on neurotransmitter systems, particularly serotonin, which plays a crucial role in migraine pathogenesis. Changes in gastric pH due to PPI use could disrupt these systems. Additionally, polypharmacy, including the use of PPIs, may alter gut microbiota, which could influence the gut-brain axis and potentially contribute to migraine episodes through disruptions in gastric signaling and nutrient absorption [17, 32, 33]. However, the exact mechanisms remain unclear, and further research is needed to establish a direct link. Although the overall estimate was imprecise, sensitivity analyses demonstrated that excluding Kang et al. 2022 or

Salvin et al. 2024 led to a statistically significant association with 0% heterogeneity, indicating that certain studies may disproportionately contribute to the observed variability. The overall heterogeneity was substantial (I^2 = 91.2%), likely reflects differences in study design, population characteristics, and confounding factors such as treatment duration and co-medications. The heterogeneity may also stem from variations in diagnostic criteria used across studies; for instance, one study used self-reported data from NHANES, while another applied ICD guidelines. These factors significantly contribute to the observed heterogeneity. This odds ratio was adjusted for several factors, including age, sex, income status, region of residence, blood pressure, blood glucose, cholesterol, weight, smoking status, alcohol consumption, GERD treatment, duration of treatment, and co-medications, ensuring the robustness of the results.

When stratified by gender, PPI use was associated with increased odds of migraine in both males and females, though with notable differences in effect size and heterogeneity. Among males, the pooled aOR was 3.875 (95% CI: 2.413–6.222) with no heterogeneity (I^2 = 0%), suggesting a consistent and significant association. Conversely, in females, the association was weaker (aOR: 2.475, 95% CI: 0.563–10.890) with high heterogeneity (I^2 = 91.1%). This high heterogeneity may be due to differences in study design and methodological approaches. Specifically, one study employed a large cohort design and included genetic data (CYP2C19 phenotypes) to assess individual variations in PPI metabolism, while another used a nested case-control design with propensity score matching. These methodological differences likely contributed to the observed variation in results. Furthermore, adjustments for confounding factors varied between studies: the first study accounted for genetic factors in PPI metabolism, while the second study controlled for a broader range of demographic and lifestyle factors, which may have influenced the outcomes.

The stronger association between PPI use and migraine in males may be due to several factors. Men may metabolize PPIs more slowly due to variations in CYP2C19 enzyme expression, leading to higher drug exposure and an increased likelihood of migraines. Additionally, hormonal differences, such as estrogen's protective effect in females, may reduce susceptibility to PPI-induced migraines in women. Further research is needed to explore these gender-specific mechanisms. The lack of significant gender interaction suggests that while the association may be present in both sexes, the variability in the female subgroup warrants further investigation. In the migraine subtype analysis, PPI use was associated with both migraine with aura (aOR: 2.079, 95% CI: 0.945–4.576) and migraine without aura (aOR: 2.524, 95% CI: 0.807–7.896). Heterogeneity was low for migraine with aura (I^2 = 25.4%) but high for migraine without aura (I^2 = 96.5%). Although no significant subgroup differences were observed, the greater variability in migraine without aura suggests that additional factors, such as genetic predisposition or concurrent medication use, may be modifying the association in this group.

Previous research explored the neurological effects of PPIs, particularly their association with headache and migraine. For instances, Makunts et al. 2019 [31] analyzed data from the FDA Adverse Event Reporting System and reported a significant association between use of PPI and migraine (OR: 2.19, 95% CI: 1.29–3.72). In contrast, Liang et al. 2015 [13] conducted a nationwide case-crossover study in Taiwan, which demonstrated a more modest increased incidence of headaches among users of lansoprazole and esomeprazole (OR: 1.20, 95% CI: 1.07–1.35). These variations in reported ORs may be attributed to differences in study design, geographic population characteristics, and the specific PPIs examined. Our meta-analysis estimates a pooled adjusted OR of 1.995 (95% CI: 0.974–4.089), indicating a non-significant increase in migraine risk among PPI users, which suggests a nuanced interpretation of the influence of PPIs on migraine development.

Further Supporting this impact, Claessens et al. 2002 [34] found that lansoprazole use was associated with headaches in 2.5% of users, with an incidence density of 7.2 per 1000 patient-months, further reinforcing the potential role of PPIs in headache development. Additionally, Davies et al. 2008 conducted a prescription-event monitoring study of esomeprazole and identified headache and migraine as common adverse events, particularly frequent during the first month of treatment. These studies, when viewed collectively, highlight the variability in the observed effects of PPIs on neurological outcomes, which may be influenced by factors such as the specific PPI used, the duration of treatment, and individual patient characteristics. While our findings suggest a trend towards an association, the evidence remains inconclusive, underscoring the need for further investigation to clarify the role of PPIs in the development of migraine and other neurological symptoms.

PPIs have also been associated with various adverse events, as reported in other systematic reviews, including an increased risk of dementia, acute kidney injury, pneumonia, and other complications [35, 36]. Nochaiwong et al. 2017 demonstrated an increased risk of adverse kidney outcomes with PPI use, reporting a relative risk (RR) of 1.44 (95% CI: 1.08–1.91). Similarly, Li et al. 2019 [37] conducted a meta-analysis showing a potential association between use of PPI and the risk of dementia and Alzheimer's disease, with pooled RRs of 1.23 (95% CI: 0.90–1.67) and 1.01 (95% CI: 0.78–1.32), respectively. These findings suggest that while PPIs may contribute to

an elevated risk of certain neurological and other complications, the evidence remains inconclusive, highlighting the need for further investigation.

This review follows a rigorous methodology in accordance with PRISMA guidelines, with a comprehensive literature search across multiple databases and the use of subgroup and sensitivity analyses to explore potential sources of heterogeneity. Additionally, the large sample size (>1.5 million participants) provides a robust estimate of the association between PPI use and migraine. The included studies provided adjusted effect sizes, accounting for various confounding factors such as gender, age, BMI, comorbidities, medication intake, dose, income, region, blood pressure, blood glucose, cholesterol, weight, smoking, alcohol consumption, GERD treatment, treatment duration, co-medications, race, poverty, caffeine intake, and others. While the impact of these factors on the pooled estimates was not quantified in depth, their inclusion enhances the reliability of the overall findings.

However, this review is not without its limitations. Substantial heterogeneity across studies limits the generalizability of the findings, as differences in study design and diagnostic criteria may contribute to this variability. Unfortunately, due to the limited number of studies included, meta-regression to quantify how these factors might influence the pooled estimates was not feasible. Secondly, the inclusion of different study designs such as cohort, case-crossover, and case-control studies introduces additional challenges. The limited number of studies also prevented performing a subgroup analysis based on study design, which could have provided more insight into how design-specific factors might influence outcomes. Third, the classification of migraine subtypes varied across studies, potentially affecting the accuracy of subgroup analyses. Additionally, only one outcome was extracted and pooled, as sufficient secondary outcomes that met our criteria were not identified.

Furthermore, while PPI dose, type of PPI, and duration were adjusted for in the analyses, the studies did not provide explicit details on these factors, making it difficult to assess their precise impact on migraine. The inclusion of only English-language studies is acknowledged as a limitation of the study, with potential language bias. Additionally, although the assessment of publication bias was not possible due to the limited number of included studies, this restriction also impedes the ability to detect small-study effects.

While the results of this study suggest an insignificant link between PPI use and migraine, it is premature to recommend changes in clinical practice based on this study alone. Healthcare providers should remain vigilant for neurological symptoms in patients using PPIs, especially those with a history of migraines. Future research should focus on prospective cohort studies, which can provide more definitive evidence of causality and clarify the mechanisms underlying the observed associations. However, the feasibility of conducting such RCTs involves significant ethical considerations, and the initiation of RCTs can only be justified with careful consideration of these factors. Additionally, these studies should strive for uniformity in diagnosing and classifying migraines and consider longitudinal tracking to assess the long-term effects of PPI use. Mechanistic studies exploring the interaction between PPIs, gut microbiota, and neuro-inflammation could provide deeper insights into the biological pathways potentially influencing migraine in PPI users.

Conclusion

This systematic review and meta-analysis found no significant association between the use of PPIs and migraine overall, despite substantial heterogeneity among the studies. However, a significant association was observed in male participants. Given the nonsignificant overall results and the prevalent use of PPIs, the evidence does not support a direct causal link. Further research is needed to clarify this association and explore the underlying causal mechanisms, especially by accounting for variables such as dose, duration, migraine triggers, diagnostic criteria, and demographic characteristics, with a particular focus on understanding the reasons for the more pronounced association in males.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02000-8.

Supplementary Material 1

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None.

Author contributions
Conceptualization: E.M., M.N.K., N.V.; Data curation: K.W.G., K.C., P.S.; Formal analysis: S.V.M., D.L., R.P.; Investigation: M.S., G.B., S.S.; Methodology: R.P., M.S., E.M.; Project administration: P.S., S.S.; Resources: N.V., G.B.; Software: M.N.K., K.C.; Supervision: P.S., G.B., M.S.; Validation: D.L., M.S.; Visualization: M.N.K., S.S., D.L.; Writing – original draft: E.M., S.S., S.V.M.; Writing – review & editing: M.N.K., P.S., K.W.G.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable, as there were no human participants involved in this study.

Consent for publication
Not applicable, as this study does not involve any individual person's data in any form.

Competing interests
The authors declare no competing interests.

Author details
[1]Center for Global Health Research, Saveetha Institute of Medical and Technical Sciences, Saveetha Medical College and Hospital, Saveetha University, Chennai, India
[2]Faculty of Data Science and Information Technology, INTI International University, Nilai, Malaysia
[3]Division of Evidence Synthesis, Global Consortium of Public Health and Research, Datta Meghe Institute of Higher Educatsion, Wardha, India
[4]Department of Pharmaceutical Sciences, Faculty of Health Sciences, Marwadi University Research Center, Marwadi University, Rajkot, Gujarat 360003, India
[5]Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India
[6]Department of Chemistry, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India
[7]Department of Microbiology, IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha 751003, India
[8]University Center for Research and Development, Chandigarh University, Mohali, Punjab, India
[9]Division of Research and Innovation, Uttaranchal University, Dehradun, India
[10]Department of Biotechnology, Graphic Era (Deemed to be University), Clement Town, Dehradun 248002, India
[11]Graphic Era Hill University, Clement Town, Dehradun, India
[12]Department of Pediatrics, Hospital and Research Centre, Dr. D. Y. Patil Medical College, Dr. D. Y. Patil Vidyapeeth (Deemed-to-be-University), Pimpri, Pune, Maharashtra 411018, India
[13]Department of Public Health Dentistry, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth (Deemed-to-be-University), Pune, Maharashtra 411018, India
[14]Department of Medicine, Korea Universtiy, Seoul 02481, South Korea
[15]Chitkara Centre for Research and Development, Chitkara University Institute of Engineering and Technology, Chitkara University, Himachal Pradesh 174103, India
[16]Medical Laboratories Techniques Department, AL-Mustaqbal University, Hillah, Babil 51001, Iraq
[17]Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, Indonesia
[18]School of Public Health, Makerere University College of Health Sciences, Mulago Hill, Kampala, Uganda
[19]Centre Centre for Research Impact and Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, Punjab 140401, India
[20]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India

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