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Expanding the paradigm of the management of headaches: integrated multidisciplinary perspectives from bench to bedside

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Expanding the paradigm of the management of headaches: integrated multidisciplinary perspectives from bench to bedside

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Network analysis of negative emotions in patients with episodic migraine: need for a multidisciplinary perspective

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Background: Episodic migraine (EM) is the second most prevalent neurological disorder worldwide and is responsible for more disability than all other neurological disorders combined. Triggers for the development of migraine include, stress, emotional burden, low blood sugar levels, tobacco, skipped meals, anxious and depressive feelings. Migraine affects both children and adults, occurring three times more frequently in women than in men.

Objective: The aim of this study was to evaluate the psychological profile of EM patients and the relationship among negative emotions in EM patients, analyzing self-efficacy measures in pain management.

Design: We performed an observational study in 60 outpatients aged 18–55 years (mean age 33.8; SD ±10.4) with EM.

Methods: All patients have been enrolled at the Headache Center of the San Salvatore Hospital of L'Aquila. The assessment comprised five standardized psychological self-assessments investigating relevant emotional dimensions and pain self-efficacy, along with two questionnaires assessing migraine-related disability. A network analysis of negative emotions was performed to evaluate which emotional traits and relationships play a crucial role in pain coping and management.

Results: Our findings indicate that migraine significantly impairs the quality of life of patients in their daily lives. Over half of the patients reported experiencing severe disability, with negative emotions significantly influencing their ability to cope with pain and maintain productivity during migraine attacks. Dysphoric variables (irritability, interpersonal resentment, and surrender) were correlated with difficulties in emotion regulation ability and with the capacity of engaging in goal-directed behaviors despite experiencing pain. The ability to regulate one's emotions and manage dysphoria were positively correlated with pain self-efficacy, whereas positive mental health was associated with individuals' confidence in performing activities despite experiencing pain.

Conclusion: Negative emotions had a negative correlation with positive mental health and were linked to a lower capacity to carry out daily activities despite experiencing migraine pain. This suggests that psychological interventions could improve mental health and potentially surpassing the effects of pharmacological interventions alone in migraine management. An integrated, patient-centered

approach may represent an effective paradigm to address and reduce the burden of migraine, leading to a reduction in healthcare costs.

KEYWORDS

migraine, health awareness, emotional dimensions, clinical psychology, wellbeing, rehabilitation, cognitive treatment

Introduction

Migraine is a neurological disorder that affects nearly 14% of the population, causing debilitating symptoms (1). Episodic migraine (EM), the most common migraine type, is characterized by the presence of less than 15 days per month with migraine symptoms (2). Patients with migraine often describe pain as initially starting as pressure at the height of the forehead but then progressing deeper into the head. Most commonly, it is characterized as pulsating, throbbing, stinging, stabbing, burning, cutting, and oppressive (3). Psychological impairment is largely associated with the EM condition, with patients frequently reporting symptoms such as insomnia, fatigue, depression, and anxiety (4–8). The association between a higher number of headache days and increased rates of anxiety, depression, and insomnia has been reported (5). Additionally, a higher number of headache days has been linked to an enhanced risk of developing psychosocial impairments (6). A migraine attack is considered much more complex than just a mere experience of pain (3). Pain management consists of a chain of behaviors that can be analyzed using three variables: (a) physical sensations, (b) automatic reactions, and (c) actions according to the interpretation (3). Physical sensations may be driven by pain localization (e.g., central or in the middle of the head), pain quality (e.g., pulsating, throbbing, stinging, stabbing, burning, cutting, and oppressive), and intensity (ranging from mild to severe). Automatic reactions involve a loss of control, often triggered by the presence of aura symptoms, which are frequently described as more unpleasant than the pain itself (3). Specifically, in the visual aura, phenomena such as flickers of light, little moons, or lightning that gradually increase in size and move further away into the periphery, have been described as disturbing and destabilizing experiences, conveying feelings of loss of control, insecurity, and fear of severe migraine attacks (3). Acts according to the pain interpretation encompass all actions adopted by patients to manage pain, including taking medications, eating something, finding a distraction, waiting out the pain, and attempting to sleep (3). So, the overall experience of each migraine attack is defined by the combination of physical sensations, automatic reactions, and conscious behaviors. The treatment of EM is mainly based on pharmacological interventions, especially now that new drugs with innovative mechanisms of action are available, such as symptomatic treatments (gepants and ditans) and preventive treatments (monoclonal antibodies targeting the calcitonin gene receptor peptide). Despite this, unmet treatment needs remain a reality in patients' lives (9). A combination of pharmacological and non-pharmacological approaches has been shown to be more effective than either approach alone in achieving positive outcomes and improving treatment adherence (10–12). Tailored pharmacological treatments combined with a multidimensional, patient-centered, behavioral treatment may reduce the burden of migraine in a biopsychosocial perspective (13). Integrated pharmacological and non-pharmacological interventions can reduce medication overuse in acute management of primary headaches (14). Therefore, it is valuable to identify triggers that may exacerbate a predisposition to migraines and to train patients in effective management techniques. Lifestyle and daily living factors, such as stressful events, an unhealthy diet, poor sleep, and lack of exercise, may trigger migraine attacks. Frequent exposure to such factors may also contribute to the progression of migraine disease and its chronicization. Similarly, specific psychological traits, even in the absence of clear psychiatric comorbidities, may contribute to the worsening of migraine frequency and severity (4). The main psychological interventions used in treating migraine include relaxation training (RT), cognitive-behavioral therapy (CBT), and biofeedback (BF) (15). Some studies demonstrated a broad range of efficacy for non-pharmacological interventions, ranging from 20 to 67%. Importantly, there is no evidence to indicate that one approach—whether CBT, RT or BF—is superior to the others. The efficacy of these interventions needs to be more thoroughly defined, as the evidence base still lacks in quality. The methodological weakness of evidence-based non-pharmacological experimental protocols lies in the absence of quantitative clinical trials. Identifying the key elements of emotional regulation in migraine patients may aid in enhancing their management through a combination of pharmacological and non-pharmacological strategies. This may pave the way for promoting education of healthcare professionals toward a biopsychological approach, ultimately leading to improvements in comprehensive headache care pathways.

Therefore, the aims of our study was to analyze the network of active negative emotions in patients with EM and to evaluate how psychological factors and behaviors interact with each other, potentially contributing to the worsening of migraine symptoms and disability.

Abbreviations: EM, Episodic migraine; RT, Relaxation training; CBT, Cognitive behavioral therapy; BF, Biofeedback; IRB, Internal review board; MIDAS, Migraine Disability Assessment Score Questionnaire; HIT-6, Headache Impact Test-6; PSEQ, Psychological measures were: Pain Self-Efficacy Questionnaire; NDS-I, Nepean Dysphoria Scale; DERS, Difficulties in Emotion Regulation Scale- Short Form; PMH, Positive Mental Health Scale; DASS-21, Depression, Anxiety, and Stress Scale-21.

Methods

Participants

Patients consecutively referring to the Headache Center of the S. Salvatore Hospital of L'Aquila in a 6-months period with a diagnosis of migraine were screened for the inclusion in the study. Migraine

diagnosis was performed according to the International Classification of Headache Disorders (ICHD) criteria 3rd edition (2), by a neurologist with expertise in headache diagnosis and management. Inclusion criteria were: (i) age > 18 years, (ii) diagnosis of episodic migraine with or without aura, and (iii) availability to participate in the study and to sign the informed consent form. Exclusion criteria were (a) previous or ongoing history of psychiatric diseases based on ICD-10 classification (b) treatment with antidepressants/mood stabilizers at the time of the study. The presence of these criteria was investigated by asking the patient if there was any previous or current diagnosis of psychiatric diseases and by consulting the digital database of the patient's previous visits available in our clinics.

Ethical approval to conduct this study was granted by the Institutional Review Board (IRB) of the University of L'Aquila, Italy (ID 29/2023). Informed consent was obtained from each participant, and the study adhered to guidelines outlined in the Declaration of Helsinki (16).

Measures

Two types of participant information were collected. First, demographics were collected through participant self-reports. We selected independent variables to include in the analysis as they were age/stage of life characteristics (e.g., employment status, marital status, and educational level) related to time from diagnosis. Second, clinical data were obtained from the participants' medical records, including current stage of disease and the type of medical (pharmacological/surgery) treatment received. The measurement was based on headache and psychological assessments. The headache measure were Migraine Disability Assessment Score Questionnaire (MIDAS) and Headache Impact Test-6 (HIT-6). Psychological measures were: Pain Self-Efficacy Questionnaire (PSEQ), Nepean Dysphoria Scale (NDS-I), Difficulties in Emotion Regulation Scale-Short Form 18 (DERS), Positive Mental Health Scale (PMH).

Migraine assessment

The migraine assessment was conducted using two self-assessment measures to evaluate the impact of migraine: the *Migraine Disability Assessment Score Questionnaire* (MIDAS) (17) and the *Headache Impact Test-6* (HIT-6) (18). MIDAS is a questionnaire that measure headache-related disability over a 3-month period in patients with migraine. It is composed of 7 questions including frequency of headaches and pain. The MIDAS score is based on five disability questions in three dimensions (school or work, household and social functioning). The MIDAS score was derived as the sum of lost days due to headache as follows: one question about the extent to which headaches interfere with nonwork activity (miss-leisure) and two questions each about work (miss work + work-half) and work at home (miss-chore + chore half). The total MIDAS score can be further used to define four grades of headache related disability, including grade I for "minimal or infrequent disability" (0–5); grade II for "mild or infrequent disability" (6–10); grade III for "moderate disability" (11–20); and grade IV for "severe disability" (>21). The Cronbach's alpha was 0.83.

The HIT-6 is a self-report that measures the impact of headache. It comprises six items that assess the adverse impact of headaches on social functioning, role functioning, vitality, cognitive functioning, and psychological distress (18). Headache impact severity level can be categorized using four headache impact severity categories: (1) little or no impact (49 or less), (2) some impact (50–55), (3) substantial impact (56–59), and (4) severe impact (60–78).

Psychological assessment

A comprehensive psychological battery including standardized self-assessments tools measuring emotional traits (depression, anxiety, stress, and psychological distress), self-efficacy skills, emotional regulation, and personality dimensions, was used. The participants completed the tests following the individual clinical interview session. Each standardized test was applied using the Italian population version. Specifically, the battery included the following tests:

- The *Depression Anxiety Stress Scales 21* (DASS-21) (19) that is a self-administered questionnaire measuring the negative emotion traits and the degree of severity of the core symptoms of depression, anxiety, and stress. It is composed of 21 questions with responses on a four-point Likert-type scale;
- The *Pain Self-Efficacy Questionnaire* (PSEQ) (20) that is a self-report questionnaire measuring the confidence of individuals experiencing ongoing pain in performing activities despite being in pain. It is composed of 10 items with responses on a 6-point Likert-type.
- The *Nepean Dysphoria Scale* (NDS) (21), a questionnaire that measures dysphoria through the following four subscales: irritability, discontent, surrender and interpersonal resentment. It is composed of 24 items with responses on a 4-point Likert-type. The reliability of test was Cronbach's $\alpha > 91$.
- The *Difficulties in Emotion Regulation Scale- Short Form 18* (DERS) (22), a test assessing individual differences in the ability to identify, accept and manage emotional experiences; the test is composed of 6 indexes: (a) Non acceptance (=lack of acceptance of one's emotions), (b) Goals (=lack of ability to engage in goal-directed activities during negative emotions), (c) Impulse (=lack of ability to manage one's impulses during negative emotions), (d) Awareness (=lack of awareness of one's emotions), (e) Strategies (=lack of access to effective emotion regulation strategies), (f) Clarity (=lack of clarity about the nature of one's emotions).
- The *Positive Mental Health Scale* (PMH) (23), a questionnaire measuring positive mental health, mainly emotional, but also psychological and social aspects of wellbeing. It is composed of 9 items with responses on a 4-point Likert-type. People who are mentally healthy tend to have stable relationships, view their lives as having purpose and direction, experience more positive affect, and are more likely to be self-accepting.

Study design, procedures, and study flow

This was an observational prospective study investigating patients consecutively referring to the Headache Center. The Medical staff in the Headache Center identified eligible patients. Informed consent was obtained at the time of enrolment. During the first visit medical staff collected clinical data, whereas trained clinical psychologists (blinded to the study's objectives) performed the psychological

assessment in a dedicated room. The psychological evaluations lasted 15 min, and the data was managed anonymously.

Statistical analysis

Descriptive statistics (mean, standard deviation, percentage) were performed: continuous variables were expressed as the mean ± standard deviation, while categorical variables were presented as frequency or percentage Partial correlation analysis was conducted to examine the relationship between all variables. The Jamovi stat was applied for statistical analyses. The level of significance adopted was $\alpha < 0.05$. Then, R4.1.1 software was used to process the network analysis. The tuning parameter of EBIC was set to 0.5 and the Pearson correlation method was used. In the network model, edges represent the net correlations between two nodes after statistical control of interference from other nodes in the network.

Results

Participants

Sixty-nine patients were considered eligible and invited to participate in the study. Out of them, 60 outpatients aged 18–55 (mean ± SD 33.8 ± 10.4) were finally included as available to participate and providing a signed informed consent. Women ($n = 50$, mean age ± SD 33.8 ± 10.6) were more represented than men (n = 10 mean age ± SD 33.9 ± 9.6). Migraine without aura was the most common diagnosis (68.4%). The mean number of monthly migraine headache days (MHDs) was 5.6 ± 1.8. On the MIDAS assessment, most patients reported severe disability (52%), while the remainder reported moderate (15%), minimal (23%), or mild (10%) disability. The HIT-6 test revealed a high negative impact of migraine on daily life: 73% of patients reported an extremely severe impact, 7% reported a severe impact, and 20% reported a moderate impact. All demographic characteristics of the participants are reported in Table 1. The raw scores, including mean values and standard deviations, obtained on the psychological testing battery are reported in Table 2.

Network structure

The network structure of different components of negative emotions is shown in Figure 1. We investigated 40 edges across negative emotions, of which 24 were positive and 16 negative. In the cross-community edges, all NDS indexes were positively correlated with DERS indexes: Irritability [Clarity ($r = 0.001$), Goals ($r = 0.001$), Impulsivity ($r = 0.001$), Non acceptance ($r = 0.001$) and Strategies ($r = 0.001$)]; Discontent: [Clarity ($r = 0.001$), Goals ($r = 0.001$), Impulsivity ($r = 0.001$), Non acceptance ($r = 0.001$) and Strategies ($r = 0.001$)]; Interpersonal resentment: [Clarity ($r = 0.001$), Goals ($r = 0.001$), Impulsivity ($r = 0.001$), Non acceptance ($r = 0.001$) and Strategies ($r = 0.001$)]; Surrender: [Clarity ($r = 0.001$), Goals ($r = 0.001$), Impulsivity ($r = 0.001$), Non acceptance ($r = 0.001$) and Strategies ($r = 0.001$)]. Even, NDS indexes were positively correlated with negative traits of behaviors (DASS-21): [Clarity ($r = 0.001$), Goals ($r = 0.001$), Impulsivity ($r = 0.001$), Non acceptance ($r = 0.001$) and Strategies ($r = 0.001$)]. Then, NDS and DERS indexes were negatively correlated with positive mental health value (PMH; $r = 0.001$). Pain self-efficacy value (PSE) correlated with Discontent and Interpersonal resentment (NDS indexes; respectively $r = 0.01$, $r = 0.01$); Goal (DERS index; $r = 0.002$); on contrary, it was correlated positively with PMH ($r = 0.04$). Finally, negative psychological dimensions (DASS-21) were correlated positively with all indexes of NDS ($r = 0.0001$), among DERS indexes almost resulted significant ($r = 0.001$; no significance for Awareness variable), and then negatively correlated with PMH ($r = 0.001$) and PSE ($r = 0.01$). The chart representation of correlation matrix is shown in Figure 2. The correlation matrix of the network is displayed in Table 1.

Discussion

Our results highlighted interesting pathways that could serve as emotional targets for interventions aimed at customizing and improving health management behaviors in migraineurs. The performed network analysis revealed how different emotions are interconnected in patients with EM, showing complex relationships within specific clusters of emotions.

The strongest positive relationships were found among emotional awareness, emotional clarity, pain self-efficacy and ability to maintain goal-directed behaviors during pain: these emotions form a sort of chain, so that one emotion switches into another, thus mutually reinforcing each other. Emotional awareness is the conscious experience of emotions while emotional clarity refers to one's ability to identify the type of emotions one is experiencing (24). The process of recognizing and regulating emotions can profoundly impact the perception of pain and one's ability to cope with it. Low emotional awareness and clarity may correlate with maladaptive behaviors in response to pain, resulting in reduced pain self-efficacy. Conversely, high awareness and clarity of one's emotions typically foster adaptability, leading to greater confidence in performing specific behaviors or tasks despite experiencing pain (25). The dysphoria variables correlated positively with difficulties in emotion regulation ability: the EM patients seemed irritated, discontent, surrendered, feeling interpersonal resentment on depending to (a) the lack of clarity regarding to the nature of one's emotions, as well, (b) the lack of ability to engage in goal-direct activities during negative emotions, (c) the lack of ability to manage own impulsivity, (d) the lack of ability to acceptance of one's emotions, and then (e) the lack of awareness of one's emotions. These negative emotions were correlated negatively with the positive mental health, whereas positive mental health was associated with the confidence that people with ongoing pain have in performing activities while in pain (= pain self-efficacy). Finally, negative psychological traits (cumulative dimensions of depression, anxiety and stress) were associated with all the examined negative emotions and dimensions, except with the lack of one's emotions awareness. Dysphoria is characterized by a dynamic state of intense discontent and unhappiness, associated with feelings of inner tension, often accompanied by a tendency to give up or an urge to resort to some action to alleviate such discontent or unhappiness (21). In patients with EM, dysphoric variables are associated with

TABLE 1 Demographic characteristics of the participants.

	EM sample (*N* = 60)
Demographics	
Age (years)	33.8 SD ± 10.4
Body mass index (BMI)	23.8 SD ± 3.31
Gender: n (%)	
Male	10 (16.6%)
Female	50 (83.4%)
Marital status: n (%)	
Single	24 (40.0%)
Married	36 (60.0%)
Educational level: n (%)	
Graduate	36 (60.0%)
No graduate	24 (40.0%)
Occupational status: n (%)	
Unemployed	4 (7.0%)
Employed	29 (48.0%)
Self-employed	11 (18.0%)
Student	16 (27.0%)
Smoking habits: n (%)	
Yes	24 (40.0%)
No	36 (60.0%)
Physical activity: n (%)	
Yes	24 (40.0%)
No	36 (60.0%)
Headache characteristics	
Type Migraine: n (%)	
With Aura	19 (32.0%)
Without Aura	41 (68.0%)
MHDs	5.6 ± 1.8
Headache intensity (0–10)	8.16 ± 1.68
MIDAS grade 1/2/3/4 (%)	10/23/15/52
Total MIDAS score	28.43 ± 25.52

TABLE 2 Performances of participants to the standardized tests.

			Shapiro–Wilk	
	Mean	SD	*W*	*p*
Headache measure				
MIDAS	28.43	25.53	0.901	0.001
HIT-6	62.92	6.52	0.967	0.109
Psychological measure				
PSEQ	24.22	14.93	0.964	0.072
DASS-21				
Depression	10.77	8.42	0.926	0.001
Anxiety	9.70	7.92	0.899	0.001
Stress	10.77	8.42	0.926	0.001
NDS				
Irritability	6.43	5.09	0.890	0.001
Discontent	5.20	3.95	0.875	0.001
Interpersonal resentment	3.68	3.75	0.854	0.001
Surrender	3.90	4.05	0.866	0.001
DERS				
Awareness	7.98	3.16	0.950	0.016
Clarity	6.13	2.91	0.887	0.001
Goals	6.05	2.42	0.921	0.001
Impulse	5.68	2.40	0.892	0.001
Non-acceptance	6.15	2.35	0.897	0.001
Strategies	5.18	2.05	0.866	0.001
PMH	17.58	5.63	0.970	0.148

the capacity to engage in goal-directed behaviors despite experiencing pain, as well as with emotional acceptance and access to emotion regulation strategies. Specifically, patients showed irritability, discontent, surrender, and interpersonal resentment associated with a lack of clarity regarding the nature of one's emotions, an inability to engage in goal-directed activities during negative emotions, difficulty in managing impulsivity, a lack of acceptance of one's emotions and a lack of awareness of one's emotions. All negative emotions were negatively correlated with positive mental health, while positive mental health was associated with the confidence that patients with ongoing pain have in performing activities despite being in pain (pain self-efficacy).

Our finding highlighted the psychological dynamics of EM patients coping with headache: they experience a multitude of emotions concurrently during pain, with difficulties in recognizing which emotion is experienced first. In this context, our study specifically investigated the network structure of negative emotions and highlighted that complex psychological dynamics might be active in EM patients dealing with headache: they experience a lack of wellness due to integrated physical and mental symptoms (headaches and negative emotions), ultimately resulting in poor health management. Psychological factors play a crucial role in influencing the perception of pain and patients' ability to manage it, maintaining good autonomy and productivity even during migraine attacks. Our findings are consistent with previous research, underscoring the severe impact of migraine on patients' daily quality of life, with depression, anxiety, stress, and sleep disorders exacerbating migraine and reducing wellbeing (4, 6, 8, 26–30). Overall, this suggests that the clinical assessment of patients with migraine should be more comprehensive, encompassing the evaluation of patients' emotional awareness and the correlation between their emotions and pain. In fact, pain sensitization is highly influenced by psychosocial factors, so that psychological interventions and emotional processing treatments may have a chance in reducing pain severity and improving pain-related disability. This aspect should be taken into consideration also in the process of development of reliable tools and patient-reported outcome measures to assess headache-related

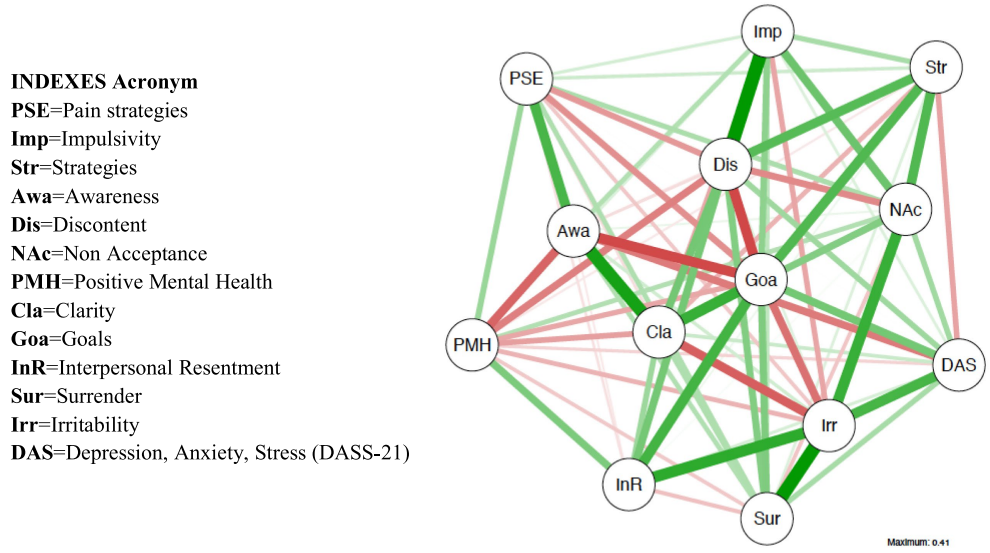

FIGURE 1
Network structure of negative emotions in EM patients. The green and red edges represent positive and negative partial correlations among nodes. The thick edges and saturated color represent a strong correlation: nodes are the variables (in this case, emotions), and edges are the relationships between the variables.

disability: in fact, it is current opinion that the scales currently used (for instance MIDAS and HIT 6) have some limitations, mainly represented by the poor correspondence between the dimensions investigated at the patient level and the drivers of reduced health, as expressed at population level, through disability weights (DW) and years lived with a disability (YLDs) developed by the Global Burden of Disease Study (GBD) (28). Our findings reveal that neglecting either integrated physical or emotional factors fails to capture the entire experience of headache disability, thereby interfering with adequate health management. Although we are in a revolutionary period for migraine therapy, with the availability of innovative treatments that differ from the previous ones due to a more specific mechanism of action, there is always a proportion of patients who do not fully improve, do not improve sufficiently, or are refractory to these treatments. In these patients, the presence of specific psychological factors or a maladaptive tendency to manage their own emotions could be the cause of the inadequate success of pharmacological treatments. Therefore, the use of non-pharmacological treatments, not to replace pharmacological ones, but to be used in a complementary manner, could be the missing piece to help all patients and reduce migraine-related disability, which is a significant source of both direct and indirect costs for society. The most recent literature review highlighted the efficacy range of Cognitive Behavioral Therapy (CBT), Relaxation Training (RT), and Biofeedback (BF) as the most commonly applied non-pharmacological interventions, ranging from 20 to 67% (15, 31). According to the biopsychosocial model, pharmacotherapy and behavioral therapy may complement each other, with the most significant reduction in headache frequency achieved by implementing a combination of the two (30).

Strengths of our study include the observational design, the rigorous selection of patients with EM, excluding those with psychiatric comorbidities or therapies, the multidisciplinary assessment performed by both neurologists and psychologists and the adoption of a network analysis model. In particular, the latter is an innovative model of analysis that enables the recognition of patterns of statistical association in multivariate psychological and behavioral data, by identifying system components (network nodes) and the relations among them (links between nodes). This analysis are often carried out with the goal of relating structural features of the network to system dynamics, without requiring strong *a priori* assumptions about associations (32).

Potential limitations of our study include the sample size, which could be expanded in future studies to provide more robust evidence, the inability to establish causal relationships among the investigated variables in the network analysis. In fact, the described relationships are purely statistical associations and causal inference is not justified, as edges between nodes may arise owing to directed causal effects or feedback loops, but also owing to unobserved common causes (33). Last, the study did not provide a follow-up measure regarding the changing frequency, severity and burden of migraine due to pharmacological interventions. Future longitudinal studies will provide follow-up information on the evolving pattern of migraine, in terms of frequency, severity and disability, as well as any associated psychological changes resulting from therapeutic interventions.

In conclusion, more effective psychological interventions for EM patients might focus on the relationship between dysphoria variables and difficulties in emotion regulation ability. Based on these preliminary findings, which need further confirmation through studies with larger sample sizes, a practical suggestion for clinicians may be to adopt an integrated biopsychosocial approach for patient care. This approach should be based on multidisciplinary assessment and management, taking into consideration both the clinical and psychological aspects of the patients. Complementary pharmacological and behavioral treatments, based on personalized

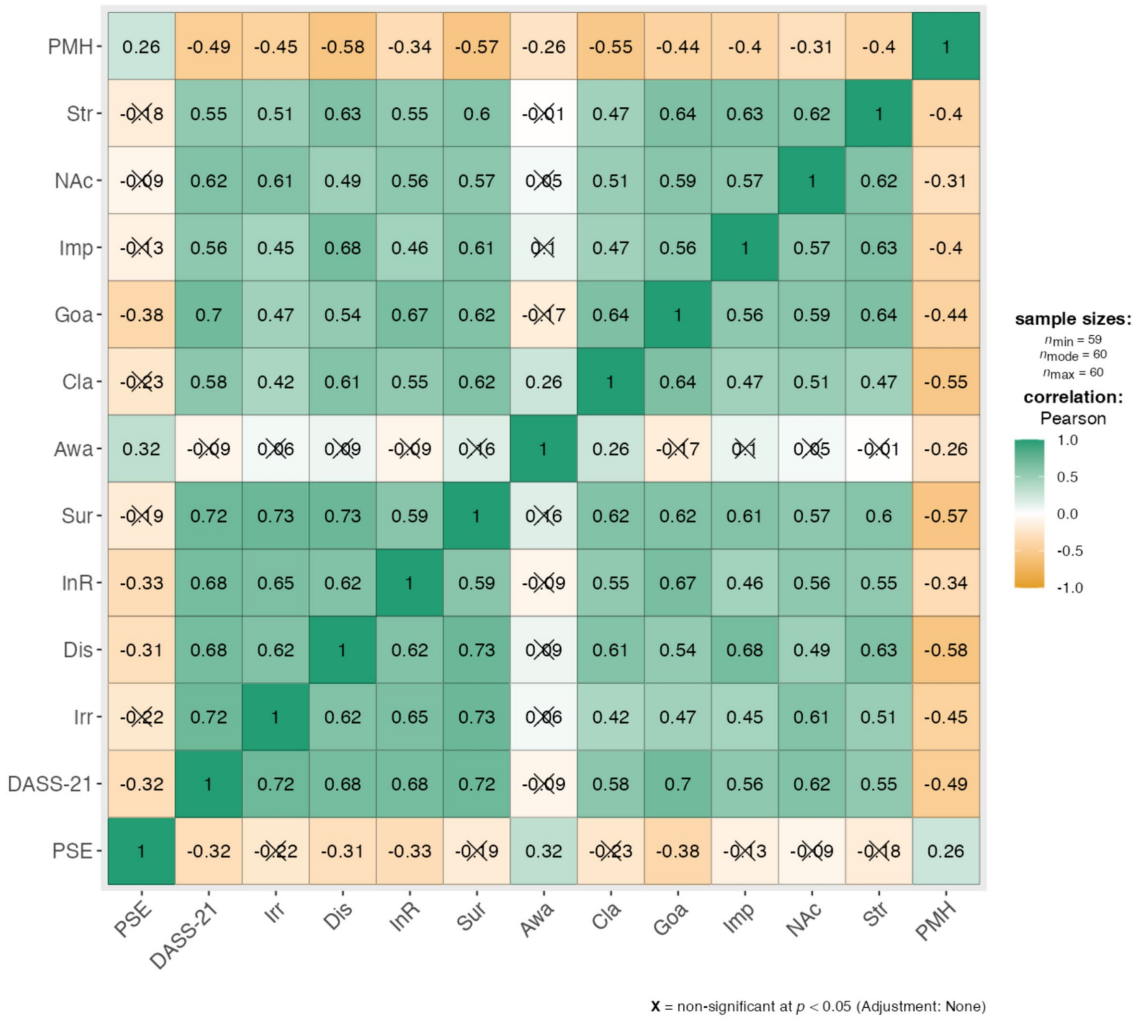

FIGURE 2
Chart representation of correlation matrix (PMH, Positive Mental Health; Str, strategies; NAc, Non Acceptance; Imp, Impulsivity; Goa, Goals; Cla, Clarity; Awa, Awareness; Sur, Surrender; Irr, Irritability; DASS-21, Depression, Anxiety, Stress; PSE, Pain strategies).

medicine to enhance the patient-centered approach, could be the focus of future research protocols. Integrated interventions should be tailored to consider the dynamics of negative emotion onset and consolidation.

This approach could address the unmet needs of patients, improve clinical care, and enhance quality of life.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

FG: Conceptualization, Data curation, Writing – original draft. DG: Conceptualization, Writing – review & editing. JR: Formal analysis, Investigation, Writing – original draft. GS: Investigation, Writing – original draft. PS: Methodology, Writing – original draft. RT: Methodology, Writing – original draft. FP: Conceptualization, Data curation, Writing – review & editing.

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Publisher's note

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K_{ATP} channels in cerebral hemodynamics: a systematic review of preclinical and clinical studies

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Cumulative evidence suggests that ATP-sensitive potassium (K_{ATP}) channels act as a key regulator of cerebral blood flow (CBF). This implication seems to be complicated, since K_{ATP} channels are expressed in several vascular-related structures such as smooth muscle cells, endothelial cells and pericytes. In this systematic review, we searched PubMed and EMBASE for preclinical and clinical studies addressing the involvement of K_{ATP} channels in CBF regulation. A total of 216 studies were screened by title and abstract. Of these, 45 preclinical and 6 clinical studies were included. Preclinical data showed that K_{ATP} channel openers (KCOs) caused dilation of several cerebral arteries including pial arteries, the middle cerebral artery and basilar artery, and K_{ATP} channel inhibitor (KCI) glibenclamide, reversed the dilation. Glibenclamide affected neither the baseline CBF nor the baseline vascular tone. Endothelium removal from cerebral arterioles resulted in an impaired response to KCO/KCI. Clinical studies showed that KCOs dilated cerebral arteries and increased CBF, however, glibenclamide failed to attenuate these vascular changes. Endothelial K_{ATP} channels played a major role in CBF regulation. More studies investigating the role of K_{ATP} channels in CBF-related structures are needed to further elucidate their actual role in cerebral hemodynamics in humans.

Systematic review registration: Prospero: CRD42023339278 (preclinical data) and CRD42022339152 (clinical data).

KEYWORDS

CBF, cerebral arteries, ATP-sensitive potassium channels, migraine, stroke

Introduction

Cerebral hemodynamics including cerebral blood flow (CBF) and cerebral vascular tone are vital parameters contributing to brain homeostasis (1). Dysregulation of cerebrovascular hemodynamics is involved in the pathogenesis of several neurological disorders such as stroke and migraine (2, 3). The molecular mechanisms involved in the modulation of cerebral hemodynamics are complex and not entirely comprehended.

Evidence from preclinical and clinical studies implicates ATP-sensitive potassium (K_{ATP}) channels in the regulation of CBF and the cerebral vascular tone (4–6). K_{ATP} channels are vastly expressed at several structures of the vasculature such as arteries, penetrating arterioles and the complex mesh of capillaries. Specifically, K_{ATP} channels are present in smooth muscle cells (SMCs), endothelial cells (ECs) and pericytes (7–12) (Figure 1). K_{ATP} channels link the cellular metabolic state to the plasmalemma's electrophysiology. They are

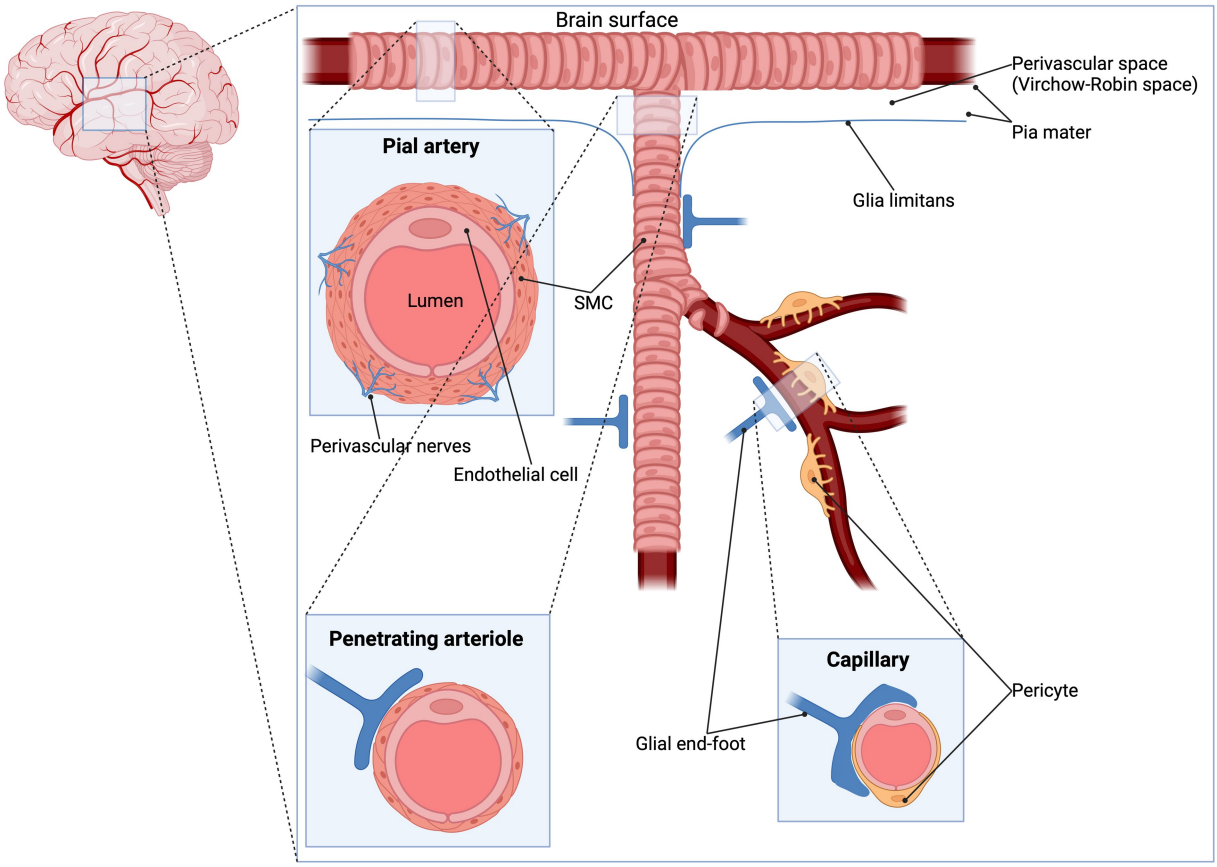

FIGURE 1
Pial artery, penetrating arteriole and capillary. The pial arterial vasculature (also known as pial collaterals or leptomeningeal anastomoses) consists of smaller arteries and arterioles that connects the three major supplying the arteries of the cerebrum: the anterior cerebral artery, the middle cerebral artery and the posterior cerebral artery (13). The pial arteries are intracranial arteries on the surface of the brain within the pia-arachnoid (leptomeninges) or glia limitans (the outmost layer of the cortex composed of glial end-feet), surrounded by cerebrospinal fluid (14) and give rise to smaller penetrating arterioles (15). An important difference in vessel architecture which might influence the CBF regulation is the number of SMC layers: penetrating arterioles contain one layer of smooth muscle while smaller pial arteries contains two to three layers of smooth muscle (16). Since K_{ATP} channels are expressed in SMC, it is expected that these channels have a higher impact in pial arteries. To date, no studies did compare the effect of KCO/KCl between these types of vessels. CBF, cerebral blood flow; K_{ATP}, ATP-sensitive potassium; KCl; K_{ATP} channel inhibitor KCO; K_{ATP} channel opener; SMC, smooth muscle cell.

activated during ischemia and hypoxia, causing potassium efflux, hyperpolarization and subsequently vasodilation (17–19) (Figure 2).

The intricate mechanisms underpinning the involvement of K_{ATP} channels in the regulation of cerebral hemodynamics have not been systematically reviewed. Here, we systemically review preclinical and clinical studies addressing the expression of K_{ATP} channel in the cerebral vasculature, and their involvement in CBF regulation and cerebral vasodilation.

Methods

We searched PubMed and EMBASE for articles assessing the role of K_{ATP} channel in the cerebral vasculature. The search was conducted on 29 January 2024, and the search string was ("K_{ATP} channels" [MeSH Terms] OR "K_{ATP} channel" [All Fields] OR "ATP sensitive potassium channel" [All Fields] OR "K_{ATP} channel expression" [All Fields] OR "K_{ATP} channel knockout" [All Fields] OR "ATP sensitive potassium channel expression" [All Fields] OR "ATP sensitive potassium channel knockout" [All Fields] AND "cerebral blood flow" [MeSH Terms] OR "cerebral blood flow" [All Fields] OR "brain blood flow" [All Fields] OR "blood flow, brain" [All Fields] OR "cerebral circulation" [All Fields] OR "cerebral circulations" [All Fields] OR "flow, brain blood" [All Fields] OR "circulation, cerebrovascular" [All Fields] OR "cerebrovascular circulation" [All Fields]).

Selection criteria and study inclusion

An *a priori* systematic review protocol was developed. The full protocol can be obtained from the corresponding author upon reasonable request. Two study protocols were registered in Prospero [ID-numbers: CRD42023339278 (preclinical data) and CRD42022339152 (clinical data)]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines and the recommendations from the Cochrane Collaboration (20). The population, intervention, comparison, outcome, and study design (PICOS) approach was chosen as follows: study design, sample characteristics of the sample, intervention, comparator and outcomes.

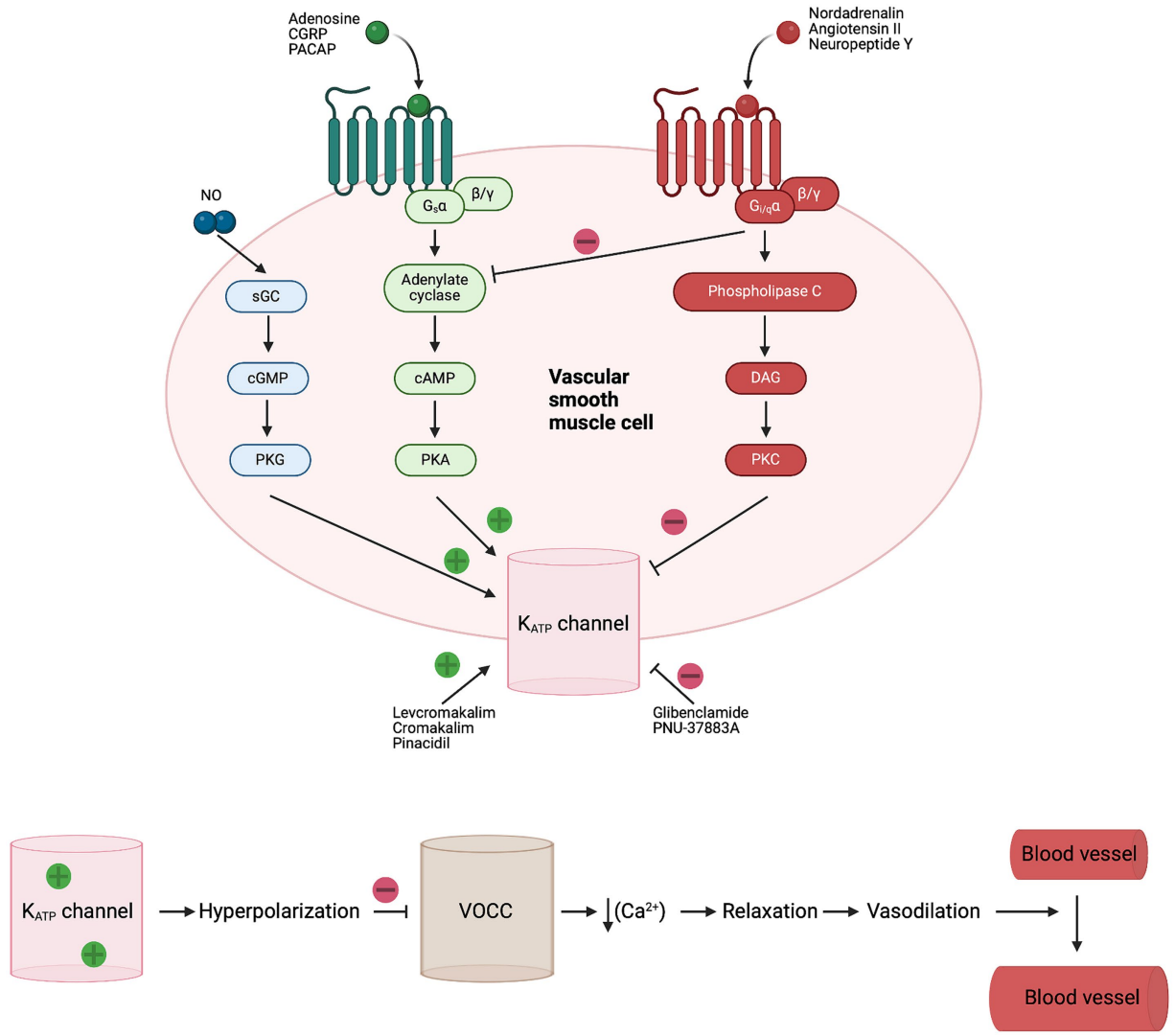

FIGURE 2
Signaling pathway and opening of K_{ATP} channels in vascular SMC. Numerous endogenous vasodilators activate K_{ATP} channels in SMC through adenylate cyclase and PKA phosphorylation. While endogenous vasoconstrictors inhibit K_{ATP} channels in SMC through DAG and PKC phosphorylation. Activation of K_{ATP} leads to hyperpolarization and closing of voltage-operated Ca^{2+} channels (VOCC), followed by relaxation of SMC and increased blood flow (17). CGRP, calcitonin gene-related peptide; DAG, diacylglycerol; Gs, G-protein-coupled receptor alpha s; Gi/q, G-protein-coupled receptor alpha i/q; sGC, soluble guanylate cyclase; K_{ATP}, ATP-sensitive potassium; NO, nitric oxide; PACAP, pituitary adenylate cyclase activating polypeptide; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; SMC, smooth muscle cell; VOCC, voltage-operated Ca^{2+} channels.

After removing duplicates, two investigators (HASD and LK) independently screened articles, first by title and abstract and then full text to confirm eligibility for this review. The references of the included studies were also screened. Any disagreements between the investigators were resolved through discussion. If the conflict remained, a third investigator (MMK) made the final decision. Studies were restricted to English language and both preclinical and clinical studies investigating K_{ATP} channel opener (KCO) or K_{ATP} channel inhibitor (KCI; Table 1) and their effects on CBF and the diameter of cerebal arteries were included. Reviews, meta-analysis, conference proceedings and case reports were excluded. For each included study, the following data were extracted: article information (title, authors, and journal), study design, characteristics of the sample intervention, technique, substances used, and outcomes. No formal meta-analysis was planned.

Results

The database search identified 294 citations of which 78 were duplicates. A total of 216 studies were screened by title and abstract and 91 were full text screened. Of these, 51 studies were included, 45 preclinical (35 studies *in vivo*, seven studies *ex vivo*, two studies *in vivo* and *ex vivo* and one study *in vivo* and *in vitro*) and six clinical studies (Figure 3). Preclinical and clinical data are summarized in Tables 2, 3, respectively.

Summary of preclinical studies

K_{ATP} channels are expressed in SMCs (50, 54), ECs (11, 52–54), and pericytes (11, 43, 51, 58, 62). *In-vivo* studies showed that K_{ATP} channel openers (KCOs) dilated pial arteries and pial arterioles measured using

TABLE 1 An overview of KCOs and KCIs included in the studies.

KCOs	
	Levcromakalim
	Cromakalim
	Diazoxide
	Pinacidil
	Aprikalim
	Iptakalim
	Nicorandil
	Y-26763
KCIs	
	Glibenclamide
	$BaCl_2$
	Tolbutamide
	Glyburide
	Hydroxylysine
	PNU-37883
	PNU-37883A

KCI; K_{ATP} channel inhibitor KCO; K_{ATP} channel opener.

a video microscaler through a cranial window in cats (4), rats (35), and pigs/piglets (5, 22–25, 28, 31). The basilar artery was also dilated upon administration of KCOs in rats (44, 45). CBF measured by laser-Doppler flowmeter through a cranial window over the region supplied by the middle cerebral artery (MCA) was increased upon administration of KCOs in mice (46–48). Using patch-clamp electrophysiology, *ex-vivo* studies showed that application of KCOs led to hyperpolarization of pericytes in mice (11) and rats (58), which was inhibited by K_{ATP} channel inhibitor (KCI), glibenclamide. In rats, endothelium removal from cerebral arterioles resulted in decreased dilation in response to administration of KCOs (52) and reduced the vasoconstrictive effect of glibenclamide (53). The majority of preclinical studies showed that glibenclamide reduced the increase in CBF upon KCO administration without altering the baseline CBF nor the baseline vascular tone (11, 28, 29, 31, 34, 35, 40, 53, 54).

Summary of clinical studies

KCOs have been used in clinical trials for the treatment of angina pectoris, asthma and hypertension. The most common adverse event mentioned during treatment with KCOs was headache (3, 68, 69).

Clinical studies assessed the effect of K_{ATP} channels in cerebral hemodynamic in healthy participants and individuals with migraine using magnetic resonance (MR) angiography and transcranial Doppler. Intravenous infusion of KCO, levcromakalim increased CBF and dilated the MCA, the middle meningeal artery (MMA) and the superficial temporal artery (STA) (3, 6, 70). Glibenclamide did not affect the baseline diameter of intra- and extracerebral arteries (6). In contrast to preclinical studies, glibenclamide failed to attenuate the vasodilation induced by levcromakalim (6) or by other potent endogenous vasodilators including the calcitonin gene-related peptide (CGRP) (67, 71) and the pituitary adenylate cyclase-activating polypeptide (PACAP-38) (64).

Discussion

The aim of the present study is to systematically review the involvement of K_{ATP} channels in the cerebral vasculature and the contribution of these channels in cerebrovascular hemodynamics. The main findings are that K_{ATP} channels are expressed in cerebral vascular SMCs, ECs and pericytes and play a key role in the regulation of CBF across species (7–12, 72).

The K_{ATP} channel is a hetero-octameric complex consisting of four regulatory sulfonylurea receptor (SUR1, SUR2A or SUR2B) subunits and four pore-forming K^+ inwardly rectifying (Kir6.1 or Kir6.2) subunits (73). Different compositions of K_{ATP} channel subunits lead to unique functions in distinct tissues (74, 75) (Table 4). K_{ATP} channels, depending on their different subunit composition, are expressed in vascular SMCs and neurons. Of note, in this systematic review, a frequently used KCO, levcromakalim, has a high affinity to the Kir6.1/SUR2B subunit in the vessels (76), while glibenclamide, a non-specific KCI, has a higher affinity to the Kir6.2/SUR1 subunit which is not present in vessels (77).

Expression of K_{ATP} channels

K_{ATP} channels are expressed in SMCs, ECs and pericytes. The latter are contractile cells found on the abluminal surface of the endothelial wall of capillaries (78). Two *ex-vivo* studies using patch-clamp electrophysiology to measure whole cell currents in brain pericytes showed that activation of K_{ATP} channels led to hyperpolarization of pericytes, and this effect was inhibited by glibenclamide (11, 58). K_{ATP} channels expressed in the endothelium of cerebral arteries might be a key component in the regulation of CBF. Endothelium removal of cerebral arterioles significantly affected the response to K_{ATP} channel modulators (52, 53). Endothelium produces numerous vasoactive mediators, including nitric oxide (NO) that influences CBF (10). Impaired endothelial function associated with hypertension (40), diabetes mellitus (35, 52), and aging (45, 46) reduced the impact of KCOs/KCIs. These findings indicate that K_{ATP} channel-induced vasodilation is endothelium-dependent. However, Janigro et al. (54) demonstrated that KCOs caused a pronounced vascular SMC-mediated and a lesser endothelium-dependent vasodilation in rats.

K_{ATP} channels and cerebral hemodynamics

Administration of synthetic KCOs (Table 1) increased the CBF measured through cranial window using a laser-Doppler flowmeter (11, 40, 44, 46, 48). Whereas, glibenclamide and other synthetic KCIs inhibited the effect induced by KCOs (40, 46, 48). The majority of the preclinical studies showed that glibenclamide did not affect the baseline CBF and the vascular tone measured by laser-Doppler flowmeter (11, 40) except one study which reported that glibenclamide injected in the cisterna magna lowered baseline CBF (38). CBF is dependent on cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR). The diameter of small arteries and pial arterioles contributes to CVR. In particular, dilation of pial arterioles might increase CBF while constriction of these vessels could decrease CBF (1).

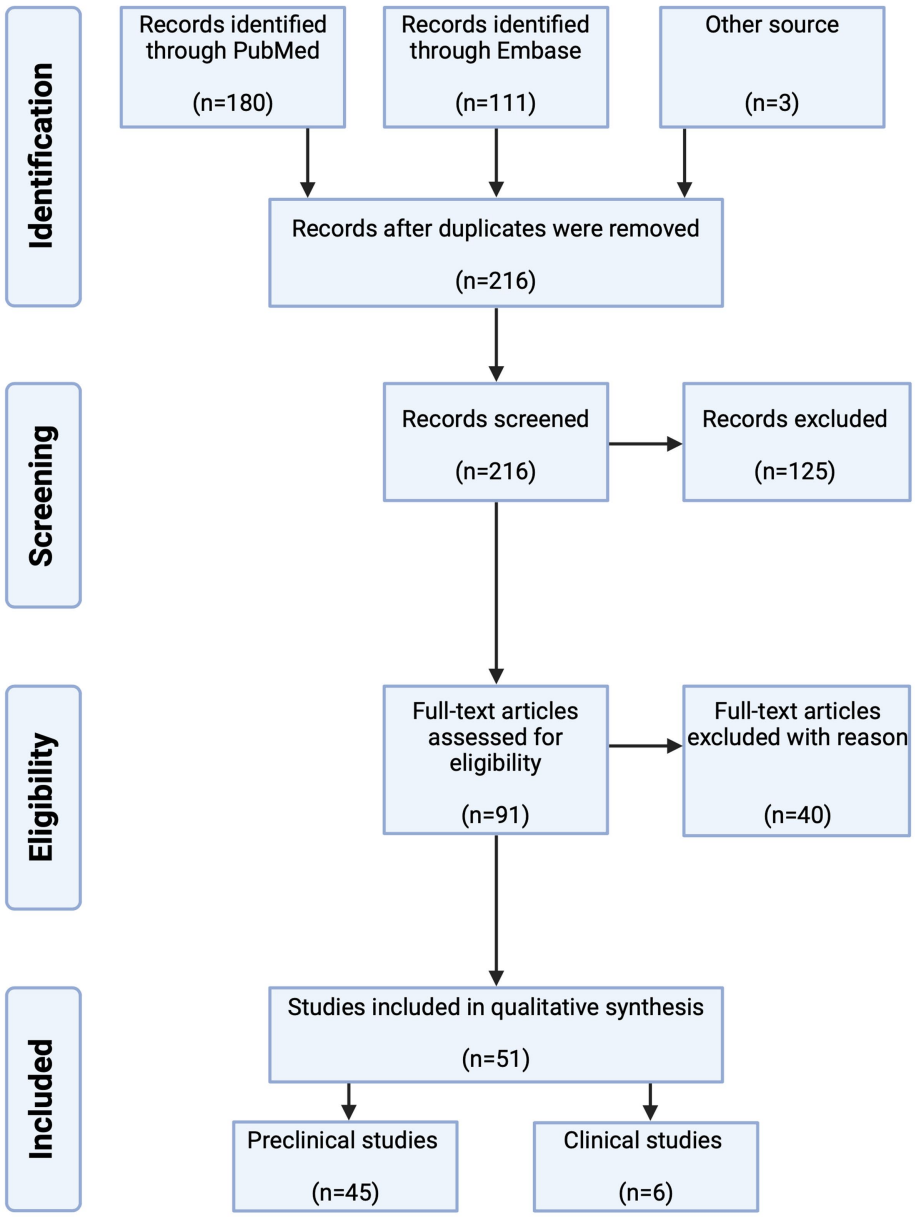

FIGURE 3
Flowchart of search strategy.

KCOs dilated pial arteries (5, 22–25, 79), pial arterioles (4, 28, 31, 35, 61), the basilar artery (44, 45), and the MCA (50, 52). Here, glibenclamide and other synthetic KCIs reversed this dilation (4, 28, 31, 35, 43–45, 61). Glibenclamide did not affect the baseline diameter of these vessels *in vivo* (28, 29, 31, 34, 35) or *ex vivo* (53, 54). However, in one study, glibenclamide induced constriction of isolated MMAs in the absence of other vasoactive stimuli but did not alter the diameter of cerebral arteries (59).

Inhalation of anesthetics such as isoflurane/sevoflurane or hypoxia caused dilation of cerebral pial arterioles which was inhibited by glibenclamide (32). Adenosine induced dilation of cerebral arterioles in pigs (29) and hyperpolarized retinal pericytes in mice and rats (11, 58) and capillary ECs in mice (11), and administration of glibenclamide inhibited the effects of adenosine. CGRP *in vivo* and *in vitro* induced dilation of dural and pial arteries. Glibenclamide attenuated the effect of CGRP *in vivo*, but not *in vitro* (60). In healthy participants, glibenclamide had no effect on CGRP-induced headache (67).

Clinical studies demonstrated that levcromakalim dilated the MMA, the MCA and the STA in healthy humans (6) and individuals with migraine (3). In contrast to the preclinical studies, glibenclamide failed to attenuate the vascular changes induced by levcromakalim (6), PACAP-38 (64), CGRP (67) or hypercapnia (65). Of note, adenosine, CGRP and PACAP-38 are potent endogenous vasodilators which activate K_{ATP} channels indirectly through adenylate cyclase and protein kinase A phosphorylation (80–82). One study, however, reported that hypoxia increased the anterior circulation of the brain and this

TABLE 2 Summary of preclinical studies.

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
1	Armstead W et al. (5)	To investigate the effect of ischemia/hypoxia on K_{ATP} induced pial artery dilation.	Cromakalim (10^{-8}–10^{-6} M).	Pigs ($n = 55$)	Diameters of pial arteries were measured using a video microscopy through a cranial window over the parietal cortex.	Ischemia or hypoxia blunted dilation of pial arteries induced by cromakalim.	Ischemia or hypoxia impaired K_{ATP} channel mediated cerebrovasodilation.
2	Ca et al. (21)	To investigate the vascular activity of mastoparan in the cerebral circulation and the role of K_{ATP} channel activation.	Mastoparan (10^{-8}–10^{-6} M). Glibenclamide (10^{-6} M).	Pigs ($n = 24$)	Diameters of pial arteries were measured with video microscaler through a cranial window over the parietal cortex.	Mastoparan, a pertussis toxin-sensitive G protein, induced pial artery dilation which was blunted by co-administered glibenclamide.	G-protein activation elicited cerebrovasodilation through interaction with K_{ATP} channels.
3	Ann et al. (22)	To investigate the effect on fluid percussion brain injury (FPI) on K_{ATP} channel activity.	Cromakalim (10^{-8}–10^{-6} M).	Pigs ($n = 144$)	Diameters of pial arteries were measured using a video microscaler through a cranial window over the parietal cortex.	Cromakalim induced dilation of pial arteries which was blunted for at least 72 h post FPI in the newborn pigs and at least 4 h post FPI in the juvenile pigs, respectively.	Newborn pigs were more sensitive to traumatic vascular injury than the juvenile pigs.
					FPI was produced using a pendulum to strike a piston on a saline-filled cylinder.	K_{ATP} channel function was impaired to a greater extent and for a longer time period in the newborn vs. the juvenile pig.	
4	Armstead et al. (23)	To investigate the role of heat shock protein (HSP) in the modulation of K^+ channel induced pial artery dilation after FPI.	Cromakalim (10^{-8} M). CGRP (10^{-6} M). HSP-27 (1 μg/mL). HSP-70 (1 μg/mL).	Pigs ($n = 30$)	Diameters of pial arteries were measured with a video microscaler through a cranial window over the parietal skull. FPI was produced using a pendulum to strike a piston on a saline-filled cylinder.	Cromakalim and CGRP induced dilation of pial arteries. Under non-FPI, co-administration of exogenous HSP-27 blunted dilation to cromakalim and CGRP. However, co-administration of exogenous HSP-70 potentiated dilation to cromakalim and CGRP. FPI increased the concentration of HSP-27 in cerebrospinal fluid and decreased the concentration of HSP-70.	HSP-27 and HSP-70 contributed to modulation of K^+ channel induced pial artery dilation.

(Continued)

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
5	Armstead et al. (24)	To investigate whether K^+ channel functional impairment arising after FPI is prevented by phenylephrine in a sex-dependent manner.	Cromakalim (10^{-8}–10^{-6} M).	Pigs ($n = 70$)	Diameters of pial arteries were measured with a video microscaler through a cranial window over the parietal cortex.	Cromakalim dilated pial arteries, that was impaired after FPI, more in males than in females.	Phenylephrine prevented impairment of K_{ATP} channel-mediated cerebrovasodilation after FPI in females.
			Phenylephrine (1 μg/kg/min).		FPI was produced using a pendulum to strike a piston on a saline-filled cylinder.	After cromakalim, phenylephrine prevented reductions in cerebrovasodilation in females, but reduced the dilation in males.	
6	Armstead et al. (25)	To investigate whether vasopressin generates superoxide anion (O_2^-) in a cyclooxygenase dependent manner which could link vasopressin release to impaired K_{ATP} channel-induced pial artery dilation after FPI.	Cromakalim (10^{-8}–10^{-6} M).	Pigs ($n = 90$)	Diameters of pial arteries were measured using a video microscaler through a cranial window over the parietal cortex.	Under non-brain injury, vasopressin co-administered with cromakalim, diminished dilation of pial arteries induced by cromakalim.	Vasopressin blunted K_{ATP} channel mediated cerebrovasodilation after FPI.
			Vasopressin (40 pg./mL).		FPI was produced using a pendulum to strike a piston on a saline-filled cylinder.	Cromakalim induced pial artery dilation was attenuated following FPI.	
7	Pastor et al. (26)	To investigate whether inhaled nitric oxide (NO) prevents impairment of cerebrovasodilation in response to cromakalim after FPI.	Cromakalim (10^{-8}–10^{-6} M).	Pigs ($n = 60$)	Diameters of pial small arteries were measured using ANOVA for repeated measures through a cranial window over the parietal skull.	FPI impaired pial small artery dilation in response to cromakalim.	Inhaled NO prevented impairment of cerebral autoregulation after traumatic brain injury through protection of K^+ channel function.
					FPI was produced using a pendulum to strike a piston on a saline-filled cylinder.	Inhaled NO prevented loss of pial artery dilation in response to cromakalim.	
8	Wei et al. (27)	To investigate whether blockade of K_{ATP} channels in pial arterioles inhibits vasoconstriction from hypocapnic alkalosis.	Glyburide (1 μM).	Cats ($n = 15$)	Diameters of pial arterioles were measured using an image-splitting device attached to a microscope through a cranial window over the parietal cortex.	Hypocapnic alkalosis induced vasoconstriction of pial arterioles that was blocked by glyburide, hydroxylysine or L-NNA.	Inhibition of K_{ATP} channel in pial arterioles inhibited the vasoconstriction from hypocapnic alkalosis.
			Hydroxylysine (1 μM).				
			N^G-nitro-L-arginine (L-NNA) (250 μM).			All the drugs did not cause significant changes in baseline diameter.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
9	Nnorom et al. (28)	To investigate whether K_{ATP} channels play a role in neonatal cerebral dilation in response to hypercapnia.	Pinacidil (10^{-5} M).	Pigs (n = NR)	Diameters of pial arterioles were measured using a video microscope through a cranial window over the parietal cortex.	Pinacidil or hypercapnia caused dilation of pial arterioles.	Hypercapnia activated K_{ATP} channels leading to cerebral dilation of arterioles.
						Glibenclamide blocked the dilation to pinacidil and hypercapnia.	
			Glibenclamide (10^{-7}–10^{-6} M).		Hypercapnia was induced by ventilation with 5% or 10% CO_2 and 21% O_2.	However, glibenclamide alone had no effect on baseline diameters.	
10	Bari et al. (29)	To investigate the effects of ischemia on cerebral responses to arterial hypoxia and adenosine.	Adenosine (10^{-5}–10^{-4} M).	Pigs (n = 22)	Diameters of pial arterioles were measured using intravital microscopy through a cranial window over the parietal cortex.	Ischemia did not alter dilation of cerebral arterioles to arterial hypoxia and to adenosine.	Cerebral dilation to hypoxia and adenosine was maintained after ischemia.
						Dilation of cerebral arterioles to arterial hypercapnia was reduced by ischemia.	
			Glibenclamide (10^{-6}–10^{-5} M).		Ischemia was achieved by increasing intracranial pressure.	Glibenclamide reduced dilations of cerebral arterioles to adenosine but did not change baseline diameters.	
11	Patel et al. (30)	To investigate the effects of endothelin-1 (ET-1) on cystathionine δ-lyase catalyzed brain H_2S production.	ET-1 (10^{-12}–10^{-8} M).	Pigs (n = 50)	Diameters of pial arterioles were measured with video microscaler through a cranial window over the parietal cortex.	ET-1 caused dilation of pial arterioles, an effect which was completely blocked by glibenclamide.	H_2S mediated the vasodilator effect of ET-1 in the cerebral circulation via a mechanism that involved activation of K_{ATP} channels in vascular SMC.
			Glibenclamide (10^{-7} M).			ET-1 increased H_2S production by the brain via cystathionine δ -lyase activation.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
12	Bari et al. (31)	To investigate whether cerebral vasodilation induced by aprikalim is dependent on production of NO.	Aprikalim (10^{-8}–10^{-6} M). Glibenclamide (10^{-5} M). N^{G}-nitro-L-arginine methyl ester (L-NAME) (15 mg/kg).	Piglets ($n = 40$)	Diameters of pial arterioles were measured using a video microscaler through a cranial window over the parietal cortex.	Aprikalim induced dilation of pial arterioles. However, L-NAME attenuated this dilation. Glibenclamide did not alter baseline diameter.	Aprikalim-induced dilation of pial arterioles is mediated partly by NO.
13	Lida et al. (32)	To investigate the effects of isoflurane and sevoflurane on pial arterioles via K_{ATP} channel activation.	Isoflurane Sevoflurane Glibenclamide (10^{-7}–10^{-5} M).	Dogs ($n = 24$)	Diameters of pial arterioles were measured using a video micrometer through a cranial window over the parietal cortex. Systemic (inhalation) and topical administration of isoflurane and sevoflurane.	Inhalation or topical application of either isoflurane or sevoflurane induced dilation of pial arterioles and glibenclamide attenuated the dilation.	Dilation of pial arterioles appeared to be activated by K_{ATP} channels.
14	Wei et al. (4)	To investigate the role of K^+ channels in the vasodilator action on pial arterioles.	Pinacidil (10^{-7}–10^{-6} M). Cromakalim (10^{-7}–10^{-6} M). Glyburide (1 μM).	Cats ($n = 54$)	Diameters of pial arterioles were measured with a Vickers image splitting device through a cranial window over the parietal cortex.	Pinacidil and cromakalim dilated pial arterioles which was inhibited by glyburide.	K_{ATP} channels played a role in the vasodilation of pial arterioles.
15	Faraci et al. (33)	To investigate whether aging is associated with impaired dilation of cerebral arterioles in response to activation of K_{ATP} channels.	Aprikalim (1–10 μM).	Rats ($n = 7$)	Diameters of cerebral arterioles were measured using a video microscope through a cranial window over the parietal cortex.	Aprikalim dilated cerebral arterioles that was similar in adult and old rats.	Activation of K_{ATP} channels were preserved during aging.

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
16	Parfenova et al. (34)	To investigate the effects of sulforaphane in intact cerebral circulation.	Glibenclamide (10^{-7} –10^{-6} M).	Pigs ($n = 28$)	Diameters of pial arterioles were measured using intravital microscopy through a cranial window.	Glibenclamide blocked the cerebral vasodilator responses to sulforaphane.	Sulforaphane-induced cerebral vasodilation was dependent on K_{ATP} channel.
			Sulforaphane (10^{-6} M–10^{-3} M or 0.4 mg/kg).			Glibenclamide did not change the baseline diameters of pial arterioles.	
17	Mayhan et al. (35)	To investigate the effects of K_{ATP} channel activation on diameter of pial arterioles and whether diabetes mellitus alters responses of pial arterioles to activation of K_{ATP} channels.	Aprikalim (0.1–10 μM).	Rats ($n = 29$)	Diameters of pial arterioles were measured using a video image-shearing device through a cranial window over the parietal cortex.	Aprikalim produced dose-related dilation of pial arterioles in non-diabetic rats but produced constriction or/and minimal dilation of pial arterioles in diabetic rats.	K_{ATP} channels regulated cerebral arterioles and were impaired during diabetes mellitus.
						The dilation of pial arterioles in non-diabetic rats was abolished by glibenclamide.	
			Glibenclamide (1 μM).			Glibenclamide did not change the baseline diameters of pial arterioles.	
18	Horinaka et al. (36)	To investigate K_{ATP} channel blocker on the CBF response to insulin-induced hypoglycemia.	Glibenclamide (1–2 μM).	Rats ($n =$ NR)	Infusion of glibenclamide in cisterna magna.	Glibenclamide had no significant effect on CBF in normoglycemic rats.	K_{ATP} channel was an important component of the mechanisms of the CBF response to hypoglycemia.
					CBF was determined by autoradiographic [^{14}C] iodoantipyrine (IAP) method (37).	Glibenclamide blocked the increases in CBF in hypoglycemia in a dose-dependent manner.	
19	Takanori et al. (38)	To investigate whether K_{ATP} channels participate in tonic regulation of CBF.	Glibenclamide (1–10 μM).	Rats ($n =$ NR)	Infusion of glibenclamide in cisterna magna.	Glibenclamide tended to lower baseline CBF in the cerebellar lobules, cerebellar cortex, pontine nuclei and spinal trigeminal nucleus.	K_{ATP} channel could play role in the tonic regulation of baseline CBF.
					CBF was determined by autoradiographic [^{14}C] IAP method (37).		

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
20	Tomiyama et al. (39)	To investigate CBF during hemodilution and hypoxia.	Glibenclamide (19.8 g).	Rats ($n = 48$)	Infusion of glibenclamide in cisterna magna.	Hypoxia induced a greater increase in CBF in the forebrain, cerebellum and brain stem than hemodilution.	K_{ATP} channels did not contribute to increasing CBF during hemodilution.
					CBF of the forebrain, cerebellum and brain stem were calculated by the indicator fractionation method with variables syringe flow, tissue weight etc.	Glibenclamide treatment attenuated the increase of CBF during hypoxia but not hemodilution.	Intravascular P_{O2} was an important regulator of cerebral vascular tone.
21	Takaba et al. (40)	To investigate the effect of K_{ATP} channel on CBF in hypertensive rats.	Y-26763 (25 mg/L).	Rats ($n = 26$)	Co-administration of Y-26763 (intracarotid infusion) and glibenclamide (intravenous infusion).	Infusion of Y-26763 increased CBF, which was inhibited by glibenclamide.	K_{ATP} channel could contribute to the regulation of CBF.
						However, glibenclamide did not alter the baseline CBF.	
			Glibenclamide (20 mg/kg).		CBF were measured using laser-Doppler flowmetry through a cranial window over the parietal cortex.	The response to Y-26763 was significantly impaired in hypertensive rats.	K_{ATP} channel was diminished in hypertensive rats.
22	Golonov et al. (41)	To investigate tolbutamide and glibenclamide effects on regional cerebral blood flow (rCBF) and arterial pressure elicited by hypoxemia.	Glibenclamide (5–200 pmol).	Rats ($n = 15$)	Microinjection of tolbutamide and glibenclamide into rostral ventrolateral medulla (RVL).	Tolbutamide and glibenclamide into RVL increased rCBF and facilitate elevations of rCBF induced by hypoxia.	K_{ATP} channels could mediate hypoxic excitation of oxygen-sensing RVL neurons.
			Tolbutamide (300 pmol in 20 nL).		rCBF were measured with a laser-Doppler flowmeter through a cranial window over the parietal cortex.		

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
23	Erdos et al. (42)	To investigate the dynamics of the rCBF changes during noxious stimulation in the thalamus and in the sensory cortex.	Glibenclamide (10 μg/rat).	Rats ($n = 10$)	Laser-Doppler flowmetry measured cortical and thalamic blood flow through a cranial window over the sensory cortex and in the medial part of the thalamus.	Noxious stimulation increased both cortical and thalamic blood flow, which was attenuated by glibenclamide.	CBF was adjusted during noxious stimulation, and this regulation involved activation of K_{ATP} channels.
					Noxious stimulation with an instrument (S44 stimulator), where sciatic nerve was electrically stimulated.		
24	Andreas et al. (43)	To investigate endothelium-derived factors on capillary ECs and K_{ATP} channels effects on capillary flow regulation and neurovascular coupling.	Pinacidil (5 mM).	Mice ($n =$ NR)	*In vivo* 4D two-photon microscopy measured the regulation of microvascular flow in somatosensory cortex.	Pinacidil induced dilation of penetrating arterioles, capillaries and precapillary sphincters.	K_{ATP} channels was found in pericytes and precapillary sphincters and had a key role for blood flow control.
						PNU-37883 abolished this vasodilator effect.	
			PNU-37883 (0.5–2.5 mM).		Pericytes responses to contractile and vasodilatory signals were measured with imaged diameter changes of penetrating arterioles, capillaries and precapillary sphincters.	Capillary blood flow was regulated primarily by pericytes and precapillary sphincters.	
25	Toyoda et al. (44)	To investigate whether K_{ATP} channels regulate CBF autoregulation during hypotension.	Levcromakalim (10^{-6} M).	Rats ($n = 20$)	Diameters of basilar artery and large and small branches from the basilar artery were measured using a video-analyzer through a cranial window over the ventral brain stem.	During hypotension, levcromakalim induced dilation of the diameters of all three vessels.	K_{ATP} channels played an essential role in the regulation of CBF to the brain stem during hypotension, mediated by compensatory dilation of small arteries, but not larger arteries.
			Glibenclamide (10^{-6}–10^{-5} M).		CBF to the ventral brain stem were measured by laser-Doppler flowmetry.	Glibenclamide impaired the dilator response of small arterioles but did not impaired the dilation of large arterioles or the basilar artery.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
26	Toyoda et al. (45)	To investigate regional differences and age-related changes in the contribution of K_{ATP} channels to vasodilator responses in the brain stem circulation.	Levcromakalim (10^{-7}–$10^{-5.5}$ M).	Rats ($n = 28$)	Diameters of the basilar artery and its branches were measured through a cranial window over the ventral brain stem using a microscope equipped with a TV-camera coupled to a video monitor.	Levcromakalim and Y-26763 increased the diameter of the basilar artery and its branches which was abolished by application of glibenclamide in both adult and aged rats.	No regional heterogeneity in vasodilator response in adult rats to K_{ATP} channel openers whereas dilator response of the large arteries due to activation of K_{ATP} channels is impaired in aged rats.
			Y-26763 ($10^{-7.5}$–10^{-6} M).			The dilator responses of the branches, but not the basilar artery, were smaller in aged rats.	
			Glibenclamide (10^{-6} M).				
27	Liu et al. (46)	To investigate rCBF response to K_{ATP} channel in Alzheimer's disease (AD) from three age groups.	Diazoxide (5 mg/kg).	Mice (3xTgAD, wild type and with Presenilin-1 mutation) ($n = 48$–78).	rCBF were measured using laser-Doppler flowmetry through a cranial window over the region supplied by the left MCA.	Diazoxide increased rCBF in young, middle-aged and old wild type mice as well as young 3xTgAD mice.	The age-exacerbated impairment of the rCBF response to diazoxide was associated to progression of Aβ pathology in AD brains.
			Glibenclamide (20 μM).			Diazoxide response to rCBF was reduced in middle-aged and old 3xTgAD mice.	
						The effect of diazoxide was abolished by glibenclamide.	
28	Liu et al. (47)	To investigate whether diazoxide modulates CBF in AD.	Diazoxide (5 mg/day).	Mice (3xTgAD) ($n =$ NR)	CBF were measured using laser-Doppler flowmetry on the surface of thinner skull over the region supplied by MCA.	Diazoxide increased rCBF in 3xTgAD mice.	Diazoxide can be a therapeutic potential drug in the treatment of AD.

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
29	Kotoda et al. (48)	To investigate the effect of nicorandil on CBF.	Nicorandil (1, 5, or 10 mg/kg).	Mice ($n = 48$)	CBF were measured using laser Doppler flowmeter through a cranial window over the region supplied by left MCA.	1 mg/kg nicorandil increased CBF while blood pressure and heartrate remained unaltered.	K_{ATP} channel was involved in CBF regulation.
			Glibenclamide (5 mg/kg).			This effect was inhibited by co-administration of either glibenclamide or L-NAME.	
			L-NAME (3 mg/kg).			However, nicorandil at higher doses (5 and 10 mg/kg) decreased CBF by decreasing blood pressure.	
30	Takaba et al. (49)	To investigate the effect of K_{ATP} opener on focal cerebral ischemia.	Y-26763 (24 μg/kg).	Rats ($n = 24$)	Trombotic occlusion of the distal MCA was produced photochemically.	The infarct volume was smaller in Y-26763-treated group than in the control group.	Activation of K_{ATP} channel appeared to be neuroprotective in focal cerebral ischemia.
					rCBF were measured by laser-Doppler flowmetry through a cranial window.	Y-26763 did not affect CBF before and after the occlusion.	
					After 3 days, the brain was dissected into slices and infarct volume of each rat was calculated as the product of the infarct times the 2-mm thickness of each section.	However, the beneficial effect of Y-26763 may be due to a direct action on neuron instead of its vasodilation effect.	
31	Nguyen et al. (50)	To investigate the mechanisms responsible for K^+ dilation of resistance-size cerebral arteries.	Pinacidil (10 μM).	Rats ($n =$ NR)	An intact MCA was dissected from the brain and the cerebral arterioles were separated from the parenchyma.	$BaCl_2$ and glibenclamide reduced dilations in cerebral arterioles and in the basilar artery induced by pinacidil.	SMCs were activated by a K_{ATP} channels.
			Glibenclamide (1 μM).		SMCs were isolated from basilar artery and patch-clamp recordings were performed.		
			$BaCl_2$ (10 μM).				

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
32	Guo et al. (51)	To investigate the impacts of iptakalim on pericyte contraction in stroke.	Iptakalim (10 mg/kg).	Mice (n = NR)	MCA occlusion (MCAO) were performed.	Iptakalim significantly promoted recovery of CBF after cerebral ischemia, reperfusion and inhibited pericytes contraction.	Iptakalim could improve microvascular disturbance by inhibiting pericyte contraction after ischemic stroke.
					Laser speckle imaging to illuminate the pial microcirculation.	Furthermore, iptakalim improved cerebral microcirculation.	
					Brain tissue were sliced and placed in a collagen-gel contraction assay to demonstrate cultured pericytes.		
33	Zimmermann et al. (52)	To investigate mechanisms underlying the diminished sensitivity of cerebral arteries in diabetic mellitus rats to K_{ATP} channel openers.	Pinacidil (10^{-9}–10^{-5} M).	Rats (n = NR)	MCA was dissected, and endothelium were removed.	Pinacidil and levcromakalim dilated MCA from both control and diabetic rats.	Diabetes mellitus resulted in a diminished response to K_{ATP} channel openers.
						However, MCA from diabetic rats were less sensitive to the drugs.	
			Levcromakalim (10^{-9}–10^{-5} M).		MCA diameter was measured with a video dimension analyzer.	Dilations to K_{ATP} openers were reduced by endothelium removal.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
34	Horiuchi et al. (53)	To investigate whether K_{ATP} channels are involved in acidosis-induced dilation of cerebral arterioles.	Glibenclamide (3 μM).	Rats ($n = 48$)	Cerebral arterioles from MCA were cannulated and diameters were measured with an inverted microscope.	Acidosis-induced dilations of the cerebral arterioles which was inhibited by either $BaCl_2$ or glibenclamide.	Acidosis stimulated K_{ATP} channels resulting in dilation of cerebral arterioles.
						Glibenclamide did not alter the baseline diameters of cerebral arterioles.	
			$BaCl_2$ (30 μM).		The endothelium from the arterioles were removed.	The dilation was significantly attenuated after endothelial impairment.	
35	Janigro et al. (54)	To investigate the effects of K_{ATP} opening on endothelium-dependent regulation of cerebrovascular tone.	Nicorandil (1 μM).	Rats ($n = 52$)	Cerebral arterioles were separated from the parenchyma.	K_{ATP} openers nicorandil or pinacidil induced cerebrovasodilation by directly acting on vascular SMC and by causing ECs to release NO.	K_{ATP} agonist caused a pronounced vascular SMC-mediated and a lesser NO and endothelium-dependent vasodilation.
			Pinacidil (1–10 μM).		The arterioles were cannulated with extra- or intraluminal application of drugs while measuring vessel diameter changes using a video analyzer.	Extraluminal application of nicorandil or pinacidil caused a more pronounced glibenclamide-sensitive vasodilation than applied intraluminally.	
			Glibenclamide (5–100 μM).		To test if the vasodilation was mediated by endothelial NOS activation: Vessels were pretreated with NOS inhibitors L-NNA or N^G-monomethyl-L-arginine (L-NMMA).	Glibenclamide applied either extra- or intraluminally did not affect baseline vessel diameter.	
36	Kinoshita et al. (55)	To investigate whether K_{ATP} channels play a part in vasodilator responses in cerebral microvessels.	Levcromakalim ($3 \cdot 10^{-8}$–$3 \cdot 10^{-7}$ M).	Rats ($n =$ NR)	Diameters of intact cerebral arterioles were measured by a video-microscopy.	Levcromakalim induced dilation of the cerebral parenchymal arterioles which was abolished by glibenclamide or lidocaine but not by $BaCl_2$.	Lidocaine could impair beneficial vasodilator responses mediated via K_{ATP} channels.
			Glibenclamide ($5 \cdot 10^{-6}$ M).				
			$BaCl_2$ (10^{-5} M)				
			Lidocaine (10^{-5}–$3 \cdot 10^{-5}$ M).		Arterioles were pretreated with prostaglandin $F_{2\alpha}$.		

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
37	Nakahata et al. (56)	To investigate whether K_{ATP} channels contribute to cerebral vasodilation mediated by mild hypercapnia.	Levcromakalim ($3 \cdot 10^{-8}$–$3 \cdot 10^{-7}$ M).	Rats (n = NR)	Brain was removed, sliced and placed in a perfusion chamber.	Mild hypercapnia (CO_2 = 50 mmHg) and levcromakalim induced significant dilation in the cerebral parenchymal arterioles, which was completely abolished by glibenclamide.	K_{ATP} channels played a crucial role in vasodilator responses produced by mild hypercapnia.
					Diameters of intact cerebral parenchymal arterioles were measured using computerized video-microscopy.		
			Glibenclamide ($5 \cdot 10^{-6}$ M).		Arterioles were pretreated with prostaglandin $F_{2\alpha}$.		
38	Movahed et al. (57)	To investigate the effects of hypoxia on vasodilator responses to K_{ATP} channel opener and NO-donor, S-nitroso-N-acetylpenicillamine (SNAP).	Levcromakalim (0.01–10 μM).	Pigs (n = 58)	Basilar artery was dissected.	Levcromakalim or SNAP induced concentrations-dependent dilations under both standard and hypoxic condition.	SNAP was a more effective vasodilator than levcromakalim during hypoxia.
					Tension experiments.	Under hypoxic conditions, vasodilation induced by levcromakalim was not significantly affected, which is more pronounced in SNAP-induced dilations.	
			Glibenclamide (10 μM).		The artery was precontracted by ET-1.	Glibenclamide attenuated levcromakalim-induced vasodilation.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
39	Li et al. (58)	To investigate the effects of adenosine on the physiology of retinal pericytes.	Adenosine (5 μM).	Rats (n = NR)	Patch-clamp electrophysiology to monitor the whole-cells currents of intact pericytes located on micro-vessels, isolated from retinas.	Hyperpolarization of retinal pericytes is due to the activation of K_{ATP} channels by adenosine or pinacidil, an effect which was blocked by glibenclamide.	Regulation of K_{ATP} channels allowed adenosine to serve as a vasoactive signal in the retinal microvasculature.
			Glibenclamide (100 nM).				
			Pinacidil (5 μM).		Membrane potential measurement.		
			Barium (3 mM).				
40	Sancho et al. (11)	To investigate whether ECs and pericytes in CNS capillaries expresses K_{ATP} channels.	Glibenclamide (20 μM).	Mice (n = NR)	Patch-clamp electrophysiology to measure whole cell current in isolated capillary ECs, pericytes and SMCs from cerebral pial arteries.	Pinacidil, adenosine or CADO, respectively, increased CBF.	K_{ATP} channels had an important role in capillary ECs and pericytes in the regulation of CBF.
			Pinacidil (10 μM).			Pinacidil, adenosine or CADO, respectively, in capillary ECs and pericytes caused membrane potential hyperpolarization, an effect that was reversed by glibenclamide and PNU-37783.	
			Adenosine analog (CADO) (1 μM).			Glibenclamide did not affect membrane currents, membrane potentials or CBF in the absence of K_{ATP} channel openers.	
			Adenosine (5–50 μM).		Membrane potential measurements from capillary ECs and pericytes on pressurized retina preparations (ophthalmic artery).	Adenosine failed to increase CBF in both ECs and pericytes specific Kir6.1 dominant-negative mice.	
			PNU-377883 (NR).		CBF measurement using laser-Doppler flowmetry through a cranial window over the somatosensory cortex.	Small K_{ATP} current in SMCs isolated from either brain pial arteries or parenchymal arterioles.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
41	Syed et al. (59)	To investigate the role of K_{ATP} channel in regulation of middle meningeal arteries (MMA).	Cromakalim (10 μM).	Rats ($n = 30$)	*Ex vivo*, diameters of intact cerebral arteries and MMA were measured using a video detector in a myograph chamber.	Cromakalim induced a greater vasodilator effect of MMAs compared to cerebral arteries.	K_{ATP} channel activity contributed to the regulation of MMA but not cerebral artery diameter.
			Glibenclamide (1 nM–10 μM).		Smooth muscle membrane potential was measured for both MMA and cerebral arteries.	Glibenclamide and PNU-37883A induced constriction of isolated MMA's but did not alter cerebral artery diameter.	
			PNU-37883A (10 μM).		*In vivo* two-photon imaging of meningeal blood vessels through a cranial window.	In MMA, glibenclamide caused a membrane potential depolarization in smooth muscle. However, in cerebral artery smooth muscle, membrane potential was not significantly different in the presence or absence of glibenclamide.	
42	Gozalov et al. (60)	To investigate the role of K_{ATP} channels in vasodilation in intracranial arteries by CGRP, NO-donor, glyceryl trinitrate (GTN) and transcranial electrical stimulation.	Glibenclamide (7 mg/kg).	Rats ($n =$ NR)	Diameters of dural and pial arteries were measured using a video-analyzer through a cranial window over the parietal skull.	CGRP, GTN and transcranial electrical stimulation induced dilation of dural and pial arteries, *in vivo* and *in vitro*.	Glibenclamide *in vivo* but not *in vitro* inhibited CGRP-induced vasodilation.
						In vivo, glibenclamide attenuated CGRP-induced dural artery dilation and transcranial electrical stimulation-induced pial and dural artery dilation.	
			CGRP (0.3 μg/kg).		rCBF were measured over the parietal bone and pial arteries by laser-Doppler flowmetry.	Glibenclamide had no effect on pial or dural vasodilation induced by GTN.	K_{ATP} channels could be involved in the migraine generating effect of CGRP.
			GTN (20 μg/kg).			*In vitro*, glibenclamide did not significantly inhibit the vasodilation induced by GTN and CGRP, respectively.	

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TABLE 2 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study population (n)	Method	Main outcome(s)	Conclusion
43	Taguchi et al. (61)	To investigate whether activation of K_{ATP} channels mediates dilation of cerebral arterioles during hypoxia.	Aprikalim (10^{-7}–10^{-6} M).	Rabbits ($n = 31$).	Diameters of cerebral arterioles were measured using a video micrometer through a cranial window over the parietal cortex.	Aprikalim induced dilation of cerebral arterioles which was inhibited by glibenclamide	Dilation of cerebral arterioles in response to hypoxia were mediated by activation of K_{ATP} channels.
			Glibenclamide (10^{-6} M).			Glibenclamide alone had no effect on baseline diameters.	
44	Hariharan et al. (62)	To investigate whether brain capillary pericytes control local blood flow via K_{ATP} channel.	Pinacidil (10 μM).	Mice (n = NR)	Diameters of pial arteries were measured through a cranial window.	Barium applied to the cortical surface prior to pinacidil ejection on a pericyte, blocked Kir2.1 channel and abolished the increase in dilation of arterioles and capillary blood flow.	Brain capillary pericytes controlled blood flow through K_{ATP} channel activity.
			Barium (100 μM).		Membrane potential measurements on capillary pericytes.		
45	Simard et al. (63)	To investigate whether SUR1 is an important element in the inflammatory response to subarachnoid hemorrhage (SAH).	Glibenclamide (10 μg/kg and 0.5 μL/h)	Rats ($n = 35$).	The model of SAH involved endovascular puncture of the ICA using a 4-0 filament, produced mild-to-moderate SAH, associated with low mortality.	Critical responses to SAH-inflammation and an increase in barrier permeability, were significantly attenuated by block of SUR1 by glibenclamide, a selective SUR1 inhibitor.	SUR1 was important in the pathophysiology of SAH.
					CBF were measured using Laser Doppler flowmeter affixed to the skull.		
					Shortly after inducing SAH (<15 min), glibenclamide was administrated (loading dose of 10 μg/kg intraperitoneally and then 0.5 μL/h infusion subcutaneously).		
					In situ hybridization was used to detect mRNA for *Abcc8* which encodes SUR1.	Immunohistochemistry for SUR1 showed minimal labeling in uninjured controls compared to 24 h after SAH in the inferomedial cortex.	

AD, Alzheimer's disease, CBF, cerebral blood flow; rCBF, regional cerebral blood flow; CGRP, calcitonin gene-related peptide; EC; endothelial cell; ET-1, endothelin-1; FPI, fluid percussion brain injury; HSP, heat shock protein; KATP, ATP-sensitive potassium; KCI; KATP channel inhibitor KCO; KATP channel opener; MCA, middle cerebral artery; MMA, middle meningeal artery; NO, nitric oxide; NR, not reported; RVL, rostral ventrolateral medulla; SAH, subarachnoid hemorrhage; SMC, smooth muscle cell.

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TABLE 3 Summary of clinical studies.

N	Author	Purpose of the study	Substance(s) and dose(s)	Study design	Study population (n)	Method	Main outcome(s)	Conclusion
1	Al-Karagholi et al. (6)	To investigate the effects of levcromakalim and glibenclamide on global CBF (gCBF) and on circumference of extracranial and intracranial arteries.	Levcromakalim (1 mg)	Double-blind, placebo-controlled, three-way crossover design.	Healthy participants ($n = 15$)	Randomization of the participants into 3 different study days, separated by at least 1 week.	Levcromakalim increased global gCBF with 14% and dilated the cerebral arteries.	K_{ATP} channels played an important role in cerebral hemodynamics.
						Day 1: Oral glibenclamide followed by levcromakalim infusion.		
						Day 2: Oral glibenclamide followed by placebo (isotonic saline) infusion.		
						Day 3: Oral placebo (multivitamin pill) followed by placebo (isotonic saline) infusion.		
						The participants underwent 5 MRI sessions: (time points: −20, 60, 120, 160 and 200 min). Administration of oral glibenclamide/placebo infusion at 0 min and administration of levcromakalim/ placebo infusion over 20 min at 140 min of the timeline of the study.		
						At each MRI-session, MR angiography and phase-contrast mapping were performed.		
						MR angiography to measure vessels: MCA, MMA and STA		
			Glibenclamide (10 mg).			Phase-contrast mapping to measure gCBF.	Glibenclamide did not alter the cerebral hemodynamics.	

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TABLE 3 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study design	Study population (n)	Method	Main outcome(s)	Conclusion
2	Kokoti et al. (64)	To investigate whether glibenclamide attenuates pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38)-induced headache and vascular changes.	PACAP-38 (10 pmol/kg/min). Glibenclamide (10 mg).	Double-blind, randomized, placebo-controlled and. Crossover design.	Healthy participants ($n = 20$)	Randomization of the participants into 2 different study days, separated by at least 1 week. Intravenous infusion of PACAP-38 over 20 min, immediately followed by either oral glibenclamide or placebo. Mean velocity of blood flow in MCA ($V_{meanMCA}$) were measured using transcranial Doppler.	PACAP-38 decreased $V_{meanMCA}$. Posttreatment with glibenclamide failed to attenuate vascular changes.	PACAP-38 induced vascular changes might be mediated by the SUR2B K_{ATP} channel.
3	Bayerle-Eder et al. (65)	To investigate whether glibenclamide alters the cerebral and ocular vasodilator response to hypercapnia.	Glibenclamide (5 mg).	Controlled, randomized, double-blind, two-way crossover study	Healthy participants ($n = 10$)	Participants received either oral glibenclamide and intravenous placebo or oral placebo and intravenous insulin. Pulsatile choroidal blood flow was assessed through laser interferometric measurements of fundus pulsation on the participant's eye. $V_{meanMCA}$ and the ophthalmic artery were measured using Doppler sonography.	Hypercapnia caused a significant increase in fundus pulsation amplitude and $V_{meanMCA}$. However, glibenclamide had no effect on hypercapnia-induced hemodynamic responses.	Hypercapnia-induced vasodilation in cerebral and ocular vessels were not mediated by activation of K_{ATP} channels.
4	Rocha et al. (66)	To investigate whether K_{ATP} channels blockade affects the increase in CBF during hypoxia.	Glibenclamide (5 mg).	NR	Healthy participants ($n = 9$)	After induction of hypoxia, oral glibenclamide was administered. Blood flow of internal carotid artery and vertebral artery were conducted via Doppler Ultrasound.	Hypoxia induced increase in the anterior circulation and were attenuated under K_{ATP} channel blockage.	Activation of K_{ATP} channels modulated vascular tone in the anterior circulation of the brain.
5	Al-Karagholi et al. (3)	To investigate whether opening of K_{ATP} channels causes migraine attack.	Levcromakalim (0.05 mg/min).	Randomized, double-blind, placebo-controlled, crossover study	Migraine patients without aura ($n = 16$)	Randomization of the participants into 2 different study days, separated by at least 1 week. Intravenous infusion of either levcromakalim or placebo (isotonic saline). $V_{meanMCA}$ were measured using a transcranial Doppler.	Levcromakalim increased diameter of STA but had no significant effect on radial artery diameter or $V_{meanMCA}$.	K_{ATP} channels had no significant on $V_{meanMCA}$.

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TABLE 3 (Continued)

N	Author	Purpose of the study	Substance(s) and dose(s)	Study design	Study population (n)	Method	Main outcome(s)	Conclusion
6	Coskun et al. (67)	To investigate the effect of glibenclamide on CGRP-induced headache and vascular changes.	CGRP (1.5 μg/min).	Randomized, double-blind, placebo-controlled, crossover study	Healthy participants ($n = 20$)	Randomization of participants into 2 different study days, separated by at least 1 week.	Glibenclamide had no effect on CGRP-induced headache and vascular changes (decrease in V_{MCA}, increase in facial skin blood flow and dilation of STA and radial artery, respectively).	CGRP-induced responses could be mediated by SUR2B K_{ATP} channel.
						Intravenous infusion of CGRP 2 h after oral pretreatment with either placebo (calcium supplement tablet) or glibenclamide.		
						Facial flushing was measured by speckle contrast imager.		
			Glibenclamide (10 mg).			MCA blood flow velocity (V_{MCA}) were measured using a transcranial Doppler.		
						Diameters of STA and radial artery were measured using an ultrasonography (Dermascan).		

CBF, cerebral blood flow; gCBF, global cerebral blood flow; CGRP, calcitonin gene-related peptide, KATP, ATP-sensitive potassium; MRI, magnetic resonance imaging; MCA, middle cerebral artery; MMA, middle meningeal artery; NR, not reported; PACAP, pituitary adenylate cyclase activating polypeptide; STA, superficial temporal artery; $V_{meanMCA}$, mean velocity of blood flow in MCA.

effect was attenuated by K_{ATP} channel blockage with glibenclamide (66). The lack of effect of glibenclamide in clinical studies could be attributed to differences in administration routes, metabolic rate and/or tissue expression of K_{ATP} channels across species. Basic mathematical modeling of pharmacokinetics and receptor potencies showed that the dose of glibenclamide used in clinical studies had receptor occupancy of 26% at the migraine relevant K_{ATP} channel subtype Kir6.1/SUR2B (83).

Limitations and future perspective

The major limitations for the preclinical studies are differences in methodological approaches including subjects, designs, concentrations and formulations of different types of KCOs and KCIs, potentially affecting the reported results (Table 2). Shortcomings of clinical trials assessing the hemodynamics role of K_{ATP} channel are (1) the use of low dose of glibenclamide, (2) including individuals from all age groups, and (3) not evaluating the long-term effect of KCOs or KCIs on cerebral hemodynamics and how endothelial dysfunction interferes with this effect. An additional question is whether K_{ATP} channels are involved in cerebral angiogenesis.

The K_{ATP} channel emerges to be a potential target for numerous pathological conditions such as migraine and ischemic stroke. Recent studies showed that K_{ATP} channel activation caused headache and migraine (3), indicating that KCIs might be a novel therapeutic approach for the treatment of headache and migraine. The fact that targeting K_{ATP} channels did not affect the baseline hemodynamic state, at least based on preclinical studies, is applicable to avoid serious adverse events. Activation of K_{ATP} channels increased CBF after cerebral ischemia in mice (51). More experiments are needed to reveal if KCOs have a clinically meaningful effect on cerebral hypoperfusion during ischemic stroke.

Other findings with direct clinical significance are that glibenclamide attenuated peripheral arterial dilation but failed to affect cerebral hemodynamics indicating an unique biochemical difference between K_{ATP} expressed in cerebral circulation and those expressed in peripheral arteries.

Several scenarios might underlie this difference, including expression of different SUR and Kir6 isoforms, different expression levels, post-translational modifications that render cerebral vascular K_{ATP} channels less sensitive to KCIs and/or existence of other cerebral regulatory mechanisms with higher impact. Western blotting and quantitative PCR could be used to compare the isoforms' expression within cerebral and peripheral arteries. Patch-clamp electrophysiology on isolated SMCs or ECs from the cerebral and peripheral arteries can assess the functional properties and thereby drug sensitivity.

These studies might allow a possible treatment avenue for individuals with hypertension without altering cerebral hemodynamics. Several clinical studies applied KCO to treat hypertension (68, 84–86). However, a common adverse event was headache, most likely due to changes in cephalic hemodynamics. Yet, more selective agonists are needed to avoid adverse events. The next step is the development of a selective KCO to avoid headache when treating hypertension. An agonist with high affinity to the Kir6.1 isoform of K_{ATP} channels could be an applicable candidate.

TABLE 4 Distribution of K_{ATP} channels.

K_{ATP} channels subtypes	Tissue expression
Kir6.1/SUR2B	Smooth muscle
Kir6.2/SUR1	Brain and pancreas
Kir6.2/SUR2A	Cardiac and skeletal muscle
Kir6.2/SUR2B	Smooth muscle

K_{ATP}, ATP-sensitive potassium; Kir, K+ inwardly rectifying; SUR, sulfonylurea receptor.

Conclusion

Preclinical and clinical data from this systematic review demonstrated that K_{ATP} channels are implicated in the regulation of cerebral hemodynamic. The main findings are that K_{ATP} channels are expressed in cerebral vascular SMCs, ECs and pericytes. KCO increased CBF and dilated cerebral arteries in both preclinical and clinical data. Glibenclamide did not change baseline CBF and cerebral diameter in preclinical studies and did not attenuate the vasodilation induced by KCOs in clinical studies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HASD: Writing – original draft, Writing – review & editing. LK: Writing – review & editing, Writing – original draft. MMK: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AD	Alzheimer's disease
CBF	Cerebral blood flow
gCBF	Global cerebral blood flow
rCBF	Regional cerebral blood flow
CGRP	Calcitonin gene-related peptide
ECs	Endothelial cells
ET-1	Endothelin-1
FPI	Fluid percussion brain injury
GTN	Glyceryl trinitrate
HSP	Heat shock protein
K_{ATP}	ATP-sensitive potassium
KCI	K_{ATP} channel inhibitor
KCO	K_{ATP} channel opener
Kir	K^+ inwardly rectifying
L-NAME	N^G-nitro-L-arginine methyl ester
L-NMMA	N^G-monomethyl-L-arginine
L-NNA	N^G-nitro-L-arginine
MCA	Middle cerebral artery
MCAO	Middle cerebral artery occlusion
MMA	Middle meningeal artery
NO	Nitric oxide
PACAP	Pituitary adenylate cyclase-activating polypeptide
RVL	Rostral ventrolateral medulla
SMC	Smooth muscle cell
SNAP	S-nitroso-N-acetylpenicillamine
STA	Superficial temporal artery
SUR	Sulfonylurea receptor
V_{MCA}	Velocity of blood flow in MCA
$V_{meanMCA}$	Mean velocity of blood flow in MCA

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New evidence that vitamin D prevents headache: a bidirectional two-sample Mendelian randomization analysis

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Background: Previous observational clinical studies and meta-analyses have yielded inconsistent results regarding the relationship between vitamin D and headache, and the causal relationship remains unclear. The aim of this study was to investigate the causal relationship between vitamin D and headache by bidirectional two-sample Mendelian randomisation (MR) analysis.

Methods: The relationship between high levels of vitamin D and headache was investigated by two-sample MR analysis using publicly available genome-wide association study (GWAS) data. The primary method was inverse variance weighting (IVW), and secondary methods were weighted median and MR-Egger methods. No heterogeneity or horizontal multidirectionality was found in the MR results. The robustness and validity of the findings were assessed using the leave-behind method.

Results: A significant causal relationship was found between high vitamin D levels and headache using the IVW method (OR = 0.848; $p = 0.007$; 95% CI = 0.752–0.956). However, in a reverse analysis, no evidence of a causal relationship between headache and high levels of vitamin D was found using the IVW method (OR = 1.001; $p = 0.906$; 95% CI = 0.994–1.006). Our MR analyses showed no significant horizontal multidimensionality or heterogeneity ($p > 0.05$). Sensitivity analyses confirmed that MR estimates were not affected by single nucleotide polymorphisms (SNPs). Confirmation that our results are robust and valid has been obtained by the leave-one-out method.

Conclusion: Our study suggests that high levels of vitamin D prevent the risk of headache. However, there is no evidence of a causal relationship between headache and high levels of vitamin D. Vitamin D may reduce the risk of headache.

KEYWORDS

vitamin D, headache, Mendelian randomisation study, single nucleic acid polymorphism, prevention

Introduction

Vitamin D is a fat-soluble vitamin that plays several important roles in the body (1). It is mainly synthesised through the skin in the presence of sunlight and can also be ingested through food. Vitamin D promotes the absorption and utilisation of calcium and contributes to normal bone development and maintenance. It plays an important role in immune regulation, cell differentiation and inflammatory responses (2–5). In recent years, studies have increasingly focused on the role of vitamin D in neuropathic pain. Vitamin D receptors are widely distributed in the central and peripheral nervous system, suggesting that vitamin D may play a role in normal nervous system function and nociceptive modulation (6). Several studies have shown an association between vitamin D deficiency and the onset and exacerbation of headache, and that vitamin D supplementation can help alleviate the symptoms of headache (7, 8).

Headache is a common neurological symptom that manifests as pain or discomfort in different areas of the head (9). Its etiology is complex and diverse, including intracranial lesions, vascular abnormalities, infection, inflammation, and metabolic disorders (10). Headache can be divided into two categories: primary and secondary; the former, such as migraine and tension headache, are mostly associated with genetic, endocrine, and environmental factors; the latter is caused by specific diseases, such as brain tumour and cerebrovascular disease. The severity, frequency of attacks and accompanying symptoms of headache vary from person to person and affect the daily life and work of patients (11).

Preliminary studies have investigated the correlation between vitamin D and headache. Some studies have shown that people with lower levels of vitamin D are at greater risk of headaches and have more severe pain (12). In addition, vitamin D supplementation appears to reduce headaches and improve patients' quality of life (13, 14). Although some relevant studies have shown a correlation between vitamin D and headache, it is difficult to establish a specific causal relationship between the two.

Mendelian randomization (MR) analysis is an emerging statistical method that uses genetic variation as an instrumental variable to explore potential causal relationships between exposure factors and disease. Mendelian randomisation analysis provides a classification effect similar to that of a randomised controlled trial (RCT) by randomly classifying genetic alleles during sperm-egg binding (15). However, MRI analyses provide stronger causal inferences than traditional observational studies and are effective in controlling for the effects of confounding factors (16). Furthermore, there is a lack of magnetic resonance studies exploring the potential causal relationship between vitamin D and headache, suggesting that further research is needed in this area.

The aim of this study was to investigate the potential causal relationship between vitamin D and headache. By integrating existing genome-wide association study (GWAS) data, we aimed to assess the effect of vitamin D levels on the risk of headache onset. This will provide a scientific basis for the development of targeted prevention and treatment strategies.

Methods

The study design

For MR analysis requires a valid instrumental variable (IV) that satisfies three key assumptions to obtain reliable results. Firstly, the IV must be strongly associated with the exposure. Secondly, the IV must be independent of any confounding factors that may affect the exposure and outcome. Finally, the IV must affect the outcome solely through the exposure (17). The study consisted of several core steps, including the use of multiple MR methods (IVW, WM, MR Egger), multiplicity assessment, and heterogeneity and sensitivity analyses. These steps were taken to select genetic IVs associated with exposure and to examine the association between vitamin D levels and headache. To further investigate the causal relationship between vitamin D and headache, a bidirectional two-sample MR study was conducted (see Figure 1). To reduce bias resulting from population stratification and racial differences, we only selected samples from the same racial group. Furthermore, this study followed the latest guidelines for MR in epidemiological studies (STROBE-MR) (18).

Data sources

The genetic association data for this study were obtained from the IEU Open GWAS database.[1] The low level vitamin D dataset (ieu-b-4812) comprises 441,291 participants with a total of 16,668,957 SNPs. The dataset on headaches (finn-b-R18_HEADACHE1) was obtained from the Finngen Consortium and includes 13,345 cases and 172,999 controls.

The selection of IV

To fulfill the initial step of the first hypothesis, we identified single nucleotide polymorphisms (SNPs) that were significantly associated with exposure based on stringent criteria ($p < 5 \times 10^{-8}$) and independence ($r^2 < 0.001$, kb = 10,000) in order to select genetic IVs that are strongly associated with exposure. However, in a reverse MR analysis with headache as the exposure, no SNPs significantly associated with exposure at $p < 5 \times 10^{-8}$ were found. The significance level was set at $p < 5 \times 10^{-6}$ for the reverse MR analysis. Furthermore, all SNPs with palindromes and ambiguities were excluded to ensure consistent effect alleles between the exposure and outcome datasets. To evaluate the strength of the instrumental variable (IV), we calculated the F statistic value using the formula $F = (N-2) * R^2/(1-R^2)$ (19). An F value greater than 10 indicates a low risk of weak IV bias and avoids weak instrumental bias (20).

Statistical analysis

This study used three methods, namely inverse variance weighted (IVW) and MR-Egger, weighted median (WM), to establish the causal relationship between vitamin D and headache. IVW is the dominant method and produces the highest statistical efficacy when all instrumental variables (IVs) are validated tools (20). Criteria for establishing causality include significant results in IVW analyses. The results of WM and MR-Egger analyses should align with those of IVW analyses (21–23).

For sensitivity analyses, we used the MR-Egger intercept to determine the presence of pleiotropy. Intercept values close to 0 and

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p-values greater than 0.05 indicate no horizontal pleiotropy (24). We then used Cochran's *Q*-test to quantify the heterogeneity of the IVW estimates. A p-value greater than 0.05 indicates no heterogeneity (25). The results of the heterogeneity analysis are shown in Table 1. Additionally, we ran the MR-PRESSO test to check for outliers (see Supplementary material). If any outliers were identified, they were removed, and the MR effect was re-evaluated. To ensure the robustness of the results, we also conducted leave-one-out analyses to examine the impact of individual SNPs on the overall causal effect (26). Final funnel plots were used to assess the symmetry of the selected SNPs, while forest plots were used to evaluate the reliability and heterogeneity of chance estimates. Scatter plots were used to visualise the relationship between exposure and outcome. Please refer to the Supplementary material for additional details.

The methodology used in the inverse MR analysis was the same as described above, which involved using SNPs associated with headache to investigate the causal effect of headache and vitamin D. The results of the inverse MR analysis were presented in RStudio. The entire analysis was conducted in R Studio (version 4.3.0) using the "TwoSampleMR" and "MRPRESSO" software packages.

Results

Finally, we included 101 and 121 SNPs in the exposure and outcome datasets, respectively. Two and five SNP deleted due to palindromes, respectively. As shown in Table 2, the results of IVW analysis indicated that high-level vitamin D were significantly

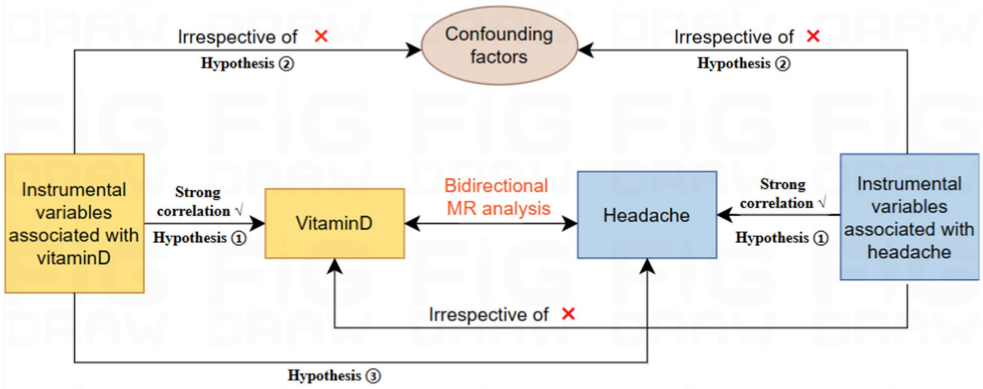

FIGURE 1
Flowchart of Mendelian randomization.

TABLE 1 The heterogeneity and sensitivity of omega-3/omega-6 fatty acids and cerebrovascular disease after removal unqualified IVs.

Exposure	Outcome	*n*SNP	MR Egger intercept		Cochran's heterogeneity			
			Intercept value	*p*	IVW-*Q* value	*p* (IVW)	Egger-*Q* value	*p* (Egger)
VD	Headache	99	0.002664378	0.3248348	121.0626	0.05703579	119.8526	0.05772855
Headache	VD	116	0.000534979	0.3054296	127.4209	0.2019028	126.2471	0.2039701

MR, Mendelian randomization; IVW, inverse variance weighted; *n*SNP, number of single nucleotide polymorphisms.

TABLE 2 Results of forward and reverse Mendelian randomization analysis.

Exposure	Outcome	SNPs	OR	*p*-value	Low	High
VD						
MR Egger	Headache	99	0.793	0.012	0.664	0.947
Weighted median	Headache	99	0.809	0.009	0.689	0.949
IVW	Headache	99	0.848	0.007	0.752	0.956
Headache						
IVW	VD	116	0.996	0.437	0.986	1.006
MR Egger	VD	116	1.001	0.953	0.991	1.008
Weighted median	VD	116	1.001	0.906	0.994	1.006

All statistical tests were two-sided. $p < 0.05$ was considered significant. *n*SNP, number of single nucleotide polymorphisms; OR, odds ratio; IVW, inverse variance weighted; SAH, subarachnoid hemorrhage; ICH, Intracerebral hemorrhage; IS, ischemic stroke.

associated with an decreased risk of headache (OR = 0.848; $p = 0.007$; 95% CI = 0.752–0.956). This finding was also supported by WM and MR Egger. The forest plots of SNP effect sizes for each phenotype in the forward analyses are presented in Figure 2. No horizontal pleiotropy was observed for any of the phenotypes (MR Egger intercept, $p > 0.05$). After removing the palindromic SNPs, there was no heterogeneity observed among the exposure-associated SNPs. The MR-Egger intercept test results indicated no outliers or evidence of horizontal pleiotropy. Additionally, leave-one-out analyses revealed that no single SNP had a potential effect on MR estimates. The funnel plots were essentially symmetrical in both the forward and reverse MR analyses, suggesting no directional horizontal pleiotropy in the selected variables. The Supplementary material display scatter plots, funnel plots, and leave-one-out methods for forward analyses, which can demonstrate the absence of outliers that may affect causality.

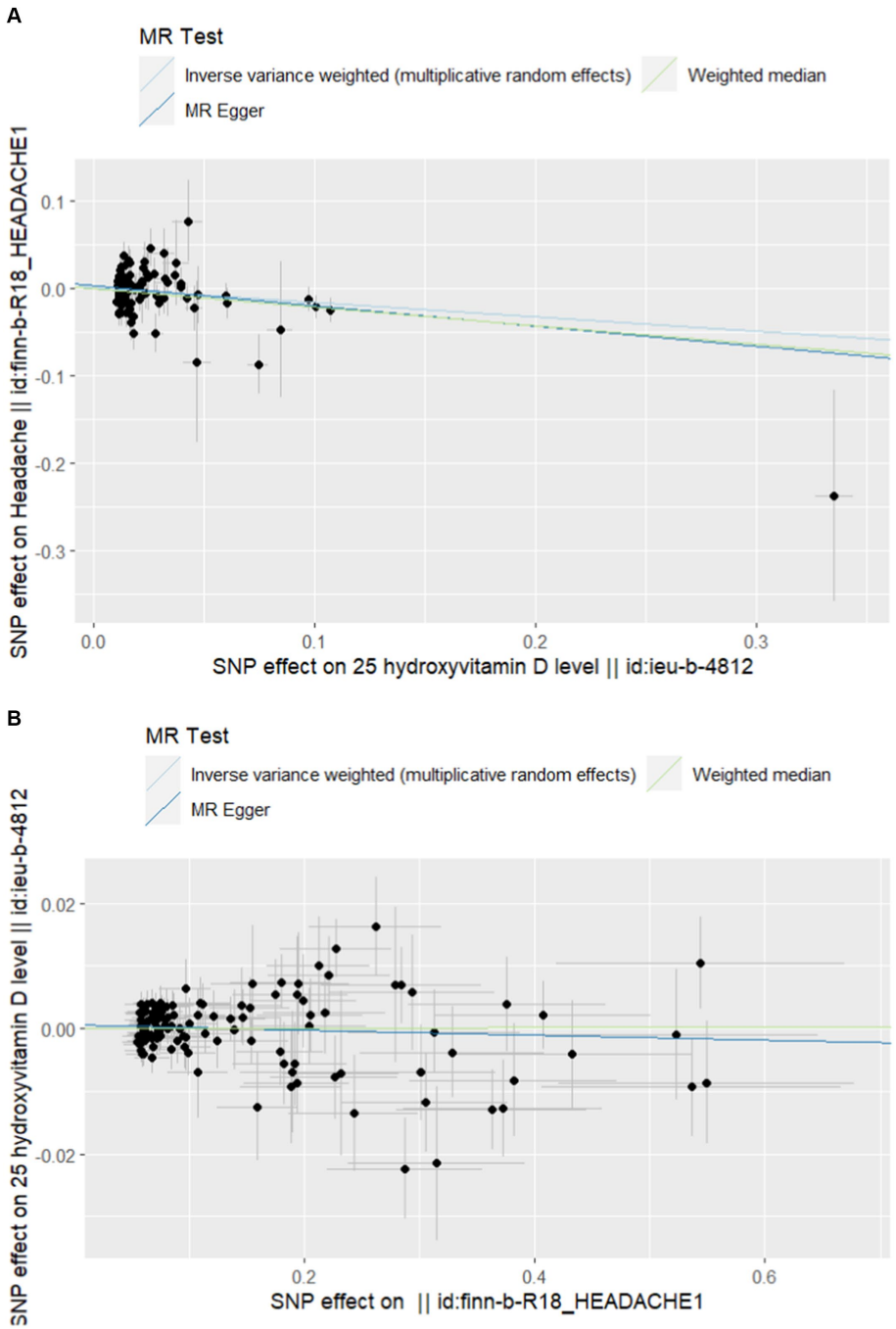

FIGURE 2
(A) Scatterplot of forward Mendelian randomization analysis. **(B)** Scatter plot of reverse Mendelian randomization analysis.

In the reverse MR analysis, none of the causal relationships between headache and vitamin D were significant when headache was considered as exposure (OR = 1.001; $p = 0.906$; 95% CI = 0.994–1.006). Table 2 and Figure 2 provided further details. The statistical analysis indicated that there was no significant causal relationship between headache and vitamin D. The Supplementary material include scatterplots, funnel plots, and leave-one-out methods for inverse analyses.

Discussion

This is the first study to explore a bidirectional causal relationship between vitamin D and headache using MR analysis. The results of the MR analysis showed that high levels of vitamin D significantly decreased the risk of headache. Furthermore, reverse MR studies did not find any evidence of a causal relationship between genetically predicted headache and vitamin D levels.

The relationship between vitamin D and headaches remains inconclusive, despite numerous studies exploring the topic. A case-control study conducted in Egypt found a significant vitamin D deficiency in migraine patients, which can significantly impact the character, duration, frequency, and severity of headache attacks (27). Similarly, a study in Turkish children also found a possible link between vitamin D deficiency and headaches (28). A cross-sectional descriptive study conducted in Norway confirmed that patients with headaches had lower average vitamin D levels compared to patients with other types of pain symptoms. Specifically, patients with headaches had a higher incidence of vitamin D deficiency (29). Quintero-Fabián et al. (30) found that vitamin D acts as an immunomodulatory hormone to reduce neuroinflammation and prevent headaches as a neurological disorder. Recent literature suggests that migraine sufferers may have a vitamin D deficiency, and taking vitamin D alongside conventional medication may reduce the frequency of migraine attacks (31). However, further verification of these results by other methods is necessary.

It is important to note that not all research findings support a link between vitamin D and headache. A randomized controlled trial conducted in Norway found that the use of vitamin D supplements did not have a significant effect on the occurrence and extent of pain or headache (32). Furthermore, a recent meta-analysis did not find any relationship between cluster headache and the three single nucleotide polymorphisms of the vitamin D receptor gene (33). The researchers also noted the lack of articles exploring the relationship between vitamin D and headaches. The relationship between vitamin D and headaches remains a controversial issue for objective reasons.

The varying results could be attributed to the fact that the majority of the studies were observational or meta-analyses and lacked the support of prospective randomized studies. Observational studies have inherent limitations, such as methodological flaws, selection bias, and insufficient adjustment for confounders, which make it difficult to establish a clear causal link. Mendelian randomization is a research methodology that can reveal the causal relationship between exposure and outcome by using genetic variation as an instrumental variable. This approach avoids the influence of non-heritable environmental factors. The study found a significant causal relationship between vitamin D and headache using two-sample MR analysis. A reverse MR study further confirmed this finding's robustness. Our study did not find significant levels of pleiotropy or heterogeneity, which increases the credibility and reliability of our findings.

However, it is worth noting that MR studies have limitations. Firstly, existing databases lack data on different levels of vitamin D, making it difficult to explore the specific association between vitamin D levels and headache. Secondly, as our GWAS data is primarily derived from European populations, our findings may exhibit some racial or geographic bias and require further validation in other ethnic groups. It is expected that more high-quality studies and data will be published in the future to provide additional insight into the relationship between vitamin D and headache. Further research and technological advances may reveal the exact link between the two, leading to new ideas and approaches for preventing, testing, and treating headache.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

HiX: Funding acquisition, Investigation, Writing – original draft, Writing – review & editing, Methodology. RJ: Software, Writing – review & editing. LX: Investigation, Software, Writing – original draft, Writing – review & editing. JZ: Software, Writing – original draft, Writing – review & editing. XT: Investigation, Writing – original draft. JL: Methodology, Writing – original draft. XG: Data curation, Writing – original draft. SZ: Methodology, Writing – original draft. HoX: Formal analysis, Writing – original draft. JH: Writing – original draft. LL: Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing, Investigation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1423569/full#supplementary-material

SUPPLEMENTARY FIGURE S1
(A) Forward Mendelian randomized leave-one graph. **(B)** Reverse Mendelian randomized leave-one graph.

SUPPLEMENTARY FIGURE S2
(A) Funnel plot for forward Mendelian randomization. **(B)** Funnel plot for reverse Mendelian randomization.

SUPPLEMENTARY FIGURE S3
(A) Forward Mendelian randomization of forest graphs. **(B)** Reverse Mendelian randomization of forest graphs.

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Identification of genetic susceptibility for Chinese migraine with depression using machine learning

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Background: Migraine is a common primary headache that has a significant impact on patients' quality of life. The co-occurrence of migraine and depression is frequent, resulting in more complex symptoms and a poorer prognosis. The evidence suggests that depression and migraine comorbidity share a polygenic genetic background.

Objective: The aim of this study is to identify related genetic variants that contribute to genetic susceptibility to migraine with and without depression in a Chinese cohort.

Methods: In this case-control study, 263 individuals with migraines and 223 race-matched controls were included. Eight genetic polymorphism loci selected from the GWAS were genotyped using Sequenom's MALDI-TOF iPLEX platform.

Results: In univariate analysis, *ANKDD1B* rs904743 showed significant differences in genotype and allele distribution between migraineurs and controls. Furthermore, a machine learning approach was used to perform multivariate analysis. The results of the Random Forest algorithm indicated that *ANKDD1B* rs904743 was a significant risk factor for migraine susceptibility in China. Additionally, subgroup analysis by the Boruta algorithm showed a significant association between this SNP and migraine comorbid depression. Migraineurs with depression have been observed to have worse scores on the Beck Anxiety Inventory (BAI) and the Migraine Disability Assessment Scale (MIDAS).

Conclusion: The study indicates that there is an association between *ANKDD1B* rs904743 and susceptibility to migraine with and without depression in Chinese patients.

KEYWORDS

migraine, depression, genetic susceptibility, polymorphism, machine learning

Introduction

Migraine is a chronic neurological disability with a range of symptoms such as nausea, vomiting, photophobia, phonophobia and sensorimotor disturbances, with each attack lasting 4–72 h (1). It affects more than 1 billion people worldwide and causes a heavy family and socio-economic burden (2, 3). The 1-year prevalence of migraine in China is 9.3%, resulting in 5.5 million life years of disability, and a majority of young women (4, 5). The etiology of migraine remains uncertain, and there is strong evidence of a genetic predisposition (6).

Recent clinical research has found that migraine is associated with an increased risk of several other disorders, such as stroke, asthma, depression, anxiety, sleep disorders, restless leg syndrome and medication overuse headache (7, 8). A cross-sectional study of comorbidities in out-patient headache patients at the Headache Center of the First Affiliated Hospital of Xiamen University showed that migraine patients with depression had poor sleep quality. Depressive disorders are equally disabling as migraine, and there is a bidirectional correlation between the two as risk factors for each other. A 2019 meta-analysis, which included 4 cohort studies and 12 cross-sectional studies, found that migraine increases the risk of depressive disorders by 2-fold (9). In another large-sample study from Taiwan region, migraineurs and their non-migraine siblings were more likely to be depressed, and those with depression and their unaffected siblings had a significantly increased risk of developing migraine (10). The cause of the co-occurrence of migraine and depressive disorders is not yet fully understood. The increased risk of interaction between these two diseases may be related to common genetic, environmental and pathological mechanisms (11).

Over the years, several genome-wide association studies (GWAS) have been conducted for migraine and depression. In 2018, Yang et al. conducted a study using single nucleotide polymorphisms (SNPs) and gene-based analyses of GWAS genotypic data, which included 30,465 cases of migraine, and 75,607 cases of major depressive disorder (MDD), and found that the two disorders have significant genetic overlap and significant cross-disease genetic correlations between the two disorders, and three SNPs (rs146377178, rs672931, and rs11858956) were found to have novel genome-wide significant associations with migraine and MDD. Furthermore, two genes, *ANKDD1B* and *KCNK5*, produced Fisher's combined gene-based *p*-values that surpassed the genome-wide significance threshold (12). Research conducted by the Brainstorm Consortium confirms that migraine, unlike other neurological disorders, shares more common genetic structures with mental disorders (13). Using the largest sample to date and novel statistical tools (including 59,674 migraine patients and 316,078 controls), Shahram et al. aimed to determine the extent to which the polygenic structure of migraine overlaps with depression and other psychiatric disorders, and identified 14 genetic loci that are commonly associated with migraine and depression (14).

Numerous GWAS studies have produced varying results, possibly due to differences in populations, research methods, and statistical tools. This reflects the complexity of exploring genetic susceptibility to disease. Our previous studies have confirmed the existence of a genetic predisposition in the Chinese migraine population that is partially identical to that in European and American populations (15–17). Given the recent findings and the paucity of relevant studies in China, we investigated the relevance of several loci of interest in the GWAS study to comorbid depression in migraineurs in southern Fujian province of China.

Materials and methods

Subjects

A total of 266 migraine patients were recruited from March 2021 to June 2023 at the Headache Centre of the Department of Neurology, the First Affiliated Hospital of Xiamen University. The third edition of the International Classification of Headache Disorders (ICHD-3) was used for diagnostic criteria, and all patients underwent a detailed clinical assessment, including age, gender, disease duration, and major migraine-related scales such as the Migraine Disability Assessment (MIDAS), Visual Analogue Scale (VAS), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Subjects with comorbidities such as tumors, other chronic medical conditions, and psychiatric disorders other than depressive disorders were excluded. Two hundred thirty-three controls were nurses and healthy volunteers from our hospital who had a routine medical check-up for non-migraine headaches and were able to complete the BDI assessment to exclude depressive disorders. The two groups were matched for age and gender and came from the same geographical area. Genomic DNA was extracted from peripheral blood lymphocytes using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China) and stored at −80°C for genotyping. Written informed consent was obtained from all participants and the study was approved by the hospital ethics committee (XMYY-2021KYSB009).

Selected SNPs and genotyping

The tagged SNPs were derived from the GWAS conducted by Yang et al. in 2018 and included rs34358 (*ANKDD1B*), rs904743 (*ANKDD1B*), rs9394578 (*KCNK5*) and rs2815095 (*KCNK5*) (12). Additionally, the most strongly associated loci with migraine and depression from the GWAS carried out by Shahram et al. in 2022 were taken into account in this study, including rs1217091, rs7592120, rs11210247, rs71327107 (14). All of these SNPs were selected because their minor allele frequency (MAF) was greater than 0.15. SNP genotyping was performed on all subjects using Sequenom iPLEX Assay technology (Sequenom, San Diego, CA, United States).

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 and R4.3.2[1] software. The minimum sample size required for this study was calculated using the "pmsampsize" R package. Univariate analysis was conducted using the t-test and Chi-square test to compare the data of two groups. Multivariate analysis was performed by constructing a random forest model using the "randomForest" package. The data set was bootstrapped multiple times to form a training set. The importance

1 https://www.r-project.org/

of sample features was evaluated using Mean Decrease Accuracy and Gini index as observation indices. The "Boruta" package was used to extract and sort the important features of the random forest model. The Boruta algorithm underwent multiple iterations to evaluate the scores of all features and determine whether their importance exceeded that of the shadow feature. In the outcome analysis, the green variables were found to be the most significant, while the yellow variables were deemed controversial and the red variables were rejected. The study analyzed the important variables using a generalized linear model (GLM), and the statistically significant risk factors were then screened and quantified using multivariate analysis.

The public statistical web tool https://wpcalc.com/en/equilibrium-hardy-weinberg/ was used to verify Hardy–Weinberg equilibrium for all polymorphisms in the control group. To account for errors in multiple comparisons, a Bonferroni correction was applied.

Results

Sample size estimation

Using the "pmsampsize" R package, the parameters were set as follows: eight candidate parameters, assuming a projected migraine prevalence of 0.15 and a *C*-statistic of 0.90, the minimum required sample size was calculated to be 235.

Baseline patient information

A total of 266 migraine cases were included, of which 236 were female (88.7%) and 30 were male (11.3%). The mean age of migraine was 34.0 ± 9.3 years, including 36 migraine with aura (13.5%) and 230 migraine without aura (86.5%). The 223 controls included 32 men and 191 women with a mean age of 33.1 ± 8.5 years. There were no significant differences in gender and age between the two groups (p = 0.309 and p = 0.245, respectively). According to the Beck Depression Inventory, 108 people with depression lasting more than 2 weeks were considered to have a depressive disorder, of which 43 were mild, 39 moderate and 26 severe (Supplementary Table S1).

Univariate analysis

All SNPs were well detected, and the genotypes of all SNPs in the control group were consistent with Hardy–Weinberg balance. The genotype and allele distribution of *ANKDD1B* rs904743 differed significantly between migraine patients and controls (Supplementary Table S2). Among migraine patients, 81.8% carried the rs904743 risk A allele, which was significantly higher than the control group (OR = 1.415, 95% CI: 1.039–1.929, p = 0.027). In addition, other polymorphisms did not differ significantly in genotype and allele frequency distribution between migraine cases and controls.

Machine learning analysis

To investigate whether the selected SNPs were risk factors for migraine in the multivariate analysis, machine learning based on big data analysis was used in this study. The presence of migraine was used as the dependent variable, and the selected SNPs were included in the random forest model as independent variables. The collected dataset was divided into two datasets with a ratio of 0.8:0.2, and the number of random seeds was set. A random forest model was used for training and the model ranked the importance of risk factors. The results showed that the top 4 risk factors were rs904743, rs9394578, rs7592120 and rs2815095, as shown in Figure 1. The results of the generalized linear model analysis indicated that rs904743 was a risk factor for the migraine group (OR = 1.36, 95% CI: 1.01–1.82, p = 0.040), whereas rs9394578, rs7592120, and rs2815095 were not statistically significant factors (Table 1).

The subgroup analysis results show that the Boruta algorithm identified rs9394578, rs904743, rs2815095, and rs7592120 as significant features of migraine with depression (see Figure 2). According to the GLM logistic analysis, only rs904743 was a significant risk (OR = 1.64, 95% CI: 1.08–2.50, p = 0.021) after Bonferroni correction (see Table 1).

Figure 3 shows the comparison of clinical and genetic characteristics between migraine with and without depression, and it was found that age, BAI and MIDAS were important difference factors, but only BAI and MIDAS reached statistical difference (both p < 0.001). Other clinical and genetic characteristics were not statistically different between the two groups.

Discussion

Our study confirmed that *ANKDD1B* rs904743 may increase susceptibility to migraine with depression in a Chinese population. This finding strengthens the reliability of previous GWAS studies (12). Other SNPs could not be replicated in this study, probably due to ethnic differences. Furthermore, the higher anxiety scores found in

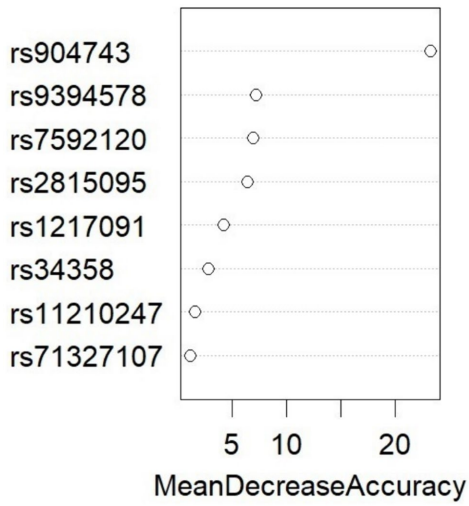

FIGURE 1
Importance of variables for all migraine derived from the Random Forest. A greater value of mean decrease accuracy indicates a greater importance of the variables.

TABLE 1 Selected susceptibility SNPs for migraine in GLM Logistic analysis.

SNP	Gene	Risk allele	All migraine[c]			Migraine with depression[d]		
			OR[a]	95% CI	*p*	OR[a]	95% CI	p_{corr}[b]
rs904743	*ANKDD1B*	A	1.36	1.01–1.82	**0.040**	1.64	1.08–2.50	**0.021**
rs9394578	*KCNK5*	A	0.54	0.22–1.33	0.179	0.25	0.06–1.01	0.051
rs2815095	*KCNK5*	T	1.61	0.65–3.97	0.301	3.61	0.86–15.22	0.080
rs7592120	—	T	1.09	0.76–1.56	0.643	1.13	0.71–1.80	0.609

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
[a]OR was the adjusted OR after multiple regression.
[b]After Bonferroni correction, significance was taken at $p_{corr} \leq 0.05/2$ in two subgroups; bold value denote significance.
[c]No. of observations = 489, AIC value = 677.399.
[d]No. of observations = 331, AIC value = 416.696.

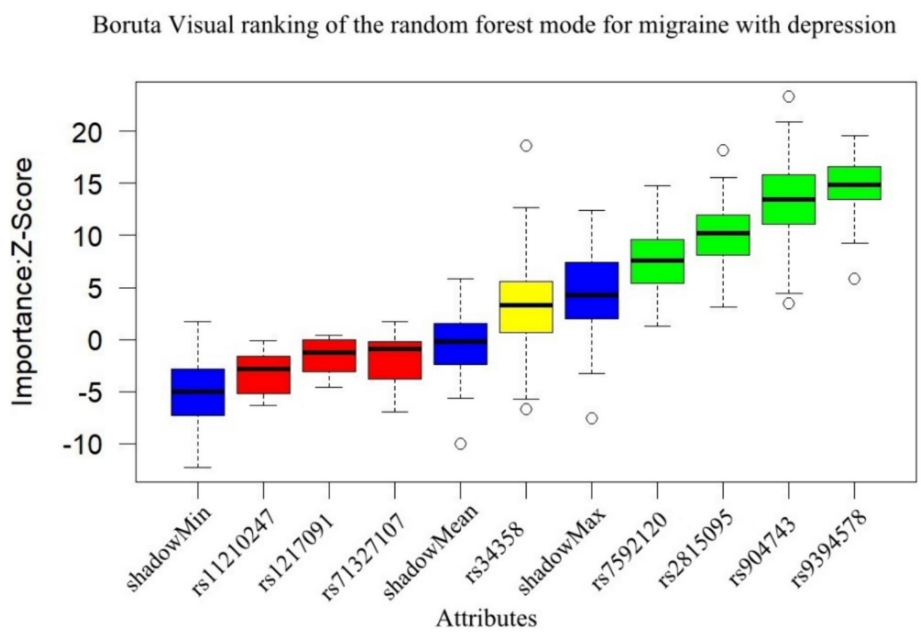

FIGURE 2
Results of Boruta algorithm for migraine with depression. Green is the important feature, yellow is the pending feature, and red is the rejected feature, and rs9394578, rs904743, rs2815095, rs7592120 were selected as important features for migraine with depression.

our study in migraine combined with depression, together with their higher MIDAS scores, can largely be explained by the fact that environmental stress and disease severity increase each other's risk. The pathogenesis of co-morbidity between migraine and depressive disorders may involve structural and functional changes in the brain, abnormalities in neurotransmitter function, genetic factors, and environmental and stress factors, and these may be the direction of future treatment (18). Two epidemiological studies of large twins found a bidirectional association between migraine and depression, with 20% of the variability in depression and migraine attributable to shared genes (19, 20). In this study, *ANKDD1B* rs904743 was associated not only with depression combined with migraine, but also with migraine susceptibility, suggesting that *ANKDD1B* gene may be a common genetic basis for both disorders.

Previous studies have found several genes that may be associated with migraine combined with depression, including the promoter region of the 5-HT transporter (5HTTLPR) *SLC6A4* gene (21), the dopamine receptor gene *DRD2* and *DRD4* (22), and the GABAergic system of the *GABRQ* and *GABRA3*genes (23). These findings support the existence of common neurotransmitter abnormalities between the two diseases. Based on the results of previous GWAS studies in migraine, Peter et al. applied two machine learning algorithms and found that *REST*, *HPSE2* and *ADGRL2* may be the main candidates for the pathophysiology of migraine combined with depression (24). However, the study by Lannie et al. suggests that migraine with and without depression are genetically distinct disorders (25). In a study based on microRNA (miRNA) biomarkers, 11 of the 12 miRNA biomarkers associated with migraine were found to be associated with major depression (26). These findings suggest that the two diseases may share complex mechanisms and shed light on developing new therapies for their treatment (27).

The function of *ANKDD1B* is predicted to be involved in signal transduction, particularly calcium homeostasis (28). Clinical studies have found that *ANKDD1B* variants may be associated with ankylosing spondylitis and hypertension (29, 30). Using large-scale summary statistics, Guo et al. found a significant association

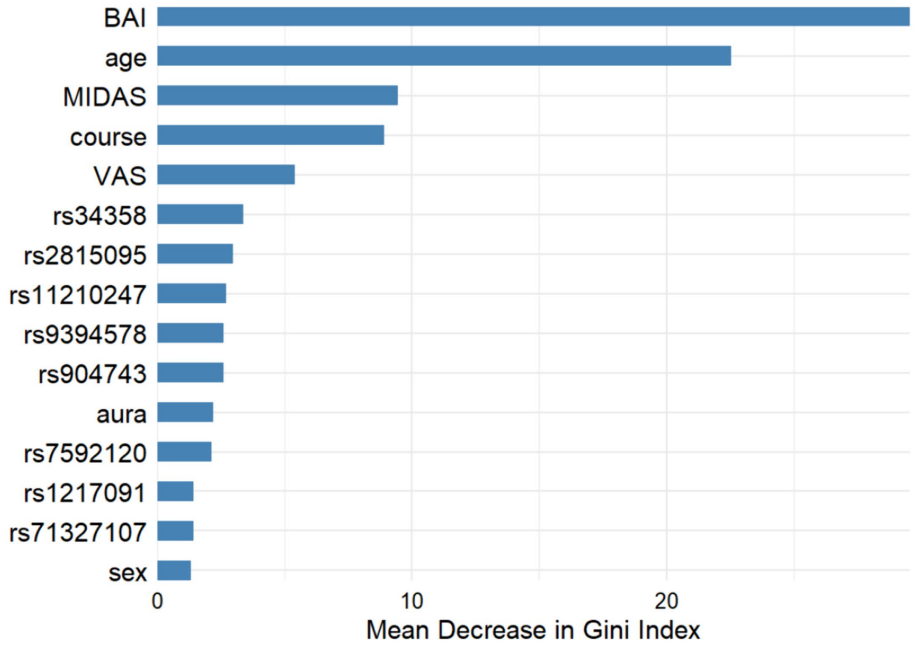

FIGURE 3
Machine learning results for migraine variables with and without depression. (1) Gini index: higher values indicate a greater role. (2) GLM logistic regression analysis suggested that the *p*-values for BAI, age, MIDAS was <0.001, 0.184, <0.001 respectively.

between diastolic blood pressure and migraine susceptibility, as well as identified five loci (*ITGB5*, *SMG6*, *ADRA2B*, *ANKDD1B*, and *KIAA0040*) that are shared biological factors for both blood pressure and migraine (28). While another study suggested a possible association between *ANKDD1B* and other genes and migraine in people of European ancestry by affecting lipoprotein subfractions (31). In the GWAS study, *ANKDD1B* and *KCNK5* were associated with migraine and MDD etiology as key genes in neural-related signaling pathways and ion channel regulatory pathways (12). The study confirmed the association between the *ANKDD1B* gene and comorbid depression in Chinese migraine patients. However, no correlation was found for *KCNK5*, which may be related to the polygenic effect of migraine comorbid depression and ethnic differences. Another population-based study in China found that *ANKDD1B* rs34358 was associated with a decreased risk of migraine as a protein-truncating variant (32). This is consistent with our overall findings, but there are differences at specific genetic locus, so further validation in a larger Chinese population is needed.

In this study, we used Random Forest and Boruta algorithms to visually rank the importance of features related to migraine comorbid depression, which gave us a more intuitive understanding of its risk factors (33). However, there is not necessarily a dependency between these selected features and the disease, so we further performed GLM analysis based on feature importance, which makes our results more convincing. Nevertheless, the study did not find the *ANKDD1B* rs904743 polymorphism to be a significant risk factor for migraineurs with or without comorbid depression. This also reflects some limitations of this study: firstly, due to the lack of long-term follow-up of migraine patients with concomitant depression during the study period, the slightly higher percentage of mildly depressed population may have attenuated the influence of genetic factors. Secondly, considering the complexity of the pathogenesis of migraine combined with depression, the sample size of this study was not large enough, and further studies with more centers and samples are needed.

Conclusion

In summary, our findings indicate that the *ANKDD1B* rs904743 variant identified in genome-wide association study was significantly associated with an increased susceptibility to migraine accompanied by depression in Chinese patients. In addition, SNPs associated with other populations were not replicated in the Chinese population, suggesting the need for larger and more innovative studies to understand the mechanisms of migraine and depression comorbidity at the genetic level.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving humans were approved by the project was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (XMYY-2021KYSB009). The studies were conducted in accordance with the local legislation and institutional

requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

XA: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. SZ: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing – review & editing, Writing – original draft. JF: Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. QL: Data curation, Methodology, Project administration, Software, Validation, Writing – review & editing. CY: Formal analysis, Methodology, Resources, Software, Supervision, Writing – review & editing. CJ: Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – review & editing. YZ: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. JaZ: Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing. JeZ: Investigation, Methodology, Project administration, Resources, Software, Writing – review & editing. CC: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. HQ: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing. QM: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Writing – review & editing. QL: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1418529/full#supplementary-material

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Cluster headache: understandings of current knowledge and directions for whole process management

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Cluster headache (CH) is a common primary headache that severely impacts patients' quality of life, characterized by recurrent, severe, unilateral headaches often centered around the eyes, temples, or forehead. Distinguishing CH from other headache disorders is challenging, and its pathogenesis remains unclear. Notably, patients with CH often experience high levels of depression and suicidal tendencies, necessitating increased clinical attention. This comprehensive assessment combines various reports and the latest scientific literature to evaluate the current state of CH research. It covers epidemiology, population characteristics, predisposing factors, and treatment strategies. Additionally, we provide strategic insights into the holistic management of CH, which involves continuous, individualized care throughout the prevention, treatment, and rehabilitation stages. Recent advances in the field have revealed new insights into the pathophysiology of CH. While these findings are still evolving, they offer a more detailed understanding of the neurobiological mechanisms underlying this disorder. This growing body of knowledge, alongside ongoing research efforts, promises to lead to the development of more targeted and effective treatments in the future.

KEYWORDS

cluster headache, pathogenesis, epidemiology, manifestation, whole process management

Introduction

Headaches are one of the most common symptoms of human suffering. However, if the headaches recur more frequently than expected and there are no triggers, trauma, or underlying disease, they are categorized as a disorder. Of these disorders, cluster headaches (CH) are one of the most severe forms (1). In the typical form of the disorder, severe unilateral headaches that occur several times a day may be a basis for differentiating CH from migraine (2, 3). The Headaches usually occur in the supraorbital, retroorbital, and temporal regions and are caused by deep cranial, and the frequency of attacks can start out as occurring every other day and then increase to a maximum of eight per day, with attacks having a diurnal rhythm, favoring nocturnal attacks (4). In addition to headache, patients with cluster headache may present with autonomic symptoms such as tearing, conjunctival injection, nasal leakage, pupil

constriction, ptosis, hyperhidrosis, eyelid edema and flushing (5). Alarmingly, cluster headache is a highly disabling headache disorder in which patients typically exhibit depressive symptoms, are more prone to suicidal thoughts and behaviors than the general population and have a significantly reduced quality of life (6). Therefore, we review the pathogenesis, diagnosis, and treatment of cluster headache and emphasize the management of cluster headache throughout the course of the disease in an attempt to improve the understanding of cluster headache and the quality of life of patients (Figure 1).

Epidemiology

Incidence and prevalence

Cluster headaches are influenced by several variables, including age, gender, and geographic location. One in 1,000 people suffers from cluster headaches, with a prevalence of 0.1%–0.2%, according to epidemiologic surveys (7). CH is the most commonly diagnosed rare headache, and in a study involving 20,083 people attending a headache center, 461 cases were diagnosed with rare headache, of which 234 (1.2%) were diagnosed with episodic cluster headache, and 39 (0.2%) patients were newly diagnosed with cluster headache, which accounted for 59.2% of the rare headaches (8). Not only is CH the most commonly diagnosed rare headache, it also has a serious impact on patients' quality of life, and the disorder is highly misdiagnosed, with actual incidence and prevalence likely to be higher.

In addition, there are variations in incidence and prevalence in different regions. For example, some studies have found that the prevalence of cluster headaches is higher in the Nordic region and lower in Asia (9). This difference may be related to factors such as geography, lifestyle, and climate.

Affecting factors

Age

Cluster headaches are most common in specific age groups, especially young and middle-aged people between the ages of 20 and 40. There is a significantly higher prevalence of cluster headache in men in this age group compared to other age groups (10). The incidence of cluster headache decreases with age, which may be related to age-related physiologic changes and lifestyle changes.

Gender

The proportion of men among cluster headache sufferers is significantly higher than that of women; 20 years ago, the ratio of men to women was about 4.7:1, and although the ratio of men to women has declined, there are still far more men than women. This may be related to the differences between men and women in terms of social roles, work pressures, and psychological endurance (11). Women may have a lower incidence due to estrogen (12). Therefore, men should be more aware of the prevention and treatment of cluster headaches than women (Figure 2).

Genetic factors

Studies have shown that cluster headache has a significant family aggregation. Patients with a family history of cluster headaches have a higher incidence, and it is more common to have multiple generations

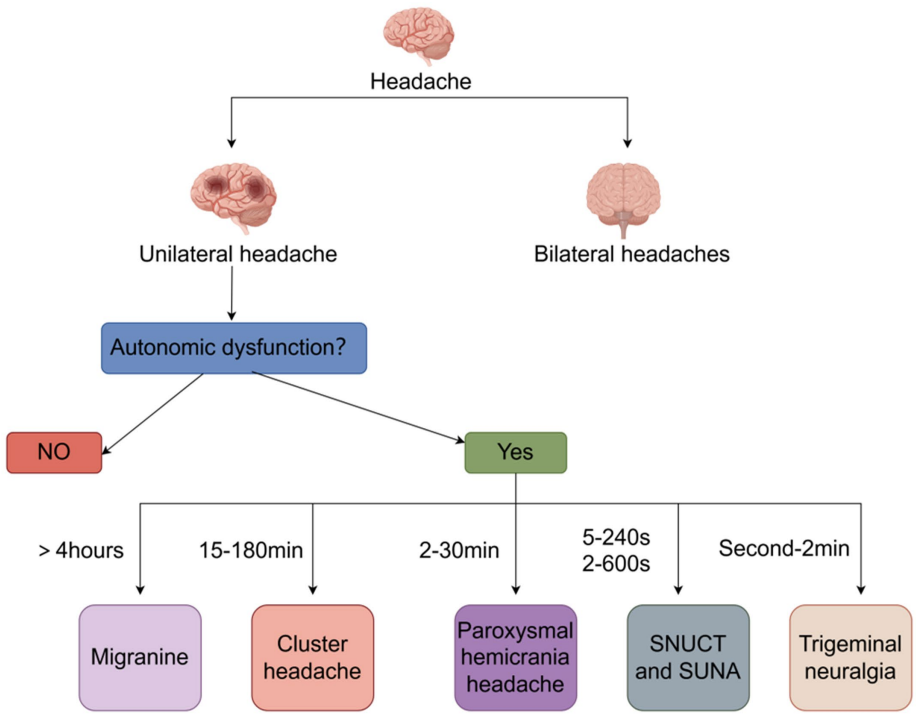

FIGURE 1
Identification of cluster headache by location, nature, and duration of pain.

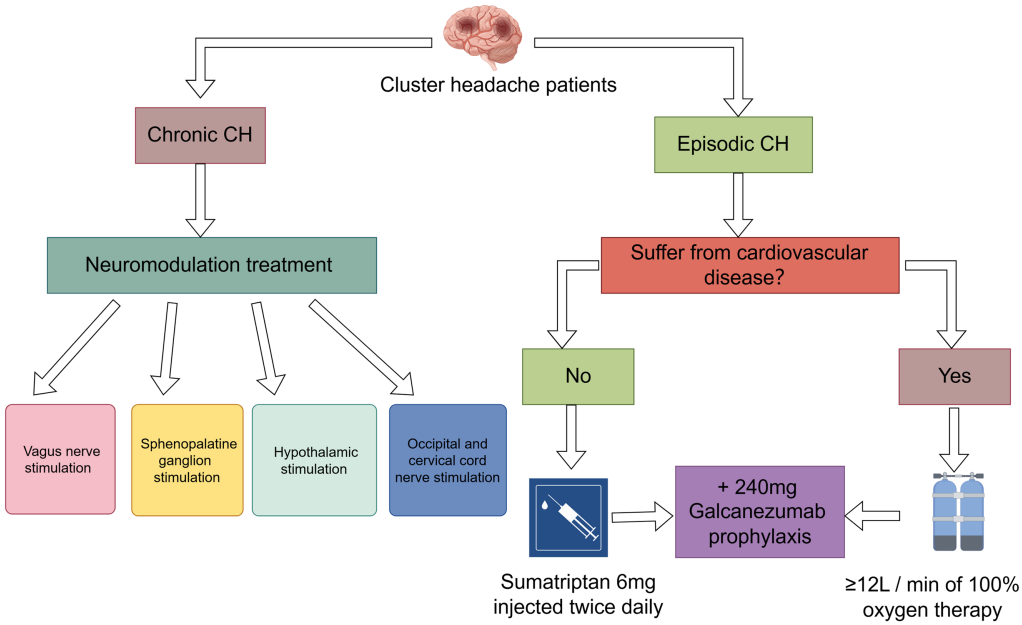

FIGURE 2
Treatment of cluster headache.

of patients in the family. A first-degree relative with cluster headaches increased the risk to the patient by 5 to 18 times, while a second-degree relative with cluster headaches increased the risk by 1 to 3 times (13, 14). And it has been shown that symptoms such as nasal congestion and conjunctival congestion are more prevalent in familial cluster headaches than in non-familial cluster headaches (15). In addition, a genetic study of CH found that a total of seven protein-coding genes (DUSP10, MERTK, FTCDNL1, FHL5, WNT2, PLCE1, and LRP1) were associated with the development of cluster headache (16). This suggests that genetic factors play a significant role in the development of cluster headache. Further research will help to reveal the specific genes and genetic mechanisms associated with cluster headache, thus providing innovative ideas and methods for the prevention and treatment of the disease.

Lifestyle habits and environmental factors

A wide range of lifestyle habits are thought to be associated with an increased risk of developing cluster headaches. Among the positive patients, about 65% are smokers and 6.5% have drinking behaviors. Regarding the relationship between sleep and CH, it is currently believed that sleep deprivation is one of the triggers of CH, and another theory is that the circadian rhythmicity of CH causes patients to passively change their sleeping habits, resulting in sleep deprivation (17, 18). Overall, poor lifestyle habits such as smoking and drinking may increase the frequency and severity of cluster headache attacks. Therefore, understanding these factors is important for the prevention and management of cluster headaches.

Clinical manifestations and characteristics

Cluster headache is defined by periods of extremely acute one-sided headache or facial pain that can last anywhere from 15 min to 3 h. This is an important marker to distinguish CH from other headaches. It is regarded as one of the most severe types of pain. The intensity of pain surpasses that of labor, kidney stones, and shattered limbs (19). Cluster headache episodes exhibit both circadian and seasonal patterns. During the day, these episodes are most frequent at 2 a.m. In terms of the year, cluster headaches are most common in October, with a peak of occurrences occurring between April and October (20, 21).

Most cluster headache attacks are sudden and violent, often catching the patient off guard, but approximately 35% of patients are able to predict CH attacks, and it is worth noting that in these 35% of patients, the proportion of women, the prevalence and seasonal rhythmicity of pre-ictal symptoms, the frequency of cluster headache attacks per day, and the total number of attacks are higher (22). In a study of pre-episode symptoms of CH, a total of 327 patients participated, of whom PES occurred in 68 cases, and the most common symptoms were head and facial discomfort (23 cases, 33.8%), followed by anxiety and restlessness (15 cases, 22.1%), sleep problems (14 cases, 20.6%), fatigue/mild headache (non-ch) (11 cases, 16.2%), neck discomfort (9 cases, 13.2%), irritability/drowsiness (6 cases, 8.8%), acoustic phobia (4 cases, 5.9%), nasal congestion/osmophobia/muffled voices/photophobia/palpitations/palpitation (3 cases, 4.4%), seizure premonitions/dizziness/frustration/feeling of coldness/swelling of ears (2 cases, 2.9%), and shadow episodes (defined as minor pain and cluster episodes of short duration/toothache/hyperesthesia/diuresis/redeyes/food cravings/hyperactivity/constipation; 1 case, 1.5%) (23). This may help clinicians treat CH prophylactically and also better understand its pathophysiology. The headache is extremely severe. The nature of the pain is throbbing, drilling, or stabbing, which causes great distress to the patient.

Headache episodes can also have a severe impact on the patient's mental state, with anxiety, an inability to meditate or concentrate, and the lifetime prevalence of depression in CH patients is 2.8 times higher

than that of healthy individuals (24). This view was proved by another experiment (25). Because the pain cannot be relieved, the patient may engage in self-injurious behaviors, such as banging their head or hitting a wall, to relieve the pain (26). This not only seriously affects the patient's daily life and work but also their mental health.

Another distinguishing feature of cluster headache is autonomic dysfunction (27). Pain is associated with the following ipsilateral cranial parasympathetic autonomic signs: conjunctival congestion; tearing; nasal congestion; rhinorrhoea; forehead and facial sweating; miosis; ptosis and/or eyelid edema; and/or restlessness or agitation (28). It is noteworthy that visual sensitivity is increased in patients with CH, especially during CH episodes; in two thirds of these cases, visual sensitivity was unilateral and predominantly ipsilateral to the cephalic side of the pain, which seems to help differentiate between cluster headaches and migraines, as photophobia in the latter is usually bilateral and more severe (29). In addition to affecting visual sensitivity, CH patients had significantly lower olfactory threshold scores and significantly impaired olfactory function compared to healthy controls (30). Patients with CH may experience these symptoms from autonomic nervous system disorganization due to cluster headaches. In addition, some patients may experience flushing, nausea, and vomiting. The onset of these symptoms is characterized by periodicity, with each attack lasting from a few minutes to several hours, followed by a relatively prolonged period of remission (31).

Pathogenesis

Currently, research on the pathogenesis of CH has focused on the hypothalamus. A higher sympathetic tone was observed by stimulating the preganglionic fibers of the pterygopalatine nerve during episodes of CH with marked parasympathetic symptoms (32, 33). In addition, male patients with CH have reduced plasma testosterone levels and are often associated with reduced thyrotropin releasing hormone (34). A study comparing gender differences in patients with CH found that although the clinical phenotypes were similar, the daily seizure cycle was 1 h earlier in men with CH than in women, and there were more women than men with chronic CH (11). Furthermore, individuals with CH commonly exhibit reduced levels of melatonin during the night and disruption of their natural sleep–wake cycle (circadian rhythm) (35). Melatonin is acknowledged as a significant biomarker for controlling physiological rhythms, and the supraoptic nucleus of the optic chiasm in hypothalamic structures controls endogenous circadian rhythms (36). The supraoptic nucleus can control the generation and release of melatonin by establishing extensive connections with several hypothalamus nuclei, the pineal gland, and other structures (37). Thus, light sources may be the strongest trigger in the pathogenesis of CH through the retino-hypothalamic pathway.

Calcitonin gene-related peptide (CGRP) has been shown to be a migraine-inducing neuropeptide, and despite differences in headache phenotypes, migraine and cluster headache share some common features in certain places (e.g., response to triptans). Calcitonin gene-related peptides may exert their cluster headache-inducing ability in three different ways. First, this may occur through the vascular action of CGRP, which may involve neurogenic inflammation. Second, a CGRP receptor component has also been identified in the human trigeminal ganglion, which has been implicated as a possible site of action for CGRP receptor antagonists in migraine therapy. Third, pterygopalatine ganglion neurons express CGRP and its receptor components. Outflow from the pterygopalatine ganglion is thought to be the initiating mechanism for cluster headache attacks, and on-demand stimulation of the pterygopalatine ganglion is a new and effective treatment for cluster headache (38). Another study also confirmed that CH activity is associated with altered CGRP expression, with higher baseline levels of CGRP in patients with remission-phase CH compared to patients with chronic CH (39). Another study confirmed this idea and found that PACAP38 and vip-induced CH episodes were independent of plasma CGRP. Pituitary adenylate cyclase-activating peptide-38 (PACAP38) and vasoactive intestinal peptide (VIP) are both members of the vip glucagon, growth hormone-releasing factor-secretin superfamily, and their possible involvement in the initiation of attacks is supported by elevated plasma levels of PACAP and VIP during spontaneous CH attacks. CH pain was located in the trigeminal ophthalmic area, and concomitant intracranial autonomic symptoms suggested the involvement of trigeminal autonomic reflexes (TARs)-although whether the intracranial autonomic symptoms were caused by the pain or actually contributed to the pain is less clear. The trigeminal autonomic reflex consists of afferent trigeminal inputs and parasympathetic nerves that travel through the SPG via the supraspinal nucleus to the facial nerve, and it is possible that the trigeminal autonomic reflex interacts with the hypothalamus in the CH; however, the exact mechanism and sequence of events are not yet fully understood (40, 41).

Furthermore, the pathophysiology of CH may potentially entail inflammatory reactions in the cerebral pathways. The concept of chronic inflammation of the cavernous sinus has been proposed, suggesting that the cavernous sinus is the only anatomical site connecting the trigeminal and sympathetic blood supply and may play a role in the pathogenesis of CH through underlying cerebrovascular events (42). These findings offer fresh insights and guidance for a more profound comprehension of the development of CH.

Whole process management

Diagnostic procedures

Differential diagnosis

To properly recognize CH, it is important to have a more in-depth understanding of the autonomic nervous system symptoms in CH and to make the correct management when autonomic symptoms occur.

According to the third edition of the International Classification of Headache Disorders (ICHD-3), cluster headache is defined as recurrent unilateral severe headache in the orbital, supraorbital, or temporal regions lasting 15–180 min with cranial autonomic symptoms, irritability, or both. Cluster headache is classified into two subtypes: episodic, with episodic (paroxysmal) episodes lasting from 7 days to 1 year separated by periods of absence of at least 3 months' duration in the past year; chronic, with episodes either without periods of relief or with periods of relief lasting less than 3 months in the past year; and chronic, with episodes either without periods of relief or with periods of relief lasting less than 3 months. Episodic, with attacks (paroxysms) lasting from 7 days to 1 year, separated by periods of absence (remission) lasting at least 3 months in the past year; chronic, with attacks that either have no remission or have been in remission for less than 3 months in the past year (43). Diagnosing

cluster headache is a complex and delicate process, with a huge number of headache patients and a high rate of misdiagnosis, especially in the differential diagnosis between cluster headache and other headache disorders. When a patient with CH is seen in an outpatient clinic, the clinician can make a differential diagnosis by looking at the location and duration of the pain, as well as the presence or absence of autonomic symptoms. The pain in CH is usually unilateral and usually lasts for 15–180 min, which is a distinctive feature that differentiates it from other headache disorders. Migraine is usually a pain that lasts for more than 4 h. Paroxysmal hemicarania headache pain usually lasts 2–30 min. Sunct suna pain usually lasts 5–240 s or 2–600 s, and trigeminal neuralgia pain usually lasts a few seconds to 2 min (44, 45).

Relevant examinations

Laboratory tests

There are no biomarkers that may be used to definitively diagnose CH, and laboratory testing is still in the development phase. The neuropeptide calcitonin gene-related peptide (CGRP) has attracted a lot of interest lately because of its extensive distribution in both neuronal and non-neuronal tissues of the body. CGRP plays a crucial role in the pathophysiology of migraine and cluster headache and blocking its function can alleviate neurogenic inflammation and sensitize pain pathways (46). Intravenous methylprednisolone and oral prednisone, used for short-term prophylaxis of episodic CH, led to a decrease in elevated plasma levels of CGRP in the blood of the external jugular vein, which was accompanied by a significant decrease in the frequency of CH onset, whereas patients with multiple sclerosis who served as a control group did not have alterations of these parameters, which seems to indicate that CGRP can be used as a biomarker for CH (47). Another study suggests that CH disease activity is associated with changes in CGRP expression (48). CGRP is not only a biomarker but also a therapeutic target for CH (49), and several studies have demonstrated the favorable efficacy of CGRP antibodies in the treatment of eCH, while they are ineffective in cCH. Galcanezumab is a highly specific and potent humanized immunoglobulin G monoclonal antibody targeting CGRP peptides. Galcanezumab is currently the only antibody approved for the treatment of CH, getting approved for the prevention of episodic and chronic migraine in the United States, Canada, the United Kingdom, and several European countries, and in June 2019, it has been approved for the prevention of eCH in the United States (50, 51).

There are also kynurenines, and the mechanisms of kynurenine involvement in CH have been described as follows: Glutamate has been shown to be involved in CH episodes. Glutamate glu acts on the n-methyl-d-aspartate (NMDA) receptor, which has an injurious sensitizing effect, and has been shown to be involved in the pathophysiology of CH. Kynurenine evolved from the catabolism of tryptophan (Trp). Some metabolites of the kynurenine pathway are neuroactive, and these metabolites are neurotransmitted by glutamatergic receptors, which modulate NMDA receptors. The kynurenines are also neuroactive. Trp catabolism, some metabolites of the kynurenine pathway are neuroactive, and these metabolites are neurotransmitted by glutamatergic neurotransmission, which plays an important role in the regulation of NMDA receptor function (52). In another study, human CH was found for the first time to be associated with abnormalities in the tryptophan metabolism kynurenine pathway (53, 54), which justifies the use of kynurenines as a direction for CH biomarker research.

Imaging examination

Currently, the main imaging research direction in CH is MRI, A study from China used resting-state functional magnetic resonance imaging (RS-fMRI) to assess the potential pathogenic involvement of low-frequency fluctuation fractional amplitude (faLFF) in CH. Specifically, faLFF is an indicator of the intensity of spontaneous localized brain activity. It is a signal that reflects the intensity of localized spontaneous activity in brain regions (55). The study showed that fALFF was reduced in the left cerebellum, left nucleus accumbens, left frontal lobe, left anterior cingulate and right postcentral gyrus in the left CH group, and in the right cerebellum, right cingulate, right superior parietal lobule, right inferior parietal lobule, right postcentral gyrus, and left precuneus in the right CH group (56), which further suggests that the complexity of the pathogenesis of CH may be due to the combined effects of multiple brain regions. Another study found that CH patients had weaker hypothalamic structural area covariance with frontal lobe (57). This observation also validates the findings of another study, who found that patients had less gray matter volume in the frontal lobes bilaterally than healthy controls and reported frontal hypometabolism in patients with CH (58, 59). Furthermore, the reduction in size of the left anterior superior temporal sulcus and the left lateral branch/glossal sulcus cortex in individuals with CH indicates a lack of proper adaptation of neuroplasticity in regions associated with social cognition. This may play a role in the development of psychiatric disorders and contribute to the severe disabling nature of CH (60). Aside from the frontal lobe, the cingulate gyrus, which has a vital function in regulating cortical responses to cluster headache, could be a potential target for neuromodulation in individuals who do not respond to medication treatment for cluster headache (61). Regarding the distinction between cluster headache and migraine by imaging, a study provides an answer: functional interactions between the left thalamus and parietal brain regions, including the precuneus gyrus and angular gyrus, are lower in patients with cluster headache compared to those with migraine (62).

In summary, the diagnostic process for cluster headaches requires a high degree of professionalism on the part of the physician. Physicians must utilize their extensive clinical expertise and practical experience to take a careful patient history and thoroughly examine the patient's symptoms as well as laboratory data, with imaging helping to help them rule out secondary conditions. They must then perform a careful differential diagnosis to distinguish CH from other forms of headache. Only through this approach can doctors make an accurate diagnosis and subsequently develop a successful treatment plan for their patients.

Therapeutic measures and management

Current treatments for CH focus on medications, oxygen therapy, and neurotherapy. We will describe each of these treatment options separately and conclude with recommended treatment management strategies.

Triptans

The main drugs currently used for the treatment of CH are the triptans, which official guidelines limit to twice daily use. Triptans can be administered in three ways: orally, subcutaneously, and as an intranasal spray. Some studies have shown that the mode of administration affects efficacy, with subcutaneous injections having the best therapeutic effect of the three modalities. Subcutaneous injection of sumatriptan resulted in complete pain relief within 20 min in 75% of subjects; sumatriptan nasal spray resulted in pain relief within 30 min in 47% of subjects (63). Prescribing tablets before nasal or injectable Triptans may delay optimal pain treatment. Oral administration is the least effective and the drug has a slow onset of action, so oral treatment is not recommended (64). Currently 6 mg subcutaneous sumatriptan or 20 mg sumatriptan and 5/10 mg intranasal zolmitriptan are recommended for the treatment of acute episodes of CH, and in his experiments, there was little difference in efficacy between 6 mg sumatriptan and 12 mg sumatriptan. Considering the possible side effects of tramadol (abnormal sensations, chest pains, sore throat, and sensation of fever), it is recommended to use 6 mg sumatriptan Tramadol is recommended to be used with 6 mg sumatriptan (65).

Oxygen therapy

Because of the vasoconstrictive properties of the triptans, they are contraindicated for use in patients with comorbid cardiovascular disease, making high-flow oxygen another treatment for acute CH (66). The exact mechanism by which oxygen therapy treats CH is uncertain. Possible mechanisms include inhibition of cranial parasympathetic pathways or trigeminal autonomic reflexes, modulation of neurotransmitters or neuropeptides such as calcitonin gene-related peptide to inhibit neurogenic plasma protein spillover, and cerebral arterial vasoconstriction (67). The currently recommended dose of oxygen therapy is inhalation of at least 12 L/min of 100% oxygen. In some cases, up to 15 L/min is required for 20 min using a non-rebreathing mask (68). Mo's research proposes that the use of an oxygen concentrator absorbs surrounding air, filters out nitrogen, and produces an oxygen-enriched body that can be used as an alternative to using an oxygen tank as a source of oxygen when dealing with CH. The advantage of oxygen concentrators is that they do not need to be reoxygenated, but generally the machines have limitations in terms of maximum oxygen concentration (≤98%) and flow rate (≤5 L/min), and when higher oxygen concentrations and flow rates are required, connecting two oxygen concentrators can be an effective way of handling them (67). However, oxygen therapy does not provide pain relief for every CH patient; in a survey involving 3,251 CH patients, 13% were found to have complete relief after oxygen therapy, of which 41% were very effective, 27% moderately effective, 12% minimally effective, and 7% completely ineffective (69). This may have some correlation with the population, region or season.

Neuromodulation treatment

Neurotherapy is primarily used to treat refractory CH. Currently in neuromodulation for CH, it is divided into four main sections: vagus nerve stimulation (VNS), sphenopalatine ganglion stimulation, hypothalamic stimulation and occipital and cervical cord nerve stimulation. Vgus nerve stimulation has been approved by the FDA for the acute treatment of episodic cluster headache attacks and as an adjunctive treatment for the prevention of cluster headache (70). Most patients experienced pain relief within 15 min, with headache being the most common adverse effect (71), followed by dizziness, sore throat, and neck pain, and no serious adverse effects were observed (72). Sphenopalatine ganglion stimulation: it is an invasive treatment that requires implantation of a device in the pterygopalatine fossa below the maxilla, and studies have shown that it is more effective than VNS (approximately 67% of CH patients have pain relief within 15 min of treatment) (73), but it also has the disadvantage of being invasive, and there is a potential for postoperative adverse events, the most common of which are sensory disturbances, postoperative pain, and swelling (74). Furthermore, sphenopalatine ganglion stimulation demonstrated favorable results in treatment assessments lasting up to 24 months and shows promise as a therapeutic approach for chronic CH (75). Hypothalamic stimulation is a neurological treatment that is closely related to the underlying causes of CH. CH patients treated with this technique have a success rate of 88 per cent and have not encountered any significant negative effects (76). However, three serious adverse events, including subcutaneous infection, perioperative loss of consciousness with hemiparesis after trial simulation, and severe voiding syncope, occurred in another study on hypothalamic stimulation (77), which is a great test of clinician competence. In addition, occipital nerve stimulation is effective in reducing the frequency of CH episodes and the level of pain (78), a notion that is supported by a number of studies with concordant findings (79, 80), and there are fewer reports of adverse safety events with occipital nerve stimulation (81).

Anti-CGRP monoclonal antibody

The involvement of CGRP in the pathophysiology of headache disorders has been well established, making CGRP and its receptor a key target for the prevention of primary headache. Therefore, the emergence of multiple antibodies against CGRP and its receptors has provided new avenues of research for the pharmacologic treatment of CH (50). The emergence of galcanezumab has brought new hope for CH. As an anti-CGRP monoclonal antibody, galcanezumab reduces the symptoms of migraine by specifically binding to the CGRP receptor and blocking CGRP signaling. The unique mechanism of action of this drug, which has the advantages of being highly targeted and having few side effects, has attracted much attention from the medical community (82). According to a study published in a prestigious medical journal, galcanezumab has shown remarkable results in the treatment of migraine headaches. One study shows that the majority of patients treated with galcanezumab experienced significant headache relief in as little as 3 weeks (83, 84). This was confirmed in another study in which the median time to remission after the first 240 mg galcanezumab treatment was 17 days and the proportion of patients with a 50 per cent reduction in the number of headache attacks per week from baseline at week 3 was 78.8 per cent; 91.5 per cent of patients with acute headache received only one GT treatment, and 74.5 per cent of patients with ECH experienced remission 1 month after GT treatment; the fewest adverse events occurred in patients using the 240 mg dose of galcanezumab. The lowest number of adverse events occurred in patients treated with the 240 mg dose of galcanezumab (85). However, currently available studies indicate that galcanezumab is only effective in the prevention of eCH and has not been found to be effective in the prevention of cCH (86). Another CGRP antibody is Fremanezumab, a human IgG2 monoclonal antibody, and two trials on fremanezumab have failed in

trials that have been conducted on fremanezumab for the prevention of episodic and chronic cluster headaches. Each trial demonstrated an inability to reduce the number of CH attacks per week (87).

Overall, the emerging therapeutic directions are still in the research stage, and their drawbacks are obvious, i.e., the lack of clinical data, but recent studies have provided clinicians with innovative ideas for choosing treatments for CH, especially for refractory CH, for which studies are now available that show favorable therapeutic outcomes.

Conclusion

Cluster headache is a common and severe primary headache disorder. The pathogenesis of cluster headache is still in the research phase, but many studies have pointed the way to the study of cluster headache pathogenesis. The identification of biomarkers and imaging assays has further advanced these studies, improving our ability to diagnose, prognose, and monitor treatment response in real time. The inherent heterogeneity of neurologic disorders, the selective permeability of the blood–brain barrier, and ethical considerations in clinical trials are formidable hurdles to overcome. The strategies we give for managing the full course of the disease still need to be individualized and studied. In conclusion, many new avenues for the treatment of CH are now available, and we can further advance these studies to improve the quality of life of CH patients.

Author contributions

X-HX: Conceptualization, Writing – original draft, Funding acquisition, Investigation, Resources, Supervision. Y-ML: Visualization, Writing – original draft, Data curation, Investigation, Methodology. L-NR: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft. X-FX: Investigation, Methodology, Supervision, Validation, Writing – original draft. Y-LD: Investigation, Methodology, Project administration, Software, Writing – original draft. C-QJ: Conceptualization, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. R-RY: Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Cost-effectiveness analysis of rimegepant for on-demand acute treatment of migraine in China

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Purpose: This study assesses the cost-effectiveness of rimegepant for the on-demand acute treatment of migraine in the Chinese population, focusing on headache relief within a 2 h timeframe. Utilizing data from Phase III clinical trials on rimegepant involving Asian populations, this analysis aims to provide essential insights for healthcare decision-making in the context of migraine management in China.

Patients and methods: Employing a decision tree model, this research evaluates the cost-effectiveness of rimegepant over a concise 2 h period, exclusively considering its direct market price of 219.00 CNY per dose for on-demand, single-use treatment upon approval in China. This model is based on pain relief outcomes from a clinical trial, categorizing health outcomes by the achievement of pain freedom and alleviation from the most bothersome symptom within two hours post-administration.

Results: The study unveils that rimegepant adds 0.0018 quality-adjusted life days (QALD) with an incremental cost-effectiveness ratio (ICER) of 122,166.07 CNY/QALD. Against a daily cost-effectiveness threshold derived from the 2023 *per capita* GDP of China (734.45 CNY/day), rimegepant falls short of proving its cost-effectiveness. A significant price reduction to approximately 1.32 CNY per dose is required for rimegepant to be considered cost-effective within this framework. Furthermore, a series of sensitivity analyses were conducted to validate the robustness of these results.

Conclusion: While rimegepant shows clinical efficacy in providing rapid relief from migraine symptoms, its current pricing exceeds the threshold for cost-effectiveness in the Chinese healthcare setting. This study underscores the need for price adjustments to enhance the accessibility and economic viability of new migraine treatments.

KEYWORDS

cost-effectiveness, rimegepant, migraine, on-demand treatment, China

Introduction

Migraine is a prevalent neurological condition characterized by recurrent, severe headaches that significantly impair the quality of life and productivity of those affected (1, 2). In China, the prevalence of migraine is estimated at 9.3%, affecting approximately 130 million people and placing substantial economic and societal burdens on the community (3, 4). The annual direct and indirect costs associated with migraine management exceed 299.4 billion Chinese Yuan (CNY), underscoring the significant economic impact of this condition (5, 6). In China, the current treatment landscape for the acute treatment of migraine primarily involves nonsteroidal anti-inflammatory drugs (NSAIDs, 69%), with ibuprofen being the most commonly used (37%), followed by aspirin (8%), opioids (7%), ergot alkaloids (6%), and triptans (3%) (7). Additionally, many individuals in China opt for herbal medicine to manage migraine symptoms.

Rimegepant, a calcitonin gene-related peptide (CGRP) receptor antagonist, is indicated for the acute treatment of migraine (8). Notably, it also reduces the frequency of migraine recurrences with repeated as-needed use. In the USA, EU, and UK, rimegepant is approved for both the acute treatment of migraine and the preventive treatment of episodic migraine (9, 10). In January 2024, the National Medical Products Administration approved rimegepant in China, but only for the acute treatment of migraine. This approval was based on clinical studies conducted in Asian populations, demonstrating its efficacy in the acute treatment of migraine (11). While studies in USA have shown rimegepant to be effective for the preventive treatment of episodic migraine (12, 13), ongoing research in Chinese populations is still needed to determine its preventive efficacy (11). Mid-term results from the study have been promising, indicating potential benefits in the preventive treatment of migraine for Chinese populations.

Despite its demonstrated efficacy, the accessibility of rimegepant is significantly hindered by its high cost, a critical barrier for the majority of Chinese patients seeking relief from migraine attacks. While Western countries have conducted several cost-effectiveness analyses focusing on the prophylactic use of rimegepant (14), which predominantly yielded negative outcomes due to the price of the drug, there remains a conspicuous void in research pertaining to its cost-effectiveness for the acute treatment of migraine, particularly within the Chinese healthcare landscape.

This study aims to conduct a comprehensive cost-effectiveness analysis of rimegepant for single-use, on-demand acute treatment of migraine among the Chinese demographic (15). By integrating data from clinical trials with the economic realities of the Chinese healthcare environment, this investigation seeks to provide essential insights for healthcare policy-making and decision-making. Beyond offering a novel perspective on patient care, this study aims to influence healthcare policy and the economic evaluation of new treatments, optimizing migraine management strategies in China and improving the lives of those afflicted by this debilitating condition.

Materials and methods

Overview

For this economic evaluation, Tree Age Pro software (version 2022, https://www.treeage.com/) was employed to develop the mathematical model that underpins our analysis. The primary aim of the study was to explore the economic and healthcare impacts of introducing rimegepant as an innovative therapeutic option for the on-demand acute treatment of migraine, in comparison to a placebo, specifically within the Chinese healthcare milieu.

Efficacy metrics, including the proportion of individuals achieving headache relief within 2 h, were derived from a targeted Phase III clinical trial within the Asian demographic (11) (ClinicalTrials.gov identifier: NCT04574362, henceforth referred to as the RMG-306 study), alongside a single-dose safety clinical trial (16) (Trial registration: China Center for Drug Evaluation, CTR20210569, henceforth referred to as the RMG-301 study). The reliance on publicly accessible data from these trials meant that our study was exempt from ethical review by the Clinical Ethics Committee of Jining First People's Hospital, in accordance with the Measures for Ethical Review of Life Science and Medical Research Involving Humans (2023).

This economic analysis was structured to comply with the Chinese guidelines for pharmacoeconomic evaluations (2020) (17), closely adhering to the prescribed methodological framework and analytical standards established for pharmacoeconomic research in China.

Model construction

In our analysis, a decision tree model was deployed to specifically address the on-demand application of rimegepant for the acute treatment of migraine. This choice of model was predicated on its aptitude for accurately depicting the immediate treatment objectives inherent in migraine management, principally the rapid alleviation of symptoms.

In Figure 1, the constructed model identifies three principal health states: pain freedom, freedom from the most bothersome symptoms, and treatment ineffectiveness. For the initial two states, subdivisions were established to mirror the timing of symptom resolution, divided into 15-, 30-, 45-, 60-, 90-, and 120 min intervals post-administration. This segmentation reflects outcomes observed in the RMG-306 study. Based on findings from both the RMG-301 and RMG-306 studies, the incidence of adverse events associated with rimegepant was found to be comparable to that of the placebo group. As a result, our model does not delineate a separate health state for adverse events.

The scenario begins with patients experiencing a migraine, extending over a 2 h period to capture potential developments following the onset of the migraine. This duration reflects the choice between a single dose of rimegepant or a placebo, acknowledging the common tendency among Chinese patients to manage short-lived headache episodes without drug intervention. Owing to the brevity of the analysis period, the study foregoes the application of a discount rate.

Economic evaluation metrics were formulated in accordance with the Chinese pharmacoeconomic evaluation guidelines (2020). Focused on the evaluation of a 2 h acute episode, the willingness-to-pay (WTP) threshold was set at three times the daily-adjusted *per capita* GDP of China for 2023. Treatment efficacy was determined through the computation of cumulative costs, quality-adjusted life days (QALD), and the incremental cost-effectiveness ratio (ICER). A treatment is considered cost-effective if its ICER does not exceed the pre-defined WTP threshold.

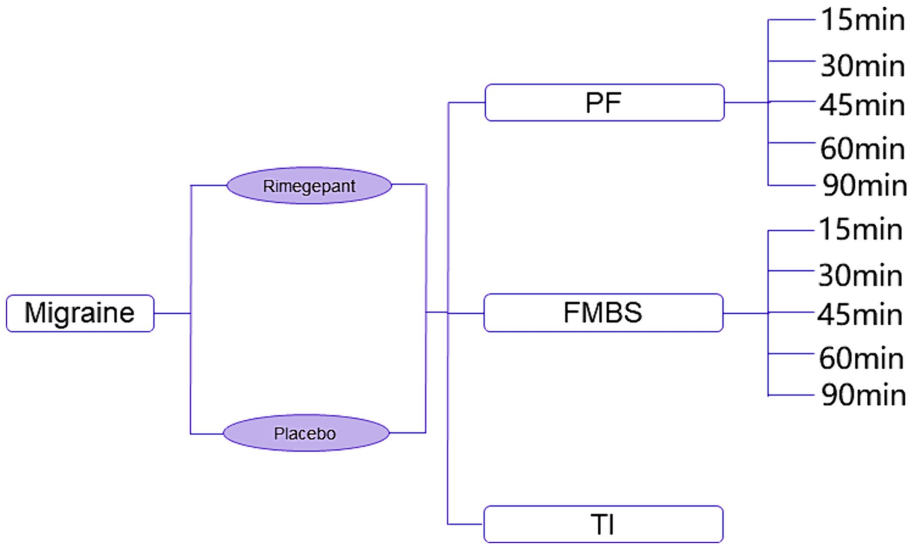

FIGURE 1
Diagram of decision tree model. PF, pain freedom; FMBS, freedom from most bothersome symptom; TI, treatment ineffectiveness.

Data and sources

Probabilities

The transition probabilities between health states in our model were directly extracted from the RMG-306 study data. The alignment of the health states within the model with the primary and secondary endpoints from the RMG-306 study eliminated the need for data conversion across different follow-up periods.

For the principal health states, occurrence rates were derived from the primary endpoints of the study. Specifically, probabilities for achieving pain freedom or freedom from the most bothersome symptoms 2 h post-administration of rimegepant or placebo were calculated by dividing the number of patients reporting these outcomes by the total number of participants in each respective group. Patients not reaching these states within the defined timeframe were classified under treatment ineffectiveness.

Further subdivisions within these principal states, aimed at capturing more specific timeframes, were based on the secondary outcomes of the study. For example, the probability of achieving pain freedom within 15 min was calculated by the ratio of patients achieving this outcome within 15 min to the total number of patients achieving pain freedom at the 2 hour mark within the same group. Similar calculations were applied for subsequent probability, ensuring the derivation of each minor probability of the state from its proportionate share of patients reaching the primary endpoint at two hours.

Table 1 presents an exhaustive overview of the numerical values of the probabilities and their corresponding mathematical distributions as inputted into our model.

Utilities

Due to the lack of direct quality of life research associated with the RMG-306 study for the acute treatment of migraine, the utility values for our study were sourced from existing cost-effectiveness analyses and the reports by the Institute for Clinical and Economic Review on migraine[1] (18).

Originally, these utility values (19) were calculated based on the number of monthly headache days (MHD) to estimate quality-adjusted life years (QALYs). For the purpose of our study, which assesses the impact of a 2 h migraine episode, these values were proportionally adjusted to quality-adjusted life days (QALD). This adjustment involves translating the data from a 30 day basis to a 2 h period to reflect the impact on quality of life during migraine episodes. In addition, for the health state associated with achieving freedom from the most bothersome symptoms, the utility estimation was specifically adjusted by applying a factor of 0.87 to the utility value for the pain freedom state (18). Table 2 provides a detailed presentation of the utility values employed in our model, including their mathematical distributions.

Cost

In our analysis, the drug costs are exclusively associated with the price of a single, on-demand dose of rimegepant, as the study does not consider the financial implications of adverse events. The standard dosage for rimegepant is set at 75 mg per administration, with a recommended limit of no more than one dose per day. Accordingly, our model includes the cost for one dose of rimegepant, reflecting its pricing strategy following its recent introduction to the Chinese market. Table 3 presents a detailed presentation of the cost data, including the average price, minimum price, maximum price, and standard deviation, along with the mathematical distribution for the price of rimegepant.

Sensitivity analysis

To assess the stability and reliability of our model in the face of parameter uncertainties, we conducted both one-way deterministic

1 https://icer.org/assessment/acute-migraine-2020/

TABLE 1 Probabilities between health states used in the model.

Drug	Rimegepant			Placebo		
Input variable	Base value	Beta distribution		Base value	Beta distribution	
		α	β		α	β
Pain freedom 2 h after dosing	0.1982	132	534	0.1068	72	602
Freedom from the MBS 2 h after dosing	0.5045	336	330	0.3576	241	433
Pain freedom 15 min after dosing	0.0379	5	127	0.0972	7	65
Pain freedom 30 min after dosing	0.0152	2	130	0.0417	3	69
Pain freedom 45 min after dosing	0.1136	15	117	0.0694	5	67
Pain freedom 60 min after dosing	0.1742	23	109	0.2083	15	57
Pain freedom 90 min after dosing	0.2803	37	95	0.2500	18	54
Freedom from the MBS 15 min after dosing	0.2024	68	268	0.3112	75	166
Freedom from the MBS 30 min after dosing	0.1310	44	292	0.1037	25	216
Freedom from the MBS 45 min after dosing	0.1458	49	287	0.1411	34	207
Freedom from the MBS 60 min after dosing	0.1369	46	290	0.1369	33	208
Freedom from the MBS 90 min after dosing	0.2054	69	267	0.1950	47	194

MBS, most bothersome symptom; min, minutes; h, hours. (1) Baseline values have been rounded to four decimal places. (2) In the deterministic sensitivity analysis (DSA), the upper and lower limits were set to ±10% of the base value. (3) In the probabilistic sensitivity analysis (PSA), the probabilities were determined using the beta distribution values obtained from the specified α and β parameters.

sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The DSA explored how variations in each individual parameter influenced the overall cost-effectiveness outcomes of the model. Parameter ranges for the DSA were derived from existing literature where possible, or otherwise set to ±10% of the base-case values to account for potential fluctuations. The PSA, on the other hand, was implemented to examine the collective impact of multiple parameter changes on the cost-effectiveness findings. This comprehensive analysis was facilitated by conducting a Monte Carlo simulation with 100 iterations, producing a range of 100 ICER estimates for rimegepant compared to the control group. Detailed descriptions of the ranges and mathematical distributions applied to each parameter in both the DSA and PSA can be found in Tables 1–3.

Results

Base-case analysis

In our study, a 2 h assessment was carried out to compare the on-demand acute treatment efficacy of rimegepant for migraine against a placebo. The incremental effectiveness attributed to rimegepant was determined to be 0.0018 QALD, with rimegepant demonstrating an effectiveness of 0.0438 compared to 0.0420 for the placebo. The administration of rimegepant was associated with an incremental cost of 219.00 CNY, resulting in an ICER of 122,166.07 CNY/QALD. Compared to the WTP threshold, established at three times the daily-adjusted 2023 *per capita* GDP of China (734.45 CNY), the ICER for rimegepant substantially surpasses this threshold. Our analysis further indicated that for rimegepant to align with the defined WTP threshold, a price reduction to 1.32 CNY or less would be necessary. The detailed outcomes of our base-case analysis are meticulously cataloged in Table 4.

Sensitivity analyses

The results of the DSA are depicted in Figure 2, utilizing a tornado diagram. This diagram elucidates the impact of individual model parameter variations on the ICER. Notably, the transition probabilities to achieving freedom from the most bothersome symptoms within the rimegepant exerted the greatest influence on the ICER, followed by the utility value representing no improvement in migraine symptoms after a 2 h period. Additionally, the transition probabilities to achieving freedom from the most bothersome symptoms within the placebo emerged as the third most influential factor. Subsequently, the cost of rimegepant also significantly affected the ICER. It is worth noting that the stability of DSA results in our study may be attributed to the decrease in numerical values after utility value transformation to QALD in our research methodology. The expected value (EV) line, representing the base-case analysis outcome of 122,166.07 CNY/QALD, serves as a reference for the baseline result. Increases in model inputs are depicted by red bars, while decreases are indicated by blue bars, with each bar reflecting the ICER range derived from varying each parameter within set boundaries.

Figure 3 displays the cost-effectiveness acceptability curve, indicating the probability of rimegepant being cost-effective across various WTP thresholds. Notably, at a WTP threshold below 30,000 CNY, the likelihood of rimegepant being cost-effective is substantially low, with only a 18% probability at a WTP of 30,000 CNY, as opposed to 82% for the placebo. However, even as the WTP threshold rises, the probability of rimegepant being cost-effective witnesses only slight increases, reaching a mere 45% at a WTP of 100,000 CNY, while the probability for the placebo diminishes to 55%.

Moreover, Monte Carlo simulations depicted in Figure 4 offer further insights. Out of 100 simulations conducted at the current price of rimegepant, none achieved cost-effectiveness, with 44% indicating a complete absence of cost-effectiveness (i.e., increased costs with diminished effectiveness relative to the placebo). The remaining 56%

TABLE 2 Utility values for health states.

Health state	Base value	Low value	High value	SD
Pain freedom 15 min after dosing	0.7573	0.7194	0.7952	0.1662
Pain freedom 30 min after dosing*	0.6449	0.6127	0.6771	0.2817
Pain freedom 45 min after dosing*	0.6764	0.6426	0.7102	0.2458
Pain freedom 60 min after dosing	0.6420	0.6010	0.6741	0.2543
Pain freedom 90 min after dosing	0.5916	0.5620	0.6212	0.2549
Pain freedom 120 min after dosing	0.5040	0.4789	0.5292	0.2835
Sustained pain in 2 h	0.4400	0.3740	0.5020	0.2477

SD, standard deviation; min, minutes; h, hours. (1) In the PSA, the probabilities were determined using the beta distribution values obtained from the specified base value and SD parameters. (2) *The higher health utility value associated with pain freedom 45 min after dosing compared to 30 min is based on data from a referenced study. Despite its deviation from common expectations, these values are reflective of the original dataset provided in the cited literature. (3) The data presented in this table represent unprocessed raw health utility values (in QALY) for headache occurrences. These values undergo transformation to QALD before being inputted into the research model.

TABLE 3 Drug dose and costs.

Drug (CNY)	Dose	Base value price	Low value price	High value price	SD*
Rimegepant	75 mg/ once	219.00	175.20	262.80	22.24
Placebo	–	0	0	0	0

CNY, Chinese Yuan; SD, standard deviation. (1) In the PSA, the probabilities were determined using the Gamma distribution values obtained from the specified base value and SD parameters. (2)* The SD of drug prices is derived from a comprehensive market survey conducted within the local price market.

TABLE 4 Base case results.

Drug	Cost	Effectiveness	ICER (CNY/ QALD)
Placebo	0	0.0420	
Rimegepant	219.00	0.0438	122166.07
Rimegepant (at a reduced price)	1.32	0.0438	734.45

ICER, incremental cost-effectiveness ratio; CNY, Chinese Yuan; QALD, quality-adjusted life days.

of simulations resulted in ICER surpassing the established WTP threshold of 734.45 CNY.

Discussion

Rimegepant has secured approval for migraine treatment and is recommended in migraine management guidelines in the United States (9), Europe (20), and China (15) albeit with its application in Chinese guidelines specifically confined to migraine management. It has been evaluated in several Phase III clinical trials internationally, addressing both treatment and prevention, and showing positive efficacy in populations across the United States (12, 13) and Asia (11), including China and Korea. Nonetheless, cost-effectiveness analyses from the U.S. perspective suggest the potential limitations of rimegepant in being cost-effective for migraine prevention, with its value for acute treatment also appearing comparatively lower (14).

Conducting a cost-effectiveness analysis of rimegepant for the treatment of migraine in China marks a novel and critical exploration, essential for appraising its financial feasibility within the Chinese healthcare landscape. Leveraging existing cost-effectiveness studies (14, 18) and quality of life research (21–23) on rimegepant, our study endeavors to bridge this gap, aiming to provide evidence-based treatment insights for migraine patients in China. Additionally, our investigation accounts for the correlation between Chinese *per capita* GDP and the costs associated with treatment, aiming to ensure that our findings are pragmatically relevant and regionally tailored.

Our study presents several key strengths. Firstly, the data on headache resolution rates within 2 h post-rimegepant administration, derived directly from the RMG-306 study—which specifically investigates migraine episodes among the Asian population—ensures an accurate depiction of real-world outcomes. Secondly, we employ an innovative approach to utility value estimation in the face of limited data availability. By adapting utility values, originally based on the number of MHD, to assess acute episodes within a concise 2 h timeframe, our study adeptly addresses the complexities involved in translating chronic condition utilities to the acute setting. Thirdly, although rimegepant has only recently been introduced to the Chinese market, leading to relatively stable pricing, our model anticipates potential future pricing variations by incorporating a 20% margin of variability in the cost rimegepant. Lastly, while our results concur with studies from the United States indicating that rimegepant lacks cost-effectiveness, our analysis goes further by determining a reference price point at which rimegepant could achieve cost-effectiveness within the Chinese context. Despite the stark contrast between our proposed price reference and the current pricing of rimegepant, it is important to note that in real-world scenarios, the majority of migraine patients often opt for transient endurance or choose to take a single dose of nonsteroidal anti-inflammatory drugs such as ibuprofen. Moreover, within the context of Chinese government-led centralized drug procurement policies, our suggested price reference remains practical and relevant.

Our study encounters several limitations that merit consideration. Firstly, our analysis is confined to the single, on-demand use scenario of rimegepant, not accounting for the recurrent nature of migraine attacks that many patients experience. Unlike its approval in Western countries for both acute and preventive treatment, rimegepant in China is only approved for the acute treatment of migraine. This limitation overlooks the long-term economic and clinical implications of repeated migraine episodes and the potential cumulative benefit of treatment. Given the high

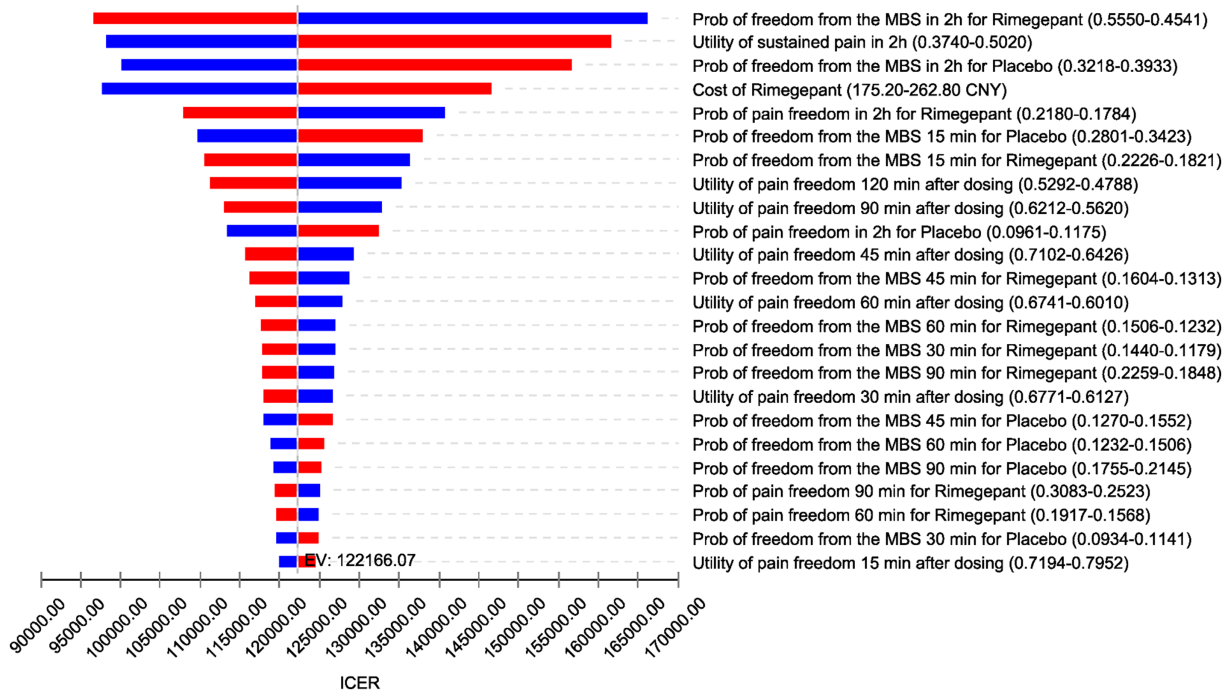

FIGURE 2
Tornado diagram (deterministic sensitivity analysis results). ICER, incremental cost-effectiveness ratio; EV, expected value; CNY, Chinese Yuan; Prob, probabilities; MBS, most bothersome symptom; min, minutes; h, hours.

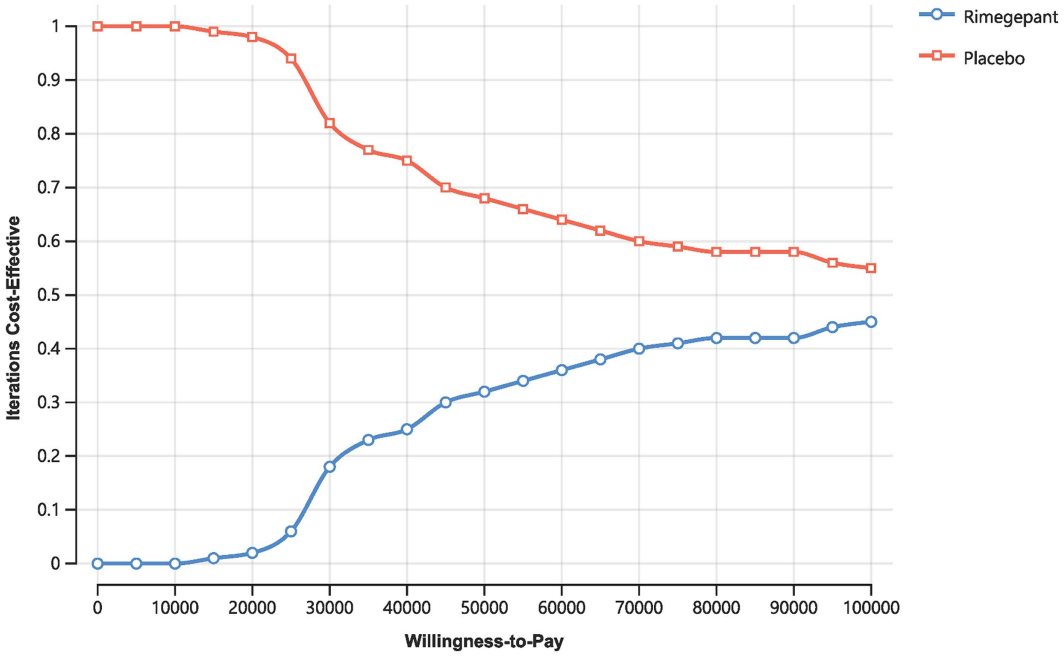

FIGURE 3
Acceptability curve.

cost of rimegepant and its impact on patient compliance, our analysis, although based on a single intake, still holds significant reference value. Secondly, the innovative methodology of deriving utility values from the number of MHD to assess a 2 h episode migraine might not fully capture the nonlinear impact short-term events could have on quality of life. This adaptation, while practical in the absence of specific utility data, introduces a degree of speculation regarding the true quality of life impact during such

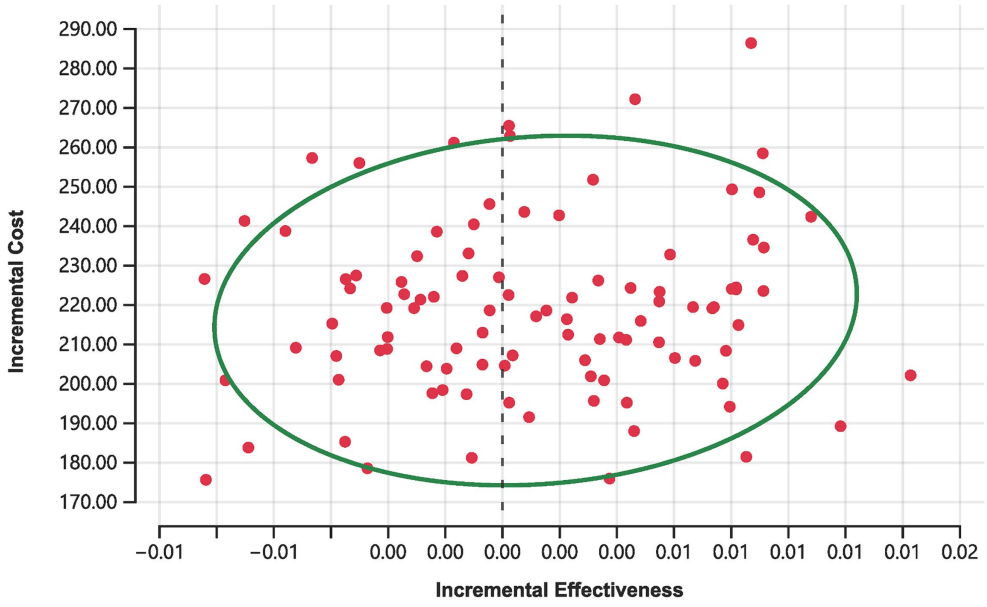

FIGURE 4
Scatter plot for rimegepant.

episodes. Sensitivity analyses indicate that our method of handling utility data may contribute to model instability. However, this instability does not affect the ultimate negative findings. In both DSA and PSA, within the predefined parameter ranges and distributions, the current pricing of rimegepant does not demonstrate cost-effectiveness. Thirdly, the cost considerations in our model are narrowly focused on the price of rimegepant alone. Given the 2 h time frame of our study, we did not incorporate the broader economic losses attributed to ongoing migraine episodes, such as reduced productivity or additional healthcare utilization. Including these broader economic impacts could potentially shift the cost-effectiveness balance more favorably. Lastly, while rimegepant has been demonstrated to be safe with a low incidence of adverse events across multiple clinical trials (11–13), our model does not account for the occurrence of such events. The exclusion of adverse event considerations may skew our cost-effectiveness analysis, underestimating the true cost and overestimating the value associated with using rimegepant for the acute treatment of migraine.

Conclusion

Within the context of Chinese economic landscape and the current market pricing of rimegepant, our study conclusively finds that the on-demand, single-use of rimegepant for the acute treatment of migraine does not demonstrate cost-effectiveness. By highlighting the economic limitations of rimegepant application under its current pricing, our analysis underscores the need for price adjustments or alternative strategies to enhance its cost-effectiveness. Our findings could inform future revisions of treatment guidelines and healthcare policies, providing critical insights for healthcare decision-making concerning the acute treatment of migraine management in China.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

STi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YY: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. STa: Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. JL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. CY: Data curation, Investigation, Methodology, Writing – review & editing. QL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YG: Conceptualization,

Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Clinical decision support system using hierarchical fuzzy diagnosis model for migraine and tension-type headache based on International Classification of Headache Disorders, 3rd edition

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Objective: To determine whether the diagnostic ability of the newly designed hierarchical fuzzy diagnosis method is consistent with that of headache experts for probable migraine (PM) and probable tension-type headache (PTTH).

Background: Clinical decision support systems (CDSS) are computer systems designed to help doctors to make clinician decisions by information technology, and have proven to be effective in improving headache diagnosis by making medical knowledge readily available to users in some studies. However, one serious drawback is that the CDSS lacks the ability to deal with some fuzzy boundaries of the headache features utilized in diagnostic criteria, which might be caused by patients' recall bias and subjective bias.

Methods: A hybrid mechanism of rule-based reasoning and hierarchical fuzzy diagnosis method based on International Classification of Headache Disorders, 3rd edition (ICHD-3) was designed and then validated by a retrospective study with 325 consecutive patients and a prospective study with 380 patients who were clinically diagnosed with migraine and TTH at the headache clinic of Chinese PLA General Hospital.

Results: The results of the diagnostic test in the retrospective study indicated that the fuzzy-based CDSS can be used in the diagnosis of migraine without aura (MO) (sensitivity 97.71%, specificity 100%), TTH (sensitivity 98.57%, specificity 100%), PM (sensitivity 91.25%, specificity 98.75%) and PTTH (sensitivity 90.91%, specificity 99.63%). While in the prospective study, the diagnostic performances were MO (sensitivity 91.62%, specificity 96.52%), TTH (sensitivity 92.17%, specificity 95.47%), PM (sensitivity 85.48%, specificity 98.11%) and PTTH (sensitivity 87.50%, specificity 98.60%). Cohen's kappa values for the consistency test were 0.984 ± 0.018 (MO), 0.991 ± 0.018 (TTH), 0.916 ± 0.051 (PM), 0.932 ± 0.059 (PTTH) in the retrospective study and 0.884 ± 0.047 (MO), 0.870 ± 0.055 (TTH), 0.853 ± 0.073 (PM), 0.827 ± 0.118 (PTTH) in the prospective study, which indicated good consistency with the fuzzy-based CDSS and the gold standard ($p < 0.001$).

Conclusion: We developed a fuzzy-based CDSS performs much more similarly to expert diagnosis and performs better than the routine CDSS method in the

diagnosis of migraine and TTH, and it could promote the application of artificial intelligence in the area of headache diagnosis.

KEYWORDS

migraine, tension-type headache, fuzzy logic, artificial intelligence, ICHD-3, CDSS

1 Introduction

Migraine and tension-type headache (TTH) are the two most common primary headache disorders, demonstrating high prevalence and socioeconomic impacts (1, 2). However, the diagnostic accuracy is only 13.8% for migraine and 5.6% for TTH according to a previous population-based study in China (3), which might lead to excessive neuroimaging examination, delayed preventive treatment, and even medication overuse.

In our previous study (4), we developed a rule-based clinical decision support system (CDSS) based on the International Classification of Headache Disorders (ICHD) (5) and achieved relatively satisfactory diagnostic accuracy for most primary headache disorders. To address the diagnostic difficulty due to the overlap between primary headaches (6–8), we also used a case-based reasoning method and ultimately increased the diagnostic accuracy for probable migraine and probable tension-type headache (9). However, one obvious drawback is that these two CDSSs lack the ability to deal with some fuzzy headache features (i.e., the duration of attacks, headache intensity and number of attacks), which are often subject to recall bias and subjective bias. Regarding the duration of attacks and the number of attacks, it is known that patients often have difficulty recalling their precise headache features. During the clinical interview, the information concerning the frequency and temporal pattern of attacks and days with headache(s) that patients provide often includes rough and imprecise estimates, and this can interfere with the quantification of the real number of headache days per month (10). Regarding headache intensity, it has been reported that recall of headache is easily affected by subjective factors, such as the mood or stress at the time of pain perception, pain intensity or mood at the time of recall, peak pain intensity, pain intensity at the end of the period and variability of pain intensity. Therefore, there may be discrepancies between the recalled and actual headache intensity (11). The imprecise description of these three headache features due to recall bias and subjective bias means that experienced doctors must deal with the boundaries of headache features in a fuzzy and approximate way, rather than using a one-size-fits-all approach as in the diagnostic criteria in ICHD. The rule-based CDSS and case-based CDSS cannot use such an approach. Therefore, it is necessary to develop a new headache diagnostic model to address fuzzy features and fuzzy information.

Fuzzy logic is a kind of artificial intelligence technology that is useful in expressing the intrinsic uncertainty and unclear boundaries of the patient features utilized in auxiliary diagnosis, and it has been found to be useful in a number of disease diagnoses, such as unstable angina (12), osteoporosis (13), and breast cancer (14). Fuzzy logic can imitate the processing of fuzzy concept judgements and reasoning as an expert does. For a system with a fuzzy model, fuzzy sets and fuzzy rules can be applied to express the transitional boundary of qualitative knowledge and experience and to solve the problem that the conventional method is difficult to use. Specially, the fuzzy diagnostic modelling of ICHD-3 is a process of translating the text-based diagnostic criteria in ICHD to digital executable models for computers with the cooperation of headache experts and knowledge engineers. Hierarchical fuzzy logic is a method of hierarchical modelling that can decompose a complex process and execute it in a sequence from simple to complex. This method has been successfully applied in other field (15, 16). In this study, we aimed to optimize the diagnostic modelling method of migraine and TTH and to design a hierarchical fuzzy inference method that can be regarded as a supplement to rule-based reasoning and case-based reasoning in the headache CDSS. Furthermore, we clinically evaluated the validity and feasibility of this system in a headache clinic of Chinese PLA General Hospital by a retrospective study and a prospective study respectively. Besides, we employ a consistency test as the method of testing to validate the diagnostic conclusions of the headache CDSS against the gold standard. We hypothesized that there was poor consistency (H_0 :kappa = 0) between the new hierarchical fuzzy inference method and the gold standard, and then carried out statistical analysis.

2 Methods

2.1 Design and construction of a fuzzy diagnostic model based on ICHD-3

2.1.1 Overview

As shown in Figure 1, the fuzzy diagnostic method is a four-step process: the first step is the modelling of the diagnostic thinking of headache experts, the second step is determining the fuzzy variables, the third step is the design of the membership functions utilized in fuzzy logic, and the last step is the design of hierarchical fuzzy inference to deal with the fuzzy information.

2.1.2 Modelling of diagnostic thinking

After excluding secondary headaches, migraine with aura, cluster headaches, and chronic headaches, the headache experts' diagnostic process for migraine and TTH is summarized as a diagnostic decision diagram, which consists of context nodes, decision nodes and action nodes, as shown in Figure 2. The context node (elliptical node) acts as a starting point of the decision diagram and indicates the beginning of diagnosis. A decision node (hexagon node) means that a decision needs to be made at this point in the process. The red arrow in Figure 2 shows how the ICHD diagnostic criteria are decomposed and ontology expressed in the migraine diagnostic criteria node. Several options are listed in the decision node, and the conditions for choosing an option are listed as well. An action node (rectangular node) is a leaf node of the model, and it needs to be clearly acted on. In this paper,

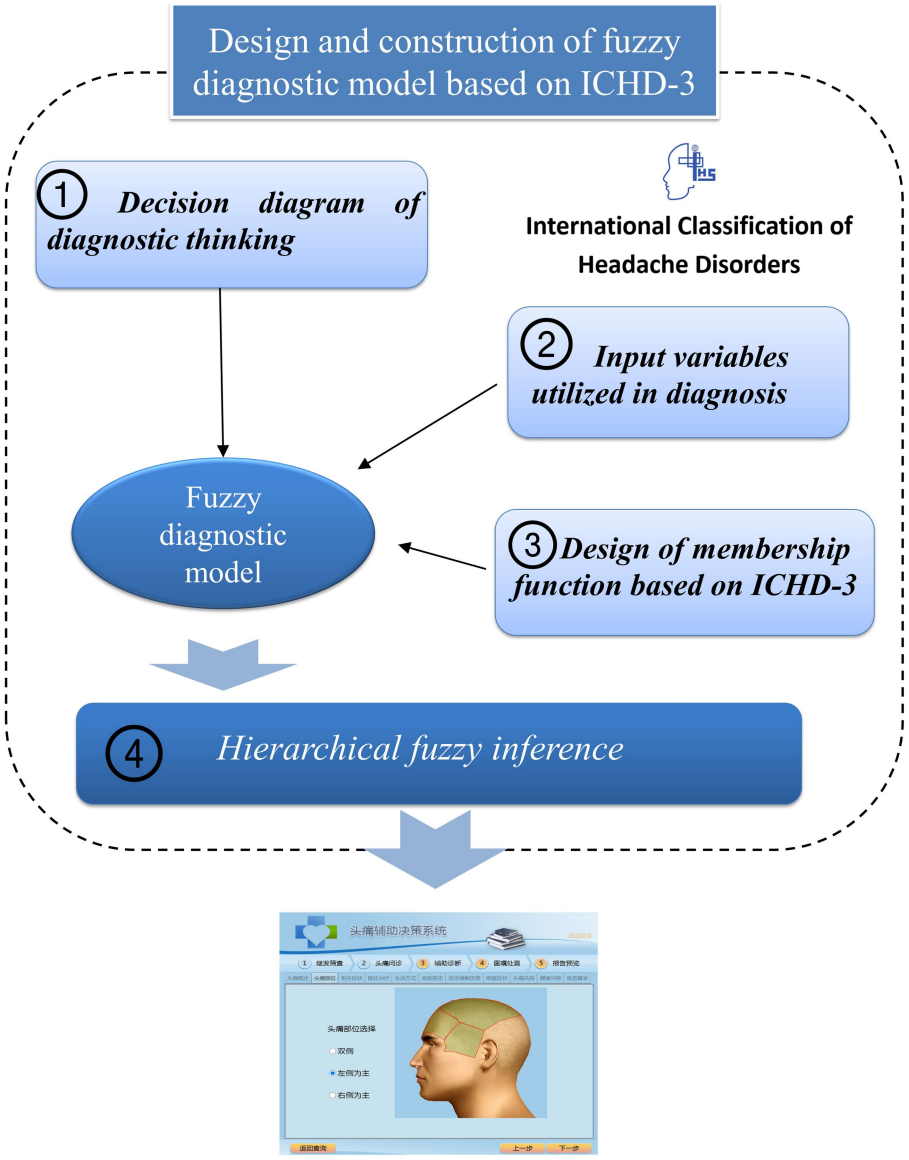

FIGURE 1
Overview of the fuzzy diagnostic method based on ICHD-3.

each action node is a diagnosis. With the above components, the decision diagram model of diagnostic thinking on migraine and TTH is built. The decision nodes can be expressed as the corresponding fuzzy rules by fuzzy logic techniques in the subsequent steps.

2.1.3 Input variables utilized in diagnosis

All the patient features mentioned in the diagnostic criteria are included in the diagnostic model. These features can be divided into two categories, numerical features and categorical features, as shown in Table 1. The headache intensity, duration of attacks, and number of attacks are numerical features, whose values need to be classified into fuzzy sets by the predefined membership functions. For example, the number of attacks can be mapped into three fuzzy sets, denoted as {low, moderate, high}, according to the ICHD-3. Other patient features are categorical features, whose sets of possible values are indicated by the ICHD-3 and can be represented by classical two-valued logic as {yes, no}.

2.1.4 Design of membership functions based on ICHD-3

Membership functions are utilized in the fuzzification and defuzzification steps of a fuzzy logic system to map the non-fuzzy input values to fuzzy linguistic terms and vice versa. The shapes of commonly used membership functions are triangle, trapezoid, rectangle, etc. The membership functions of fuzzy sets are often designed by domain experts based on their experience, so in this paper, we design the membership functions based on ICHD-3. For example, in the diagnostic criteria of migraine, at least five attacks are required, so 5 is the boundary value of the number of attacks. For TTH, the number of attacks should be at least 10, so 10 is also a key boundary value. The membership function of the number of attacks is as shown in Figure 3A. Similarly, for the headache intensity and duration of attacks, we can obtain their membership functions as shown in Figures 3B,C.

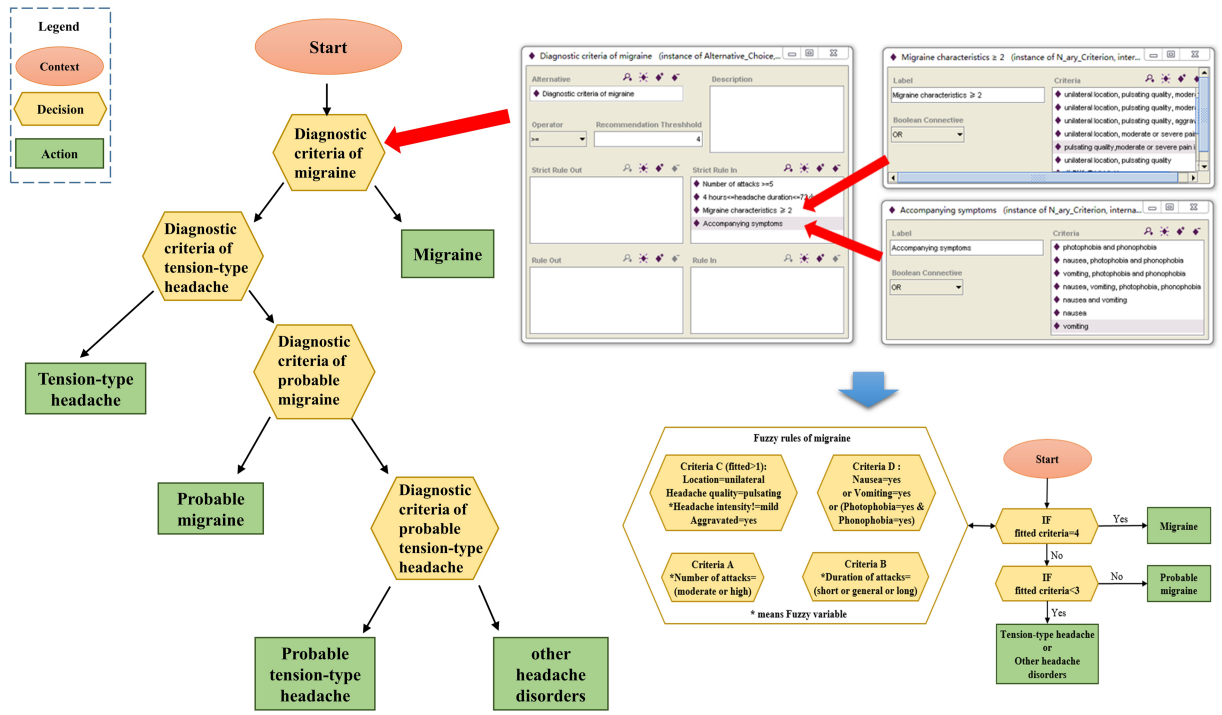

FIGURE 2
Diagnostic decision diagram model of migraine and TTH.

TABLE 1 Patient features utilized in the diagnosis of migraine and tension-type headache.

Numerical features	
Name	Fuzzy set
Headache intensity	{mild, moderate, severe}
Duration of attacks	{very short, short, moderate, long, very long}
Number of attacks	{low, moderate, high}

Categorical features	
Name	Crisp set
Headache quality	{pulsating, non-pulsating}
Headache location	{unilateral, bilateral}
Aggravation by or causing avoidance of routine physical activity	{yes, no}
Nausea	{yes, no}
Vomiting	{yes, no}
Photophobia	{yes, no}
Phonophobia	{yes, no}

2.1.5 Hierarchical fuzzy inference

To express the diagnostic criteria in ICHD-3 more exactly, we designed a hierarchical fuzzy method with three levels, as shown in Figure 4.

The first level takes criterion C as a small fuzzy system and then adds its inference results into another large fuzzy system. The second level uses traditional two-valued logic to judge whether the patient's symptoms fulfil criterion D. The third level is the final fuzzy system, which takes the results of the previous two levels as input variables and then carries out a fuzzy inference process. Table 2 shows examples of fuzzy rules, in which fit and unfit indicate whether diagnostic criterion C is fulfilled.

Then, in the last step, the weight-based defuzzifier is computed using the results of the membership functions as values and the activation degrees (α) as weights. The activation degree of each fuzzy rule can be computed according to the value of the input variables. Taking the first rule in Table 2 as an example, its activation degree is calculated by Equation (1):

$$\alpha = \mu_{\text{unilateral}}\left(x_{\text{headachelocation}}\right) \wedge \mu_{\text{throbbing}}\left(x_{\text{headachequality}}\right) \wedge \mu_{\text{mild}}\left(x_{\text{headacheintensity}}\right) \quad (1)$$

where $\mu_{\text{mild}}\left(x_{\text{headacheintensity}}\right)$ is the membership degree of $x_{\text{headacheintensity}}$ in the mild fuzzy set.

Considering that one of the output variables Typeofheadache (for migraine) contains the constant terms *migraine* = 2, *probablemigraine* = 1, and *others* = 0, its crisp output value computed with the weighted-average defuzzifier is given by:

$$f_{\text{Typeofheadache}}\begin{pmatrix} x_{\text{Numberofattack}}, \\ x_{\text{Headacheduration}}, \\ x_{\text{criterionC}}, x_{\text{criterionD}} \end{pmatrix} = \frac{\begin{array}{l}\alpha_1 \text{migraine} + \\ \alpha_2 \text{probablemigraine} + \\ \alpha_3 \text{others}\end{array}}{\alpha_1 + \alpha_2 + \alpha_3} \quad (2)$$

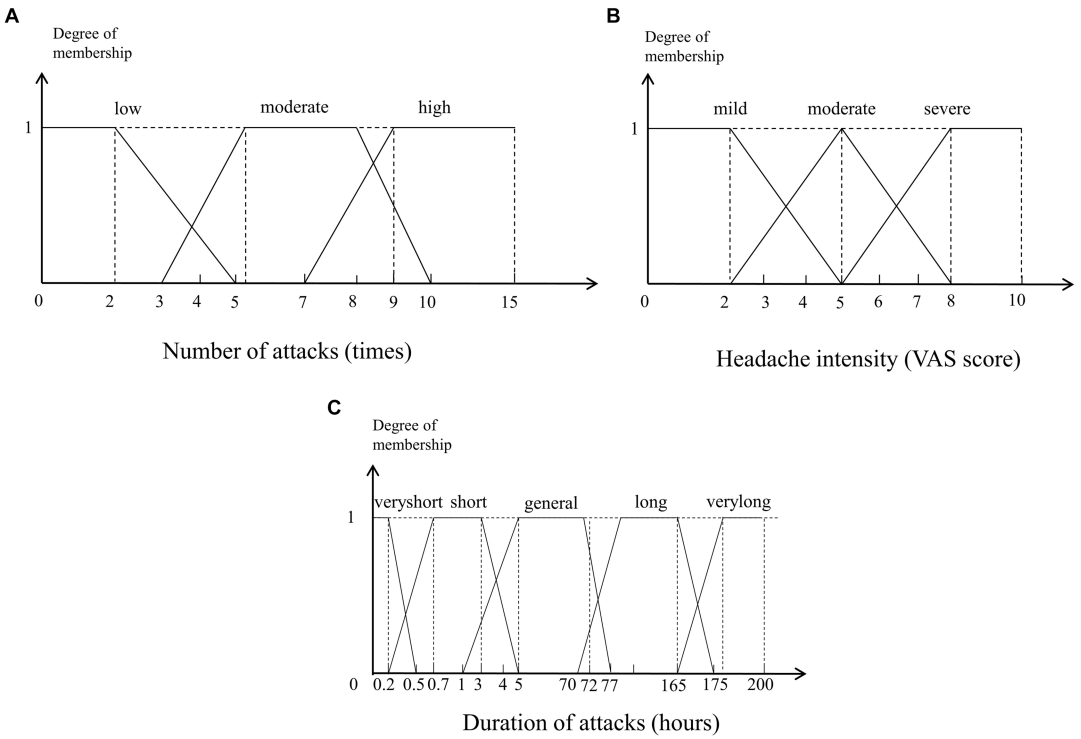

FIGURE 3
Membership functions of the numerical variables. **(A)** Number of attacks (times). **(B)** Headache intensity (VAS score). **(C)** Duration of attacks (hours).

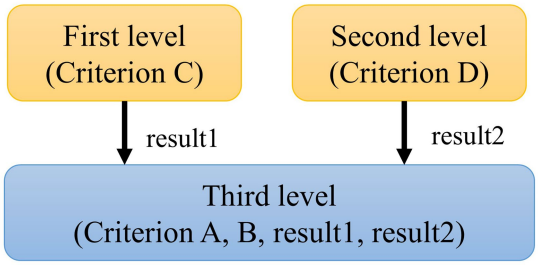

FIGURE 4
Hierarchical fuzzy inference based on ICHD-3.

The closer the output value is to each given constant term, the more likely the CDSS is to diagnose the patient as suffering from that type of headache. For example, the closer the output value is to 2, the more likely it is that the patient is suffering from migraine. The closer the output value is to 0, the more likely the patient is to have another type of headache. Similarly, the output variable Typeofheadache (for tension-type headache) is computed by:

$$f_{\text{Typeofheadache}}\begin{pmatrix} x_{\text{Numberofattack}}, \\ x_{\text{Headacheduration}}, \\ x_{\text{criteriaC}}, x_{\text{criteriaD}} \end{pmatrix} = \frac{\begin{array}{l}\alpha_1 \text{Tension type headache} + \\ \alpha_2 \text{Probable tension type headache} + \\ \alpha_3 \text{others}\end{array}}{\alpha_1 + \alpha_2 + \alpha_3} \quad (3)$$

where *tensiontypeheadache* = 2, *probabletensiontypeheadache* = 1, and *others* = 0.

2.2 Participants and validation

2.2.1 Validation

To evaluate the validity of the presented method, a retrospective study and a prospective study were designed and conducted in Chinese PLA General Hospital respectively. For the retrospective study, the process of evaluation was as follows: first, the diagnosis in each case was reconfirmed by three headache experts and the diagnosis of the expert group was regarded as the gold standard; then, the fuzzy-based CDSS made diagnosis according to the clinical symptoms of each case input by a neurologist who did not know the experts' diagnosis. For the prospective study, the fuzzy-based CDSS was applied in a real clinical environment. The process of evaluation was as follows: when a patient came to the headache clinic, his/her clinical symptoms were input into the CDSS after an in-depth clinical interview was conducted with a neurologist, and a diagnosis conclusion was made by the CDSS; then the patient would enter into the three headache experts' offices, and independent diagnoses was made by the three experts respectively. The final decision of the expert group was by a simple majority. The diagnostic procedures of the headache expert group and the fuzzy-based CDSS were independent and completed on the same day. The process of retrospective study and prospective study are shown in Figure 5.

2.2.2 Participants

The retrospective study included the electronic medical records of 343 consecutive migraine and TTH patients enrolled at the headache clinic of the International Headache Center at Chinese PLA General Hospital between November 2018 and February 2019. Eighteen patients were excluded from the analysis because of missing data. Two

patients diagnosed with migraine with aura were also excluded because it is very easy to be diagnosed by our previous rule-based methods due to the specificity of aura and is not within the scope of our study. The diagnoses of the remaining cases (325 cases) were migraine without aura (MO) (131, 40.31%), PM (80, 24.62%), infrequent/frequent TTH (70, 21.54%), and PTTH (44, 13.54%). The prospective study was also conducted in the headache clinic of Chinese PLA General Hospital from June 2022 to January 2023. Three hundred and eighty four patients were enrolled and 4 patients were excluded because of migraine with aura. The diagnoses of remaining cases (380 cases) were MO (179, 47.11%), PM (62, 16.32%), infrequent/frequent TTH (115, 30.26%), and PTTH (24, 6.31%). The demographics and clinical characteristics of the retrospective study cohort and the prospective study cohort are shown in Table 3.

TABLE 2 Examples of fuzzy rules.

#Rule	Rule
1	IF **headachelocation** is bilateral and **headachequality** is unthrobbing and **headacheintensity** is *mild* and **physicalactivity** is yes, then result is unfit
2	IF **headachelocation** is bilateral and **headachequality** is unthrobbing and **headacheintensity** is *moderate* and **physicalactivity** is yes, then result is fit
3	IF **numberofattacks** is *low* and **headacheduration** is *general* and criteria C is no and criteria D is yes, then typeofheadache is others
4	IF **numberofattacks** is *moderate* and **headacheduration** is *general* and criteria C is no and criteria D is yes, then typeofheadache is probablemigraine

The bold font indicates variables in the rules.

2.2.3 Statistical analysis

A diagnostic test is a procedure performed to confirm or determine the presence of disease in an individual suspected of having a disease. In this study, the diagnostic tests were performed by comparing the diagnosis of fuzzy-based CDSS and the headache experts' decisions for each headache case both in the retrospective study and the prospective study. SPSS for Windows (Version 16.0) was used for the statistical analysis. We measured the diagnostic performance of the proposed method using the following metrics: sensitivity, specificity, PPV, NPV, total consistency rate (π) and Youden index.

Sensitivity refers to the proportion of those who have the disease (when judged by the "Gold Standard") that received a positive result on this test. Specificity refers to the proportion of those who do not have the disease (when judged by the "Gold Standard") that received a negative result on this test. The total consistency rate (π) represents the degree to which the diagnostic results of the diagnostic method to be evaluated accord with the results of the gold standard diagnostic method. The Youden index indicates the ability of diagnostic methods to detect patients and nonpatients. The mistaken diagnosis rate (α), also known as the false positive rate, is the probability that a healthy person is diagnosed as a patient by the diagnostic method to be evaluated. The omission diagnostic rate (β), also known as the false negative

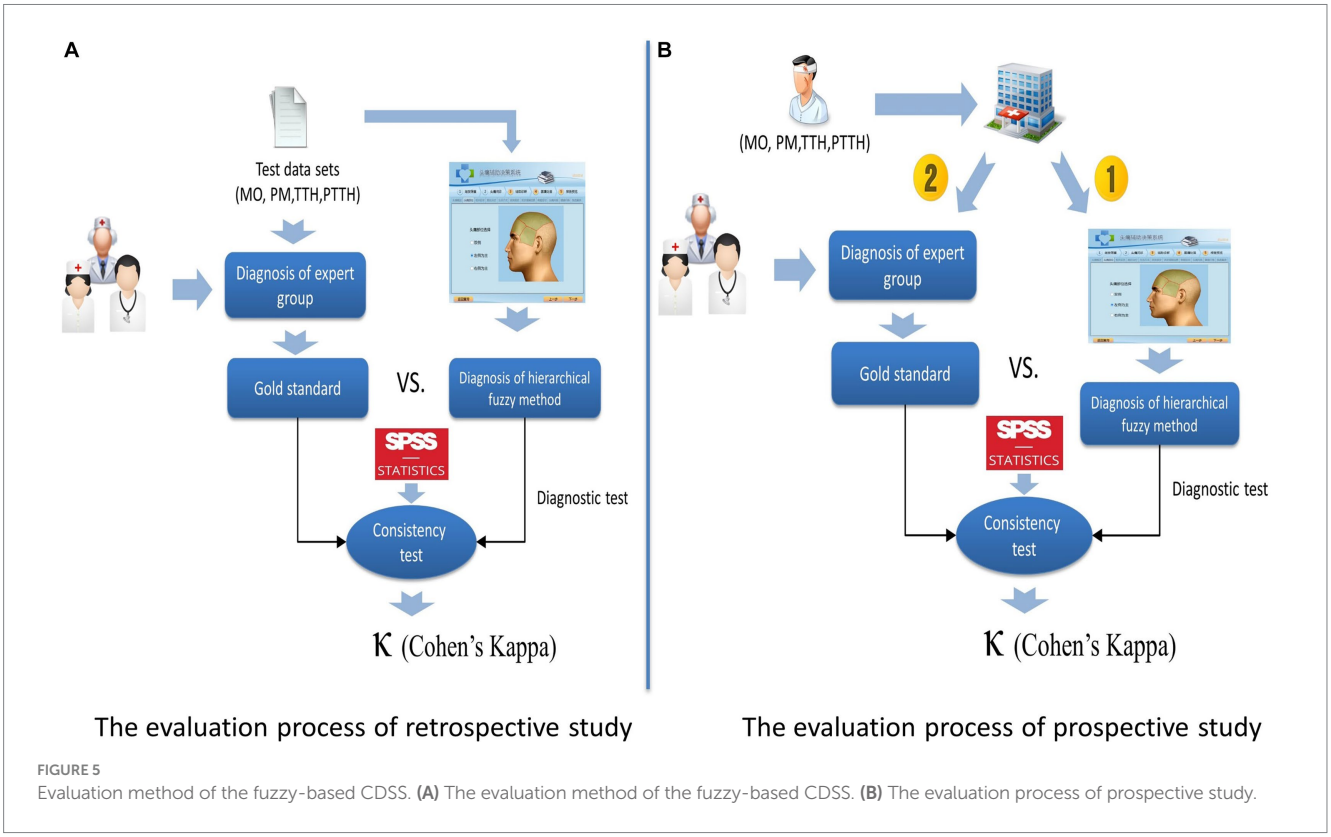

FIGURE 5
Evaluation method of the fuzzy-based CDSS. **(A)** The evaluation method of the fuzzy-based CDSS. **(B)** The evaluation process of prospective study.

TABLE 3 Basic demographic and clinical characteristics of the study cohort and the prospective study cohort.

Characteristics	Retrospective study (N = 325)	Prospective study (N = 380)
Sex (male/female)	109 (33.5%)/216 (66.5%)	86 (22.6%)/294 (77.4%)
Age (mean, SD)	38.7 (12.7)	39.6 (12.3)
Duration of attacks (mean, SD) (hours)	17.0 (28.2)	24.3 (27.1)
Course of headache (mean, SD) (months)	75.4 (94.3)	91.2 (103.5)
Number of attacks (<5/6–9/>10)	22 (6.8%)/21 (6.4%)/282 (86.8%)	18 (4.7%)/34 (8.9%)/328 (86.3%)
Location (unilateral/bilateral)	91 (28%)/234 (72%)	178 (46.8%)/202 (53.2%)
Headache quality (pulsating/non-pulsating/other)	172 (52.9%)/142 (43.7%)/11 (3.4%)	230 (60.5%)/137 (36.1%)/13 (3.4%)
Headache intensity (mean, SD) (VAS score)	6.0 (1.8)	6.4 (1.5)
Aggravated by routine physical activity (yes/no)	151 (46.5%)/174 (53.5%)	225 (59.2%)/155 (40.8%)
Nausea (%)	33.8	47.1
Vomiting (%)	16.9	50.8
Photophobia (%)	26.8	48.9
Phonophobia (%)	31.1	62.6

rate, represents the probability that a patient is evaluated as healthy by the diagnostic method to be evaluated. The positive predictive value (PPV) denotes the probability that subjects with a positive diagnosis truly have the disease. The negative predictive value (NPV) is the probability that subjects with a negative diagnosis truly do not have the disease.

In addition, a consistency test was also performed, and Cohen's kappa (κ) was calculated for the agreement between diagnoses. The consistency test cannot only indicate whether two methods are consistent but also evaluate the degree of consistency by calculating Cohen's kappa value. Kappa is calculated by Equation (4):

$$\text{Kappa} = \frac{P_A - P_e}{1 - P_e} \tag{4}$$

where P_A is the actual observed consistency rate and P_e is the expected consistency rate. Generally, if $\kappa \geq 0.85$, the consistency is considered very good; if $0.6 \leq \kappa < 0.85$, the consistency is good; if $0.45 \leq \kappa < 0.6$, the consistency is moderate; and if $\kappa < 0.45$, the consistency is poor. A 5% level of significance and 95% confidence intervals (CI) were utilized in this study.

2.2.4 Real case study

Finally, we selected two real cases from the CDSS headache database and performed case studies by demonstrating the computational procedure of our proposed method to show the feasibility of the method.

3 Results

3.1 The GUI of the fuzzy-based headache CDSS

The main functions of the CDSS in this paper are shown in Figure 6. The CDSS is available at the website and can be visited with a web browser on desktop computers and mobile devices. Figure 6A shows the login interface; every doctor authorized to use the system is assigned a username and a password. Figure 6B shows the user interface for recording the patient's headache features. All the input items of the system interface come from the ICHD-3, and they include all the necessary information for diagnosis. The doctor can interview a patient according to the tips in the GUI, which can help to save much time and prevent the doctor from missing critical information. Figure 6C shows the user interface for recording the headache location. After the previous step, the CDSS can make a diagnosis by fuzzy logic, as shown in Figure 6D. The doctor needs to decide whether to accept the diagnosis of the CDSS. If not, the doctor needs to input a different diagnosis into the CDSS. The doctor can click on the "Diagnostic criteria" button if it is not clear why the CDSS has made a certain diagnosis, and the CDSS will display the latest diagnostic criteria to help the doctor better understand the ICHD-3.

3.2 Diagnostic performance of the fuzzy-based CDSS

3.2.1 Retrospective study

As shown in Table 4, the fuzzy-based CDSS correctly recognized 128/131 patients (97.71%) with migraine without aura (MO), 69/70 patients (98.57%) with TTH, 73/80 patients (91.25%) with probable migraine (PM), and 40/44 patients (90.91%) with probable tension-type headache (PTTH).

To demonstrate the feasibility of the proposed method, we also compared the diagnosis of the ICHD-rule-based CDSS with the gold standard. As shown in Tables 4, 5, compared with the ICHD-rule-based CDSS, the fuzzy-based CDSS shows significantly improved diagnostic classification performance (95.4% (310/325) vs. 90.2% (293/325), $p < 0.01$).

The sensitivity, specificity, total consistency rate (π), positive predictive value (PPV), negative predictive value (NPV) and Youden index of both CDSSs are shown in Table 6. The diagnostic ability of the two methods is similar in the diagnosis of MO, but compared with the ICHD-rule-based method, the classification performance of the fuzzy-based method is greatly improved in the diagnosis of TTH, PTTH and PM. In particular, for PM and PTTH with less typical symptoms, the fuzzy-based method significantly improves the Youden index by the fuzzy processing of the numerical boundaries of headache features, which shows that it can effectively reduce the mistake diagnostic rate and omission diagnostic rate. In general, the hierarchical fuzzy-based CDSS is better than the ICHD-rule-based CDSS in the diagnosis of PM and PTTH.

3.2.2 Prospective study

In the prospective study, the fuzzy-based CDSS correctly recognized 164/179 (91.62%) of MO, 106/115 (92.17%) of TTH, 53/62

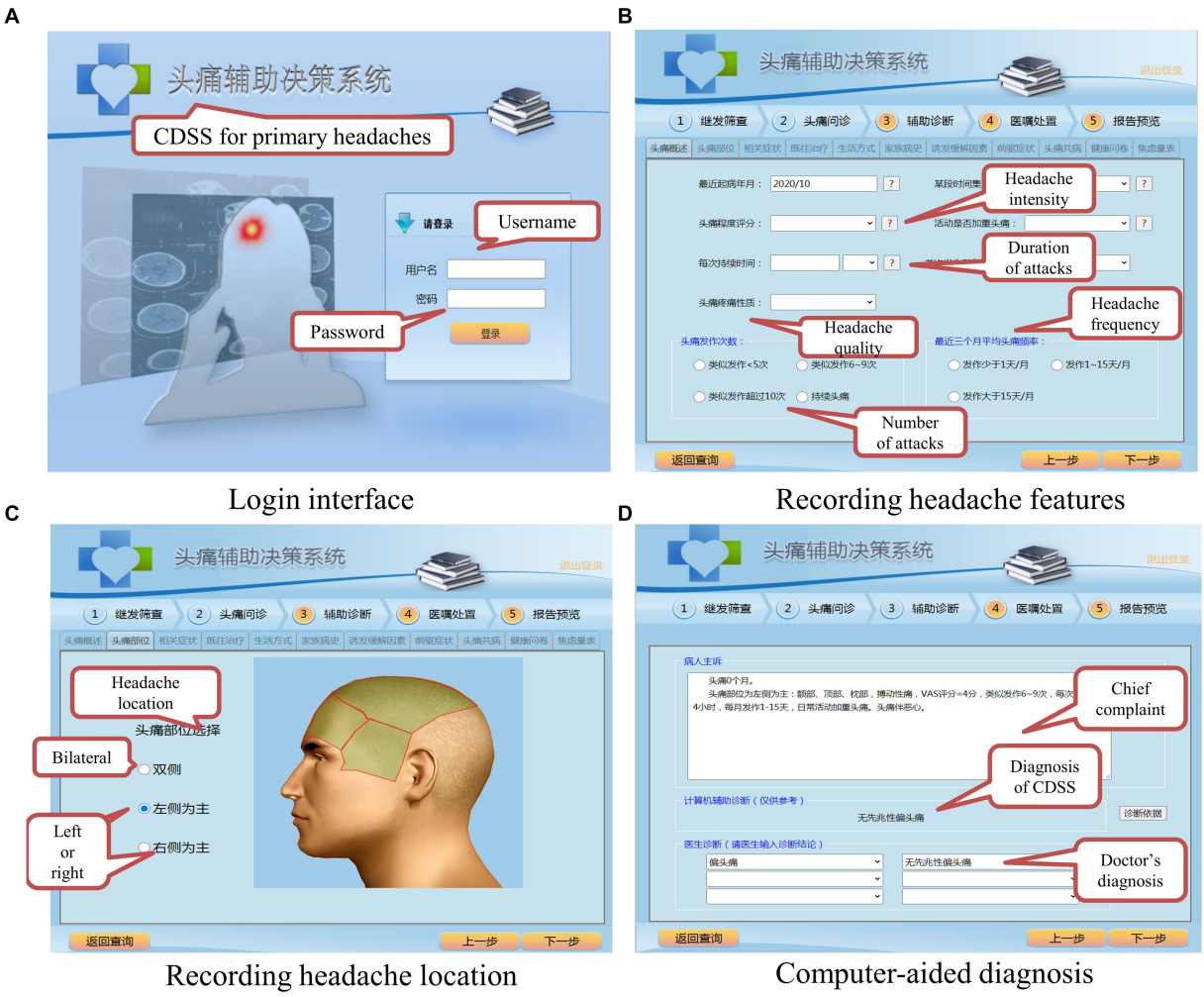

FIGURE 6
Main functions of the fuzzy-based CDSS. **(A)** Login interface. **(B)** Recording headache features. **(C)** Recording headache location. **(D)** Computer-aided diagnosis.

TABLE 4 Agreement between the fuzzy-based CDSS and headache expert group diagnoses.

Fuzzy-based CDSS	Headache expert group				
	MO	TTH	PM	PTTH	Total
MO	128	0	0	0	128
TTH	0	69	0	0	69
PM	3	0	73	0	76
PTTH	0	1	0	40	41
Others	0	0	7	4	11
Total	131	70	80	44	325

MO, migraine without aura; TTH, tension-type headache; PM, probable migraine; PTTH, probable tension-type headache; others, other headache disorders.

TABLE 5 Agreement between the ICHD-rule-based CDSS and the headache expert group diagnoses.

ICHD-rule-based CDSS	Headache expert group				
	MO	TTH	PM	PTTH	Total
MO	126	0	0	0	126
TTH	0	64	0	0	64
PM	5	3	69	0	77
PTTH	0	2	0	34	36
Others	0	1	11	10	22
Total	131	70	80	44	325

MO, migraine without aura; TTH, tension-type headache; PM, probable migraine; PTTH, probable tension-type headache; others, other headache disorders.

(85.48%) of PM, and 21/24 (87.50%) of PTTH. The agreement between the fuzzy-based CDSS and the gold standard is shown in Table 7.

The main indicators of diagnostic test for the fuzzy-based CDSS are shown in Table 8. From Table 8, we can see that although the diagnostic sensitivity of each headache decrease slightly compared with that of the retrospective study, the total consistency rate (π) remains at a high level (>90%). This means that our fuzzy-based method has good stability even in the real clinical environment.

TABLE 6 Comparison between the rule-based CDSS and fuzzy-based CDSS for diagnostic tests.

	ICHD-rule-based CDSS				Fuzzy-based CDSS			
	MO	PM	TTH	PTTH	MO	PM	TTH	PTTH
Sensitivity(%) (95% CI)	96.18 90.87-98.59	86.25 76.31-92.61	91.43 81.65-96.47	77.27 61.78-88.01	97.71 92.94-99.41	91.25 82.25-96.11	98.57 91.23-99.93	90.91 77.42-97.05
Specificity(%) (95% CI)	100 97.58-100	96.73 93.43-98.47	100 98.15-100	99.29 97.17-99.88	100 97.58-100	98.78 96.17-99.68	100 98.15-100	99.64 97.72-99.98
PPV(%) (95% CI)	100 96.31-100	89.61 80.03-95.09	100 92.95-100	94.44 79.99-99.03	100 96.37-100	96.05 88.12-98.98	100 93.43-100	97.56 85.59-99.87
NPV(%) (95% CI)	97.49 93.91-99.07	95.56 91.98-97.65	97.70 94.82-99.06	96.54 93.53-98.23	98.48 95.25-99.61	97.19 94.05-98.76	99.61 97.50-99.98	98.59 96.19-99.55
Youden index	0.9618	0.8298	0.9143	0.7656	0.9771	0.9003	0.9857	0.9055
π	0.9846	0.9415	0.9815	0.9631	0.9908	0.9692	0.9969	0.9846

MO: migraine without aura; TTH: tension-type headache; PM: probable migraine; PTTH: probable tension-type headache; others: other headache disorders.

3.3 Consistency test of the fuzzy-based CDSS

We performed a consistency test between the fuzzy-based method and the gold standard to evaluate the consistency of the two methods. The results of the consistency test are shown in Table 9. In the retrospective study, the values of κ for MO (0.984 ± 0.018, $p < 0.001$), TTH (0.991 ± 0.018, $p < 0.001$), PM (0.916 ± 0.051, $p < 0.001$), PTTH (0.932 ± 0.059, $p < 0.001$) are all much greater than 0.85, and in the prospective study, the values of κ for MO (0.884 ± 0.047, $p < 0.001$), TTH (0.870 ± 0.055, $p < 0.001$), PM (0.853 ± 0.073, $p < 0.001$), PTTH (0.827 ± 0.118, $p < 0.001$) are all greater than 0.80, so we reject the null hypothesis (H_0: kappa = 0) proposed in the Introduction section. These results indicate that there is good consistency between the fuzzy-based CDSS and the headache experts, and they show that the diagnostic ability of the fuzzy-based method is very close to that of headache experts.

3.4 Case study of the fuzzy-based CDSS

To further illustrate the effectiveness of the proposed hierarchical fuzzy method, we selected two cases from the database as case studies.

3.4.1 Case 1

A 42-year-old woman visited our hospital with a complaint of 4 headache episodes over the last 3 months, and her headache had the following features: a unilateral location, a pulsating quality, mild to moderate pain, and aggravation by routine physical activity. Each episode lasted from 2 h to half a day. The pain was accompanied by symptoms of nausea and vomiting, with no photophobia or phonophobia. CT scanning was performed on December 1, 2018, and the results were normal. Her father has similar headaches.

It is notable that the patient's number of attacks was 4, and this did not fulfil the minimum diagnostic criteria for migraine (at least 5 attacks). Additionally, criterion B for migraine was not met. In theory, the patient's symptoms did not fulfil any diagnostic criteria in ICHD-3. However, clearly, the patient had a migraine-like attack, so the diagnosis of the headache experts was probable migraine.

In the fuzzy-based CDSS, the membership degree of 4 for the "low" category is 1/3 and that for the "moderate" category is 1/2. In Equation 2, $\alpha_1 = 0.25$, $\alpha_2 = 0.75$, $\alpha_3 = 0.3333$, and $f_{\text{Typeofheadache}}$ for migraine is 0.9375, which is closer to the probable migraine category (*migraine* = 2, *probablemigraine* = 1, and *others* = 0). In Equation 3, $\alpha_1 = 0$, $\alpha_2 = 0$, $\alpha_3 = 1.33333$, and $f_{\text{Typeofheadache}}$ for tension-type headache is 0, which comes closer to the other headache category (*tensiontypeheadache* = 2, *probabletensiontypeheadache* = 1, and *others* = 0). Taking into account these two results, the patient was diagnosed with probable migraine by the fuzzy-based CDSS.

3.4.2 Case 2

A 38-year-old woman reported that the number of attacks was 3 in the past 3 months, and each attack lasted almost 20 min. Her headache features were bilateral location, no pulsating quality, VAS score of 3, and no aggravation by routine physical activity. The pain was not accompanied by symptoms of nausea, vomiting, photophobia or phonophobia. No abnormality was found on routine examinations.

Although criterion A (number of attacks) and criterion B (duration of attacks) were not fulfilled according to the diagnostic criteria of tension-type headache, the patient was still diagnosed with probable tension-type headache-like attacks by the expert group because of the lack of accompanying symptoms and fully fulfilling criterion C of tension-type headache. In Equation 2, $\alpha_1 = 0, \alpha_2 = 0, \alpha_3 = 1.4$, $f_{\text{Typeofheadache}} = 0$. In Equation 3, $\alpha_1 = 0$, $\alpha_2 = 0.7333$, $\alpha_3 = 0.6666$, and $f_{\text{Typeofheadache}} = 0.5238$, which is closer to 1, so synthesizing these two results, the diagnosis of the fuzzy-based CDSS was probable tension-type headache, which is the same as that of the expert group.

4 Discussion

To solve the problem of the imprecise description of fuzzy headache features (i.e., the duration of attacks, number of attacks and

TABLE 7 Agreement between the fuzzy-based CDSS and the gold standard in the prospective study.

Fuzzy-based CDSS	Headache expert group				
	MO	TTH	PM	PTTH	Total
MO	164	4	3	0	171
TTH	5	106	5	2	118
PM	5	0	53	1	59
PTTH	1	3	1	21	26
Others	4	2	0	0	6
Total	179	115	62	24	380

MO, migraine without aura; TTH, tension-type headache; PM, probable migraine; PTTH, probable tension-type headache; others, other headache disorders.

TABLE 8 The diagnostic performance of the fuzzy-based CDSS in the prospective study.

	MO	PM	TTH	PTTH
Sensitivity(%) (95% CI)	91.62 86.30-95.07	85.48 73.72-92.75	92.17 85.26-96.13	87.50 66.54-96.71
Specificity(%) (95% CI)	96.52 92.66-98.47	98.11 95.74-99.23	95.47 92.02-97.53	98.60 96.56-99.48
PPV(%) (95% CI)	95.91 91.42-98.19	89.83 78.50-95.80	89.83 82.56-94.40	80.77 60.02-92.69
NPV(%) (95% CI)	92.82 88.21-95.79	97.20 94.56-98.63	96.56 93.36-98.31	99.15 97.33-99.78
Youden index	0.8814	0.8359	0.8764	0.8610
π	0.9421	0.9605	0.9447	0.9789

MO: migraine without aura; TTH: tension-type headache; PM: probable migraine; PTTH: probable tension-type headache.

TABLE 9 Consistency test and Cohen's kappa for each headache between the gold standard and the fuzzy-based CDSS in the retrospective study and prospective study.

	Cohen's kappa (retrospective study)	Cohen's kappa (prospective study)
MO	0.984 ± 0.018, $p < 0.001$	0.884 ± 0.047, $p < 0.001$
TTH	0.991 ± 0.018, $p < 0.001$	0.870 ± 0.055, $p < 0.001$
PM	0.916 ± 0.051, $p < 0.001$	0.853 ± 0.073, $p < 0.001$
PTTH	0.932 ± 0.059, $p < 0.001$	0.827 ± 0.118, $p < 0.001$

MO, migraine without aura; TTH, tension-type headache; PM, probable migraine; PTTH, probable tension-type headache.

headache intensity) caused by recall bias and subjective bias, we proposed a hierarchical fuzzy headache diagnostic inference method based on ICHD-3. This hierarchical method comprises two levels. First, we match patients' symptoms against the diagnostic criteria C and D for migraine and tension-type headache, as outlined in the ICHD-3. Second, the outcomes from these matches are integrated with the already fuzzified criteria A and B for the second-step diagnosis. This hierarchical method serves as a complement to the rule-based reasoning method and is activated only when a probable migraine or probable TTH diagnosed by the rule-based reasoning. Furthermore, a fuzzy-based CDSS was established, and the validity of the CDSS was evaluated by a retrospective study and a prospective study. The evaluation results show that the fuzzy-based CDSS has good diagnostic performance and that its diagnosis results have good consistency with headache experts' diagnoses. We hope that the developed headache CDSS can help non specialists distinguish between probable migraine and probable TTH in primary hospitals.

4.1 Comparison to prior works

Currently, some scholars have also tried to develop various headache CDSSs based on different artificial intelligence methods. Generally, there are two feasible methods. One is based on the diagnostic criteria in the ICHD, which can be regarded as a knowledge-driven method. Some scholars have established heuristic rules based on headache diagnosis (17, 18). The other type of method is based on clinical data. With the development of data science, some scholars have tried to build intelligent computer-aided diagnosis models based on machine learning techniques (19–23), which could be called data-driven methods. Each of these methods has merits and shortcomings, but considering the acceptability to clinicians, CDSSs based on ICHD-3 may be a better option. This is because it is difficult to explain the mathematical principles of the models generated by machine learning algorithms to doctors, and these models are similar to "black boxes" for doctors. However, traditional rule-based reasoning is unable to handle the fuzzy boundaries of headache features, and few scholars have paid attention to this problem. Therefore, in this study, we proposed a "rule-based reasoning + hierarchical fuzzy logic" method, a new hybrid intelligent technique, to develop a fuzzy-based headache CDSS. Rule-based reasoning is the "backbone," which is used to express the logic of the reasoning, and fuzzy logic is utilized to deal with the fuzzy boundary values of some features, such as the headache intensity, number of attacks, and duration of attacks. With the ability to imitate experts dealing with boundary values, fuzzy logic enhances the capability of the CDSS to handle uncertain information. Hence, these two intelligent methods used in the CDSS combine the advantages of both and are complementary to each other. Compared with the routine CDSS method, all the performance metrics of the fuzzy-based CDSS are significantly improved to varying degrees. Moreover, this work shows the potential to be extended to other primary headaches as well.

The fuzzy-based headache CDSS is designed for doctors who are not familiar with the diagnostic criteria of primary headaches and can help general practitioners and junior doctors diagnose headaches in a clinical setting, which is meaningful for headache diagnosis at the rural and community levels. It is hoped that this will change the status quo of the low diagnosis rate by general practitioners in China at present. In addition, the web-based CDSS is convenient for doctors to use to access the latest diagnostic criteria of primary headaches.

4.2 Limitation

According to the results in Table 6, although our method is better than the routine CDSS, there is still a certain gap between our method and the gold standard. After in-depth analysis, we think that the main

reason for the difference is the completeness of diagnostic model. For example, if two of the patient's symptoms do not fulfill the diagnostic criteria slightly, our method cannot draw a definite diagnosis, while doctors can diagnose her as probable migraine through other relevant symptoms, such as the menstrual cycle.

There are also some other limitations of this study. First, this study focused only on migraine and TTH and did not cover other primary headache disorders, so we will design a similar method to address cluster headaches and other primary headache disorders in the next stage. Second, the inference process of the fuzzy-based CDSS does not include the weight of each headache feature. Many studies have shown that adding different weights to each attribute is helpful in improving the diagnostic accuracy of a CDSS. In addition to the weights of the headache features, we will add a weight to each fuzzy rule to make the inference conclusion more accurate. Last, but importantly, the amount of data we currently used for the retrospective and prospective study in this paper is quite limited. In the future, as more and more data accumulates, we will also conduct large-scale, multi center clinical validation of the system to ensure the reliability of our conclusions.

5 Conclusion

In this paper, a hierarchical fuzzy inference method was designed, and a fuzzy-based headache CDSS was developed, which solved the problem of fuzzy headache features that are caused by recall bias and subjective bias. The evaluation results proved that the hierarchical fuzzy method can diagnose migraine and tension-type headache with high sensitivity and specificity, better than the routine CDSS method, and its diagnostic level is close to that of headache experts. In the future, we aspire to integrate the latest artificial intelligence technologies, encompassing fuzzy knowledge graph and fuzzy deep learning, into the realm of headache CDSS, with the goal of enhancing not only the diagnostic accuracy but also the interpretability of these systems, ultimately facilitating improved headache diagnosis accuracy among general practitioners, junior doctors, and community doctors.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Chinese PLA General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZY: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft. HL: Formal analysis, Investigation, Writing – original draft. XH: Formal analysis, Investigation, Writing – review & editing. YR: Investigation, Writing – review & editing. ZW: Investigation, Writing – review & editing. ZD: Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The role of digital device use on the risk of migraine: a univariable and multivariable Mendelian randomization study

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Background: The pervasive integration of digital devices into daily life has raised concerns about their potential health impacts. This study aimed to explore the causal relationships between digital device use and the risk of migraine using Mendelian randomization (MR).

Methods: Genetic data on digital device use and migraines were sourced from large-scale genome-wide association studies conducted by the UK Biobank, the FinnGen study, and the International Headache Genetics Consortium. Univariable MR (UVMR), meta-analysis, and multivariable MR (MVMR) approaches were conducted to explore and verify the causal effects of digital device use (including mobile phone use, computer use, playing computer games, and watching television) on migraine risk. Sensitivity analyses were conducted using Cochran's Q, MR-Egger intercept test, MR pleiotropy residual sum and outlier, MR Radial, MR Steiger, and leave-one-out methods.

Results: UVMR analyses revealed that genetically predicted mobile phone use was significantly associated with an increased risk of overall migraine (odds ratio [OR] = 2.39, $p = 9.78e\text{-}5$) and migraine without aura (MO) (OR = 2.25, $p = 0.024$). Additionally, there were significant positive associations between genetically predicted television watching and the risk of overall migraine (OR = 1.63, $p = 2.12e\text{-}5$) and MO (OR = 2.10, $p = 4.98e\text{-}5$). These results were further supported by the meta-analysis and MVMR analysis. Sensitivity analysis indicated no heterogeneity or pleiotropy.

Conclusion: This comprehensive MR study provides preliminary evidence for the causal impact of mobile phone use and television watching on the risk of migraines. Further studies are needed to explore these associations across different populations.

KEYWORDS

digital device, migraine, univariable Mendelian randomization study, multivariable Mendelian randomization study, casual effect

1 Introduction

Migraine is a prevalent and debilitating neurological disorder characterized by recurring headaches, frequently accompanied by nausea, vomiting, and light and sound sensitivity (1). Affecting over 100 million people worldwide, primarily those under 50, it is the second leading cause of years lived with disability globally across all age groups (2, 3). Given its severe physical

and mental impact on patients, preventing migraine attacks is crucial. Previous studies have identified several risk factors, including sleep patterns, dietary habits, physical activity, and medication use, which contribute to migraine (4). Thus, identifying additional triggers and developing strategies to mitigate them are essential for migraine prevention.

With continuous technological advancements, electronic devices have gradually integrated into our lives, becoming an indispensable part of modern life. Existing studies have found that artificial intelligence equipped with digital devices plays an important role in the diagnosis, prevention, and management of migraines (5). Although these devices offer significant convenience in medicine, work, and entertainment, their use also results in prolonged screen time and sedentary behavior, posing potential health risks (6). Digital addiction, which is closely related to genetic predisposition (7), significantly affects brain function and structure (8). Prolonged exposure to blue light and electromagnetic radiation may cause neurological dysfunctions such as headaches, sleep disorders, negative emotions, memory decline, and attention deficits (6). Observational studies have found that frequent use of electronic devices is associated with an increased risk of migraine, particularly among students (9, 10). However, traditional observational studies are prone to interference from confounding factors, which limit the reliability of establishing causal relationships, thus making it difficult to establish a clear causal relationship between digital device use and migraine risk.

Mendelian randomization (MR) is an epidemiological method used to assess causal inference by utilizing genetic variations strongly associated with the exposure of interest as instrumental variables (IVs) (11). Currently, MR is being increasingly applied in clinical research to effectively predict drug efficacy, optimize experimental designs, and expand feasibility trials (12–14). Since genetic variations are present at birth and remain stable throughout life, MR analysis results are less likely to be influenced by reverse causation and confounders. Therefore, we utilized a comprehensive MR analysis to explore the causal effects of electronic device use on migraine (15, 16).

2 Materials and methods

2.1 Study design

Three core assumptions ensure the validity of MR results (17). First, the relevance assumption requires genetic variants to be strongly associated with the exposure of interest. Second, the independence assumption ensures these genetic variants are free from confounders that could affect the exposure–outcome relationship. Third, the exclusion restriction assumption requires the genetic variants to influence the outcome only through exposure, not via any other pathways.

Figure 1 illustrates the study design. Initially, we conducted univariable MR (UVMR) to assess the causal relationship between digital device use and the risk of overall migraine and its subtypes, using data from two separate genome-wide association studies (GWAS). Subsequently, we performed a meta-analysis to combine the results, followed by multivariable MR (MVMR) to account for potential confounders, involving stroke, hypertension, physical activity levels, smoking, alcohol consumption, body mass index, insomnia, and major depression (18, 19).

All GWAS data were sourced from publicly accessible repositories, ensuring transparency and reproducibility. Ethical approval was obtained for the original GWAS data used in this study, adhering to ethical standards and guidelines governing such research. This study was reported in accordance with STrengthening the Reporting of OBservational studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines (Supplementary Table 1.1) (20).

2.2 Data source

2.2.1 Genome-wide association studies data for digital device use

The GWAS data on four types of digital device use, including mobile phone use, television watching, computer use, and playing computer games, were obtained from the UK Biobank (Supplementary Table 2.1). The UK Biobank is a large-scale biomedical database and research resource containing comprehensive genetic and health data from half a million UK participants and is widely used in various health-related research (21). Digital device use was based on self-reported data. Mobile phone use was defined as the frequency of making or receiving calls by mobile phone per week over the past 3 months ($n = 386{,}626$ participants). Television watching was measured by daily viewing time ($n = 437{,}887$), computer use was assessed through daily computer usage time ($n = 360{,}895$), and computer gaming habits were evaluated based on gaming practices ($n = 462{,}433$).

2.2.2 Genome-wide association studies data for migraine

The GWAS data on migraine were sourced from two large datasets. FinnGen was the primary discovery cohort, a public–private partnership project in Finland that combines genetic data with digital health records from national health registries (22). Migraine phenotypes were classified based on the International Classification of Diseases (ICD 10) code: R10, comprising 20,908 cases of overall migraine, 8,970 cases with aura (MA), and 7,593 cases without aura (MO). The replication cohort, from the International Headache Genetics Consortium (IHGC), comprises 48,975 European cases of overall migraine excluding the 23andMe cohort owing to permission restrictions (23). MA and MO cases included 6,332 and 8,348 European cases, respectively (24). Migraine cases were characterized by clinical phenotyping or self-reported information in IHGC. Detailed information is provided in Supplementary Table 2.1. We did not interpolate missing data for the GWAS in this study.

2.3 Genetic instrument selection

To select robust IVs, only single nucleotide polymorphisms (SNPs) with a p-value <5e-8 and minor allele frequencies >0.01 were selected. SNP independence was ensured using the 1,000 Genomes Project European reference panel, applying the linkage disequilibrium (LD) criteria of $r^2 < 0.001$ within a 10 Mb window (25). F-statistics were calculated to assess the strength of each SNP. F-statistic >10 was considered a strong instrument (26). The formulas for calculating the F-statistic and R^2 were as follows, where, N is = sample size, and k is = number of IVs.

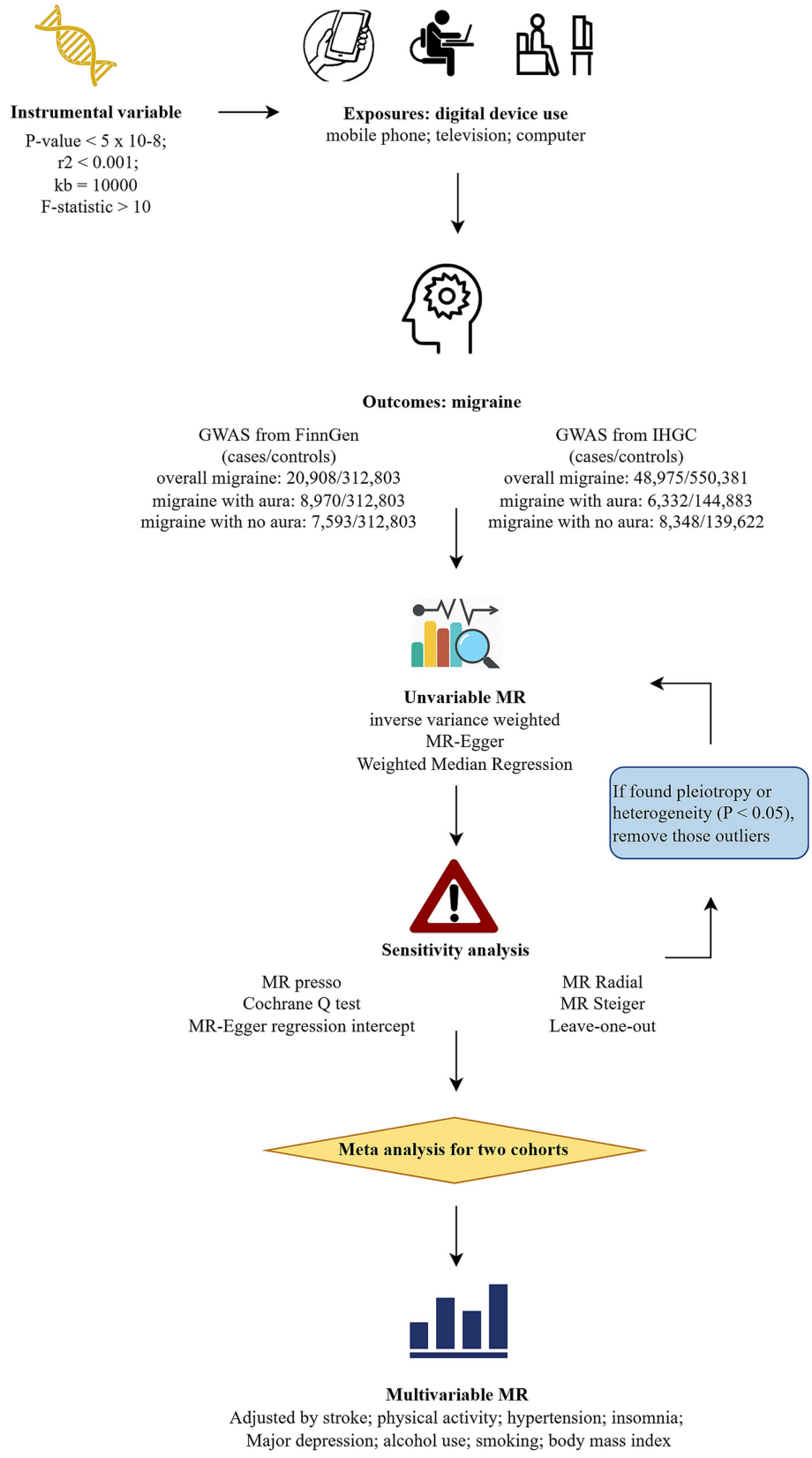

FIGURE 1
Flowchart of study design. MR, Mendelian randomization; GWAS, genome-wide association studies; IHGC, international headache genetics consortium; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

$$F = \frac{R^2(N-k-1)}{k(1-R^2)}$$

$$R^2 = \frac{BETA^2}{(BETA^2 + SE^2)N}$$

2.4 Univariable Mendelian randomization and sensitivity analysis

The effect alleles were aligned between the GWAS datasets for digital device use and migraine. The UVMR approach was conducted to examine the potential causality between digital device use and migraine risk using three methods. The inverse-variance weighted (IVW) method was the primary analysis, offering the most precise estimates when assuming no horizontal pleiotropy among genetic instruments (27). MR-Egger regression allowed for the detection and correction of pleiotropy, accounting for the average pleiotropic effect of the instruments (28). The weighted median method provided a robust causal estimate even when up to 50% of the genetic instruments were invalid, calculating the median of ratio estimates, weighted by their variances (29). Causality was considered stable if the three methods had consistent results, with scatter plots used to illustrate these results.

Detecting pleiotropy and heterogeneity is crucial in studies to ensure that IVs satisfy the core assumptions of valid causal inference. Therefore, several sensitivity analyses were used to validate the robustness of the MR analyses. The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect and correct pleiotropy by removing outliers, while MR-Egger regression estimated the intercept to detect pleiotropic bias. A non-zero intercept indicated the presence of directional pleiotropy (30, 31). Cochran's Q test was calculated using MR-Egger and IVW methods to assess heterogeneity among the genetic instruments (32). MR Radial was conducted to further detect and correct outliers. MR and sensitivity analyses were repeated after removing these outliers (33). Furthermore, the MR Steiger test was employed to estimate the potential reverse causality between digital devices and migraine (34). Leave-one-out (LOO) analysis was performed to detect any pleiotropy driven by a single SNP.

2.5 Meta-analysis of the estimates

A meta-analysis was conducted to combine the causal estimates derived from the IVW analyses of both the discovery and replication datasets, subsequently validating the causal association between digital device use and migraine. When the I^2 value exceeded 50%, a random-effects model was utilized to combine the results. Otherwise, fixed-effects models were applied (35).

2.6 Multivariate Mendelian randomization

MVMR was performed utilizing the IVW method to clarify the independent effects of digital device usage on migraine accounting for potential confounders including stroke, hypertension, physical activity levels, smoking, alcohol consumption, body mass index, insomnia, and depression (36).

2.7 Statistic analysis

The associations between genetically predicted digital device use and the risk of migraine were presented as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were conducted using R software (version 4.3.1). MR analyses were performed using the TwoSampleMR package, and meta-analyses were conducted using the meta package.

Considering the likelihood of false positives, the Bonferroni method was conducted for multiple testing corrections. A p-value <0.0042 (0.05/3/4) was considered statistically significant evidence of a causal relationship, while p-values <0.05 but above the Bonferroni-corrected threshold indicated a potential causal association. In this study, we used the generative AI technology ChatGPT (version: GPT-4, model: GPT-4 (2023), source: https://openai.com/) provided by OpenAI to assist in translation and editing of the manuscript.

3 Results

For digital device use, the F-statistics for IVs were all greater than 10, ranging from 29.7 to 151.8, indicating no weak instrument bias (Supplementary Tables 3.1–3.4). The average F-values for the SNPs related to the four types of devices were as follows: mobile phone use (38.0), computer use (38.1), playing computer games (39.5), and television watching (41.5).

3.1 Discovery results of univariate Mendelian randomization

The IVW estimates revealed that genetically predicted mobile phone use was associated with an increased risk of overall migraine (OR = 2.39, 95% CI 1.54–3.70; p = 9.78e-5) and MO (OR = 2.25, 95% CI 1.11–4.53; p = 0.024). Similarly, television watching was positively associated with an increased risk of overall migraine (OR = 1.63, 95% CI 1.30–2.04; p = 2.12e-5) and MO (OR = 2.10, 95% CI 1.47–3.01; p = 4.98e-5), but neither was significantly associated with MA.

Negative associations were observed between computer use (OR = 0.67, 95% CI 0.46, 0.97; p = 0.035) and playing computer games (OR = 0.41, 95% CI 0.18, 0.91; p = 0.028) with MO, though neither was significantly associated with overall migraine or MA. After Bonferroni correction, mobile phone use was significant with an increased risk of overall migraine, while television watching was significant for both overall migraine and MO. All results of UVMR are presented in Supplementary Tables 2.2–2.4, and scatter plots are shown in Supplementary Figures S4–S6.

No significant pleiotropy or heterogeneity was detected after excluding outlier SNPs, indicating a robust causal inference and alignment with core MR assumptions. The detailed results of the pleiotropy and heterogeneity tests are presented in Supplementary Tables 2.5, 2.6, while information on outlier SNPs is presented in Supplementary Tables 2.10, 2.11 of the same article. The LOO analysis suggested that our findings were not driven by any

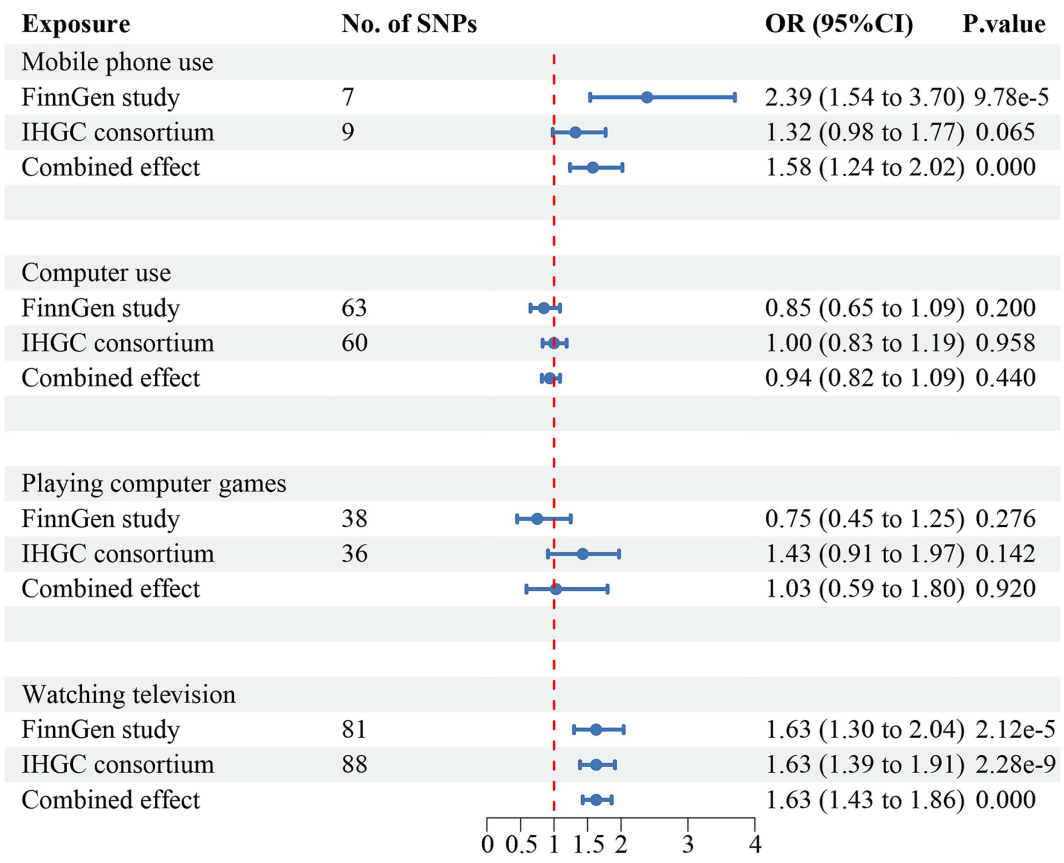

FIGURE 2
Causal association between digital device use and overall migraine. Estimated ORs for the effect of digital device use on migraine, obtained from an IVW analysis, per outcome database separately and combined over the two databases using meta-analyses. CI, confidence interval; SNPs, single-nucleotide polymorphisms.

single SNP, indicating the robustness of the causality between the use of digital devices and migraines. Additionally, no individual SNP significantly altered the overall conclusion, further supporting the reliability of our MR results (Supplementary Figures S1–S3).

3.2 Combined results for migraine from a meta-analysis

The meta-analysis of the causal effects of digital device use on overall migraine, MA, and MO are shown in Figures 2–4, respectively. The IVW estimates from two separate datasets verified a significant causal association between mobile phone use and overall migraine (OR = 1.58, 95% CI 1.24, 2.02; $p = 0.000$) and suggestive evidence for MO (OR = 1.73, 95% CI 1.05, 2.83; $p = 0.031$) Television watching was significantly associated with overall migraine (OR = 1.63, 95% CI 1.43, 1.86; $p = 0.000$) and MO (OR = 1.92, 95% CI 1.47, 2.50, $p = 0.000$). No causal relationships were found between computer use, playing computer games, and any migraine subtypes.

3.3 Multivariate Mendelian randomization

MVMR analysis, adjusted for relevant confounders, confirmed that watching television independently increased the risk of migraine (OR = 2.01, 95% CI 1.32, 3.07; $p = 0.001$) and MO (OR = 3.56, 95% CI 1.90, 6.66; $p = 6.99e\text{-}5$). Similarly, mobile phone use was independently associated with an increased risk of migraine (OR = 1.40, 95% CI 1.03, 1.90; $p = 0.032$) and MO (OR = 1.88, 95% CI 1.20, 2.96; $p = 0.006$). These results are consistent with those from the UVMR analysis and the meta-analysis (Supplementary Tables 2.7–2.9).

4 Discussion

This study employed comprehensive MR analysis to investigate the causal relationships between the use of various digital devices and the risk of migraine and its subtypes. The findings suggested potential adverse effects of frequent mobile phone use and prolonged television watching on migraine risk, particularly in individuals with migraine without aura. However, no robust evidence was observed for causality between computer use or playing video games and migraine or its subtypes.

4.1 Comparison with previous studies

Previous observational studies have indicated the detrimental effects of excessive electronic device use on migraine, especially among younger populations (37–40). For instance, a cross-sectional

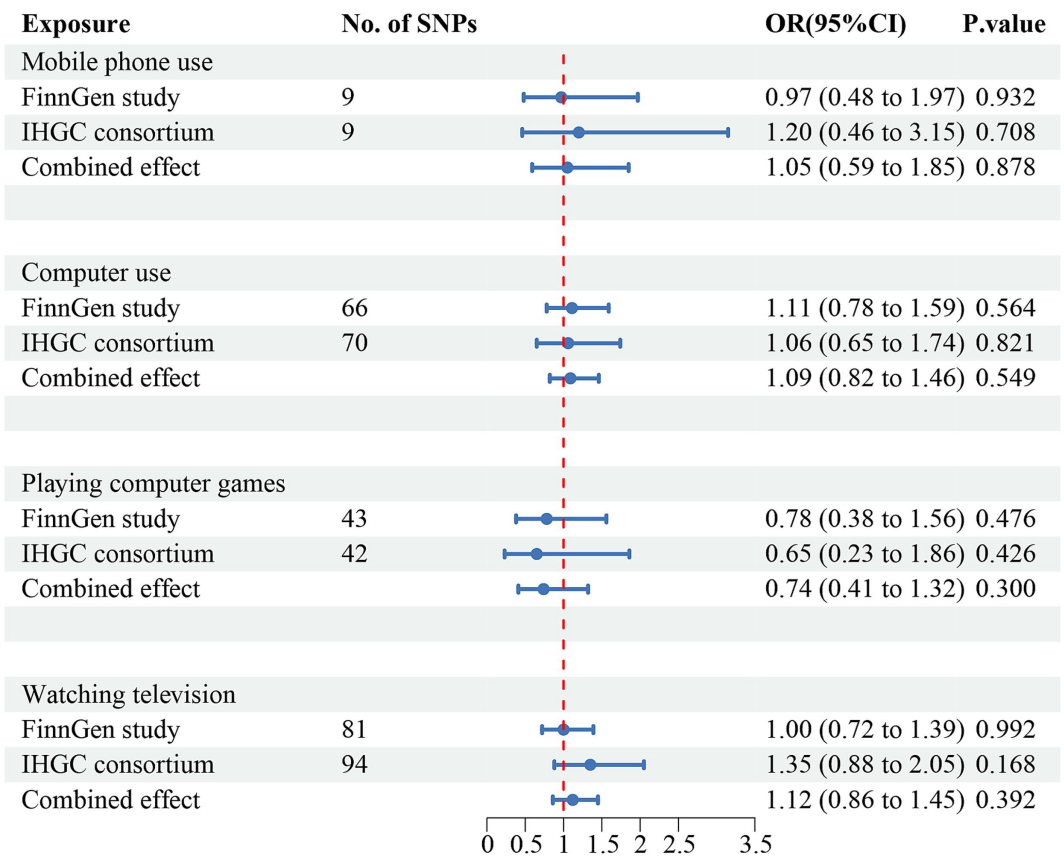

FIGURE 3
Causal association between digital device use and migraine with aura. Estimated ORs for the effect of digital device use on migraine, obtained from an IVW analysis, per outcome database separately and combined over the two databases using meta-analyses. CI, confidence interval; SNPs, single-nucleotide polymorphisms.

study conducted in Saudi Arabia involving 504 medical students found that using various electronic devices for ≥4 h daily was associated with a higher risk of headaches compared to those with <4 h daily. Notably, over 70% of students reported that reducing or stopping the use of electronic device use helped alleviate their headache symptoms (10). Our study builds on this evidence by providing potential causal inferences for mobile phone use and television watching on migraine, however, there is no consistent causal relationship between computer use and playing video games.

For mobile phone use, in line with our MR findings, a meta-analysis that combined the results of 30 cohorts involving multiple ethnicities and populations aged 9–63 years found a positive correlation between weekly mobile phone usage and the risk of migraines, suggesting that mobile phone radiation may be a risk factor for migraine (41). Additionally, a large Danish nationwide prospective cohort study investigated whether mobile phone usage was correlated with neurological disorders and found that increased mobile phone usage raised the consultation rates for migraine and dizziness (42). Similarly, a cross-sectional study by Butt et al. (43), involving approximately 400 patients experiencing migraine aged 18–65 years without other neurological diseases found that prolonged smartphone use was linked to increased migraine duration and frequency. Similarly, Brindova et al. (44) found that watching television for more than 3 h daily was correlated with an elevated incidence of headaches in adolescents. Consistent with another MR study (14), our results indicate an adverse effect of genetically predicted television watching on migraine risk, particularly for MO.

Regarding computer use and playing video games, observational evidence of computer use on elevated migraine risk was provided in a workplace study conducted in the Philippines (45). Additionally, a cross-sectional study among Peruvian medical students indicated that playing computer games could increase the probability of migraine (46). Langdon et al. (47) reviewed electronic device types linked to headache triggers and concluded that extended computer use and video gaming are common migraine triggers in children. However, our MR analyses do not support these claims, as we found no significant causal relationship between computer use or video gaming and migraine. These inconsistencies may be attributed to differences in the ages of the study populations, the motivations for device usage, and environmental factors across different studies. For example, computer use in the workplace often involves more work-related stress than computer use for entertainment activities (46). PC gaming or computer use may impose more burden on migraines in adolescents than adults (48).

4.2 Potential mechanism

The connection between electronic device use and migraines can be explained by several mechanisms, prolonged exposure to blue light, and electromagnetic radiation. A clinical trial found that migraine

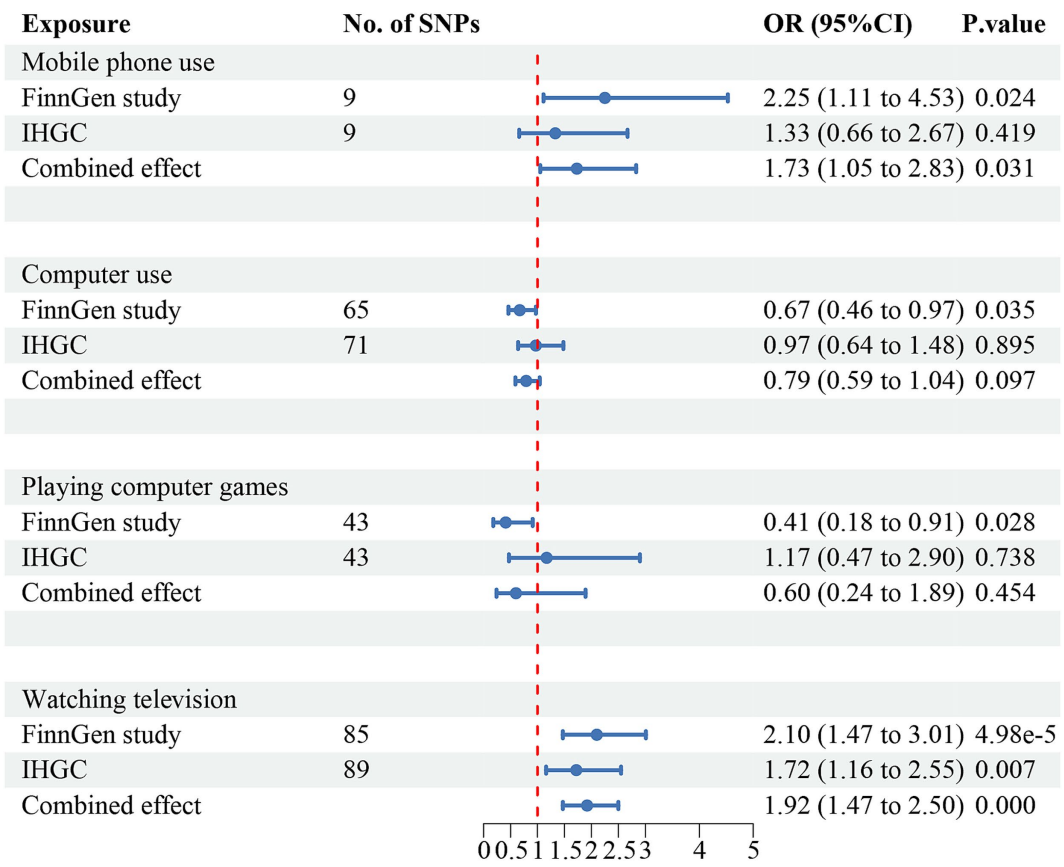

FIGURE 4
Causal association between digital device use and migraine with no aura. Estimated ORs for the effect of digital device use on migraine, obtained from an IVW analysis, per outcome database separately and combined over the two databases using meta-analyses. CI, confidence interval; SNPs, single-nucleotide polymorphisms.

patients exhibited a significant and sustained decrease in pain perception thresholds following light stimulation compared to healthy individuals (49). This phenomenon may be attributed to blue light's stimulation of intrinsically photosensitive retinal ganglion cells, which subsequently affects the conduction of the trigeminal nociceptive pathway. These findings suggest that visual stimuli could trigger migraine (50). In addition, blue light exposure can disrupt sleep and maintain brain alertness, especially excessive use of electronic devices before bedtime, which imposes a burden on migraine (51–53).

The nervous system is highly sensitive to electromagnetic radiation. Prolonged exposure can lead to neurotransmitter metabolism disorders and oxidative stress in central nervous system cells (8), both of which are closely linked to migraine pathogenesis. An epidemiological survey found that among 293 French individuals with electromagnetic hypersensitivity (EHS), the prevalence of migraine was approximately 65% (54). Another study conducted in Thailand found that electromagnetic radiation emitted by smartphones may be one of the triggers of migraines among adolescents, considering that this radiation could affect the opioid receptor system and reduce the pain threshold (55). Studies have found that long-term exposure to electromagnetic radiation can cause metabolic disorders of amino acids such as glutamate and GABA in brain tissue, the balance between excitation and inhibition within the central nervous system. This imbalance may lead to the abnormal activation of the pain perception system, triggering migraine (56, 57). Moreover, the abnormal expression of serotonin has also been reported to be affected by microwave radiation (58, 59), which may cause local vasodilation, thereby triggering migraine.

Additionally, an imbalance between oxidants and antioxidants in the brain leads to oxidative stress during exposure to microwave radiation (60), which induces inflammation and triggers migraines (61). A case report showed that a patient with EHS experienced severe migraine symptoms after exposure to digital devices, including cell phones and television, and further examination showed elevated levels of circulating antibodies against oxidized low-density lipoprotein (LDLox), a marker of oxidative stress (62). The mechanism underlying the impact of electronic devices on migraines is rather complex and multifaceted, requiring further research.

Several factors related to electronic device usage may influence its causal relationship with device use. Prolonged screen time has been shown to affect mental health, leading to insomnia and depression (63). Additionally, excessive electronic device use is often associated with poor lifestyle habits such as a lack of physical activity and prolonged sedentary behavior, contributing to obesity, hypertension, and cardiovascular diseases. These behaviors are often linked to unhealthy dietary habits, including smoking and excessive alcohol consumption (64). Both lifestyle and mental health factors commonly associated with digital device use are

recognized as risk factors for migraines (65). Our MVMR analysis underlined the independent effects of smartphone use and watching television on migraines after accounting for these confounders.

4.3 Strengths and limitations

Our study has several strengths. First, we employed UVMR analysis using SNPs as IVs to assess the causal effects of electronic device usage on migraine risk. This method minimizes confounding factors since alleles are randomly allocated to offspring during fertilization. Additionally, we increased the statistical power and reliability of our findings by combining data from two large GWAS databases. Through MVMR, we further explored the independent causal relationship between digital device use and migraines. Additionally, multiple sensitivity analyses were conducted to clarify the reliability of the findings, which revealed no significant pleiotropy or heterogeneity.

Despite these strengths, our MR study has some limitations. First, while the MR analysis method aims to reduce confounding factors, some unmeasured confounders and weak IVs may still influence the outcomes (12). However, we used strict IV selection criteria, and the MVMR helped adjust for some pleiotropic factors related to migraine, minimizing these risks of bias. Second, due to the inherent limitations associated with GWAS data, exposure and outcome phenotypes rely on self-reported data, which may lead to recall bias. Additionally, the non-linear associations between digital device usage and migraine could not be assessed in this study. Third, the GWAS data used in this study were from European populations, lacking diversity in sample composition. Without subgroup analyses based on age and sex, these results may not be relevant to other demographic groups. Furthermore, there was a lack of information on other digital device usage, including tablets and laptops, as well as the specific contexts and motivations for electronic device usage. Future research should refine the categories, motivations, and environments surrounding electronic device use to provide a clearer understanding of the factors contributing to migraine risk.

5 Conclusion

In conclusion, our study provides evidence of the possible causal relationship between frequent mobile phone use, television watching, and migraine risk, particularly migraine without aura. Future research is needed to validate these associations in non-European populations and across different age or sex groups to ensure broader generalizability.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The First Affiliated Hospital of Henan University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZH: Writing – review & editing, Writing – original draft, Validation, Conceptualization. FQ: Writing – review & editing, Data curation. JY: Writing – review & editing, Formal analysis. MZ: Writing – review & editing, Project administration, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1462414/full#supplementary-material

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Efficacy of different acupuncture-related therapies for tension-type headache: a systematic review and network meta-analysis

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Background: Tension-type headache (TTH) is among the most common primary headache disorders, characterized by recurrent episodes that are difficult to manage, thus posing a significant public health challenge. Acupuncture, a well-recognized non-pharmacological treatment, is frequently employed for pain management, including TTH. However, the variety of acupuncture techniques and inconsistent treatment outcomes underscore the need for a thorough evaluation. This study aims to update the current evidence on acupuncture and related therapies for TTH, evaluate the efficacy and safety of various acupuncture therapies, and identify the most effective therapeutic strategies, providing valuable guidance for clinical practice.

Methods: We systematically searched randomized controlled trials (RCTs) from four English databases (PubMed, Embase, Cochrane Library, and Web of Science) and four Chinese databases (Wanfang, VIP, CNKI, and SinoMed), including gray literature, up to April 19, 2024. The outcome measures included headache frequency, duration, pain intensity, and responder rate. A Bayesian network meta-analysis was conducted using Stata 17.0 to assess the relative effectiveness and safety of the different acupuncture therapies. This study was registered with the Prospective Register of Systematic Reviews (CRD42024537187).

Results: A total of 42 RCTs, encompassing 4,103 participants and 21 distinct treatment therapies, were included in the analysis. The network meta-analysis yielded the following findings: (1) regarding responder rate, several acupuncture or combined acupuncture and medication approaches, such as electro-acupuncture (EA) + cupping therapy (CT) [odds ratio (OR) = 28.66, 95% CI: 1.68 to 487.35], manual acupuncture (MA) + bloodletting therapy (BT) (OR = 6.07, 95% CI: 1.81 to 20.29), plum blossom needle tapping (PBNT) (OR = 3.76, 95% CI: 1.04 to 13.65), and scalp acupuncture (SPA) (OR = 3.65, 95% CI: 2.29 to 5.83), were significantly more effective than western medicine (WM) alone, with EA + CT (92.1%) being the most effective. (2) In terms of reducing headache frequency, EA (85.9%) was the most effective, followed by MA + PBNT (80.9%) and MA + WM (78.4%). Compared to WM, both MA + PBNT (SMD = −1.76, 95% CI: −3.31 to −0.22) and EA (SMD = −1.75, 95% CI: −3.30 to −0.20) significantly reduced headache frequency. (3) For shortening headache duration, EA (83.9%) emerged as the most effective treatment, followed by MA + WM (73.5%) and laser acupuncture (LA) (68.5%). (4) In terms of pain intensity reduction, the

MA + WM combination (89.4%) was superior to other treatments, with SPA + WM (77.7%) being the next most effective. Compared to herbal medicine (HM), both MA + WM (SMD = −2.37, 95% CI: −4.20 to −0.55) and MA alone (SMD = −1.00, 95% CI: −1.75 to −0.24) significantly alleviated pain intensity.

Conclusion: This comprehensive analysis of 21 acupuncture and related therapies demonstrates that EA is the most effective in reducing headache frequency and shortening headache duration, while EA + CT and MA + WM are the optimal therapies for enhancing responder rate and reducing pain intensity, respectively. However, clinical decisions should be individualized based on the specific needs of each patient.

Systematic review registration: The study protocol was registered on the PROSPERO database under registration number CRD42024537187 (https://www.crd.york.ac.uk/prospero/#recordDetails).

KEYWORDS

acupuncture, tension-type headache, systematic review, network meta-analysis, clinical efficacy

1 Introduction

Tension-type headache (TTH) is a prevalent primary headache disorder, commonly encountered in clinical practice. It is typically characterized by mild to moderate tightening, pressing, or dull pain, often bilaterally located in the temporal regions and potentially extending to the forehead and occipital areas (1). TTH is marked by persistent, recurrent episodes that are challenging to manage effectively. This condition frequently leads to negative emotional states, including irritability, insomnia, anxiety, and depression, which can, in turn, exacerbate headache recurrence. This vicious cycle significantly impairs patients' ability to learn and work, thereby diminishing their quality of life and contributing to substantial social and economic burdens (2, 3). The global incidence of TTH has remained consistently high in recent years. The Global Burden of Disease (GBD) study reported 882.4 million new cases of TTH worldwide in 2017 (4), with further research indicating that 26% of the global population experiences TTH annually (5).

Western medicine offers various treatment strategies tailored to different types of TTH (1, 6). For infrequent episodic TTH, symptomatic relief is typically achieved through the use of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) (7). In contrast, the management of chronic or frequent episodic TTH often involves preventive treatments, including tricyclic antidepressants such as amitriptyline and mirtazapine (7, 8), in combination with non-pharmacological interventions like physical exercise or cognitive behavioral therapy (9, 10). However, prolonged or excessive use of analgesics or NSAIDs may result in adverse effects, such as gastrointestinal ulcers and renal impairment (11). Furthermore, tricyclic antidepressants, including mirtazapine, are associated with side effects like urinary retention, constipation, and cognitive dysfunction (12, 13). These limitations highlight the need for more effective non-pharmacological treatments (7).

Acupuncture, a cornerstone of traditional medicine with a history spanning thousands of years, has been extensively studied and recognized for its significant efficacy in pain management (14). The analgesic effects of acupuncture are attributed to mechanisms such as the modulation of the central and peripheral nervous systems (15), the promotion of endogenous opioid peptide release (16), and the regulation of cytokine and other immune-active substances (17). Due to its potent pain-relieving effects and minimal side effects, acupuncture has been widely adopted in the treatment of TTH (14, 18). Various acupuncture techniques are used in TTH management, including manual acupuncture, electroacupuncture, scalp acupuncture, and bloodletting therapy (19–21).

However, the absence of direct head-to-head comparisons among different acupuncture therapies leaves the optimal treatment for TTH undetermined. This study seeks to evaluate the safety and efficacy of various acupuncture therapies through a Bayesian network meta-analysis, employing indirect comparisons to provide evidence-based support for the clinical management of TTH.

2 Methods

2.1 Registration

This study was conducted in accordance with the AMSTAR2 guidelines (A Measurement Tool to Assess Systematic Reviews) and reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines specific to Network Meta-Analyses (Supplementary Table S1). The study protocol was registered on the PROSPERO database under registration number CRD42024537187.[1]

Abbreviations: BT, Bloodletting therapy; CIs, Confidence intervals; CT, Cupping therapy; DIC, Deviance information criterion; EA, Electro-acupuncture; GBD, Global Burden of Disease; HM, Herbal medicine; IHS, International Headache Society; IQRs, Interquartile ranges; LA, Laser acupuncture; MA, Manual acupuncture; MD, Mean difference; NSAIDs, Non-steroidal anti-inflammatory drugs; OR, Odds ratio; PBNT, Plum blossom needle tapping; RCTs, Randomized controlled trials; ROB, Risk of bias; SE, Standard errors; SMD, Standardized mean difference; SPA, Scalp acupuncture; SUCRA, Surface under the cumulative ranking curve; TTH, Tension-type headache; VAS, Visual Analog Scale; SA, Sham acupuncture; PT, Physical training; UC, Usual care; WM, Western medicine; CT, Cupping therapy; RT, Relaxation training; WL, Waiting list.

1 https://www.crd.york.ac.uk/prospero/#recordDetails

2.2 Search strategy

We performed a comprehensive literature search across eight databases: four English-language databases (PubMed, Embase, Cochrane Library, and Web of Science) and four Chinese-language databases (Wanfang, VIP, CNKI, and SinoMed). To ensure the inclusion of all relevant studies, we manually searched the reference lists of the included articles and related reviews. Gray literature, such as theses and conference proceedings, was also reviewed. There were no restrictions on publication date or language. The search utilized terms related to acupuncture (e.g., "acupuncture," "electroacupuncture," "manual acupuncture," "moxibustion," "scalp acupuncture," "auricular acupuncture"), TTH (e.g., "tension-type headache," "vascular tension headache," "idiopathic headache," "headache"), and study design (e.g., "randomized controlled trial" or "clinical trial"). For the Chinese databases, equivalent Chinese terms were employed. The complete search strategy is detailed in Supplementary Table S2.

References retrieved from the databases were managed using EndNote (version 20) software. The following study characteristics were summarized in a Microsoft excel spreadsheet: publication year, author, population, intervention type, outcome measures, control group, and demographic details (e.g., gender, age).

2.3 Eligibility criteria

2.3.1 Inclusion criteria

Study design: RCTs.

Participants: Patients diagnosed with TTH based on the International Headache Society (IHS) criteria (22). A detailed review of the studies published before 2018 was conducted, focusing specifically on key factors like headache frequency, duration, and symptom characteristics, to assess compatibility with the IHS 2018 criteria. Studies that did not meet the specific IHS 2018 standards were excluded to maintain diagnostic uniformity.

Interventions: Any form of acupuncture, including body acupuncture, scalp acupuncture, auricular acupuncture, or electroacupuncture.

Control groups: Studies where the control group received an alternative form of acupuncture or related therapy, including sham acupuncture, usual care, waitlist, or other active treatments (e.g., guideline-recommended pharmacotherapy, physical exercise, relaxation training, cognitive therapy).

Outcomes: The primary outcome was responder rate, and the secondary outcomes were headache frequency, headache duration, pain intensity and adverse reactions.

Publication types: Journal articles and theses.

Data requirements: Studies must include original data on relevant outcomes, or data that could be extracted from figures and tables.

2.3.2 Exclusion criteria

- Studies where the intervention group received additional treatments beyond acupuncture or related therapies.
- Duplicate data.
- Animal studies.
- Studies published solely as conference abstracts, dissertations, study protocols, or books.

2.4 Outcome measurements

2.4.1 Primary outcome

Responder rate: A participant with a > 50% reduction in monthly headache days after treatment (23).

2.4.2 Secondary outcome

Headache frequency: Number of headache days within the specified period.

Headache duration: Lasting hours of headache within the specified period.

Pain intensity: Visual Analog Scale (VAS).

Adverse reactions: Subcutaneous hematoma, pain in acupuncture site, temporary headache triggered by needling, etc.

2.5 Data extraction

Two independent reviewers extracted data from the eligible studies, capturing details on publication (author, year of publication, country), study characteristics (sample size, intervention type), participant characteristics (sample size, age, gender), and study design (randomized controlled trials). The primary outcomes of interest were responder rate, headache frequency, headache duration, and pain intensity.

Outcome data before and after the intervention (mean ± standard deviation) were extracted and summarized to evaluate the effectiveness of various acupuncture techniques in treating TTH. When studies reported standard errors (SE), confidence intervals (CIs), or interquartile ranges (IQRs) instead of means and standard deviations, these were converted to mean and standard deviation values using the RevMan 5.3 calculator.

2.6 Quality and risk of bias assessment

Two independent reviewers assessed the risk of bias in the included studies using the Cochrane Risk of Bias tool (ROB 2.0), evaluating 6 domains, including randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall evalution. This tool categorizes risk into three levels: low, high, and unclear. Given the nature of interventions, blinding of participants and personnel were generally considered high risk. Discrepancies between reviewers were resolved through discussion with the corresponding author to reach consensus.

2.7 Data analysis

In this study, we performed a Bayesian network meta-analysis using STATA 17.0. To begin, a network evidence diagram was created, where node size indicates the number of studies for each intervention, and line thickness between nodes represents the frequency of comparisons between intervention pairs. For networks containing closed loops, a global inconsistency test was conducted with a significance level of $\alpha = 0.05$. A p-value of <0.05 suggests inconsistency, indicating the need for sensitivity analysis to examine potential

heterogeneity. In the absence of closed loops or if no significant inconsistency is observed ($p > 0.05$), a consistency model is applied to the network meta-analysis, followed by the creation of a forest plot. Additionally, we utilized the node-splitting method to assess local inconsistencies. A p-value <0.05 in this context suggests local inconsistency, requiring careful interpretation of these results.

Additionally, to ensure the model alignment in our analysis, we performed model comparison using the deviance information criterion (DIC). This metric evaluates the relative fit of fixed-effect and random-effect models, with lower DIC values indicating better model adequacy. Consistency between fixed-effect and random-effect models is confirmed when the DIC difference is less than 5. This approach allowed us to select the most appropriate model for each cohort, enhancing the precision of our analysis.

For effect size determination, continuous variables such as headache frequency, duration, and pain intensity are assessed using the mean difference (MD) when outcome units are consistent. For continuous variables with non-uniform units, the standardized mean difference (SMD) is employed to account for variability. The responder rate, a binary variable, is measured using the OR, with a 95% CI calculated for analytical accuracy. Results of the network meta-analysis are displayed in a league table format, providing a comparative ranking of each intervention. Additionally, we construct a surface under the cumulative ranking curve (SUCRA) to represent the efficacy rankings of interventions, with SUCRA values ranging from 0 to 100%. Higher SUCRA values reflect greater effectiveness, while lower values suggest less efficacy. Finally, we generate a comparison-adjusted funnel plot to detect potential publication bias and small-study effects.

3 Results

3.1 Search results

A comprehensive literature search was conducted across eight databases, covering all publications up to April 2024. This search identified 2,442 studies from English-language databases (PubMed, Web of Science, Cochrane Library, Embase) and 8,724 studies from Chinese-language databases (Wanfang, CNKI, VIP, SinoMed). After removing 5,638 duplicate records using EndNote, 5,458 studies were excluded based on title and abstract screening.

The full texts of the remaining 71 studies were retrieved for detailed evaluation, but three studies were excluded due to the unavailability of their full text. Of the 68 studies assessed in full, 26 were excluded for the following reasons: insufficient data ($n = 8$), acupuncture not being the primary intervention ($n = 2$), TTH not being the primary focus ($n = 9$), non-randomized controlled trial design ($n = 4$), focus on placebo effects ($n = 1$), focus on psychological test efficacy ($n = 1$), and use of non-standard diagnostic criteria ($n = 1$), and the details for exclusion are listed in Supplementary Table S3. Consequently, 41 studies were included in the final analysis. The study selection process is depicted in Figure 1.

3.2 Characteristics of included studies

Table 1 presents a summary of the key characteristics of the 42 randomized controlled trials (RCTs) included in this analysis. The sample sizes of these studies ranged from 30 to 270 participants, with the average age of participants spanning from 30 to 51 years. All studies included both male and female participants. The research teams were based in nine different countries: China ($n = 30$), Germany ($n = 5$), Sweden ($n = 1$), Australia ($n = 1$), South Korea ($n = 1$), Iran ($n = 1$), Brazil ($n = 1$), Denmark ($n = 1$), and the United Kingdom ($n = 1$).

Among the studies, one trial featured four participant groups, four trials included three groups, and the remaining studies were two-group trials. The interventions in the treatment groups varied, including manual acupuncture ($k = 20$), acupuncture combined with herbal medicine ($k = 8$), electroacupuncture ($k = 4$), bloodletting therapy ($k = 2$), acupuncture combined with bloodletting therapy ($k = 1$), scalp acupuncture ($k = 1$), electroacupuncture combined with cupping therapy ($k = 1$), laser acupuncture ($k = 1$), plum-blossom needle therapy ($k = 1$), acupuncture combined with plum-blossom needle therapy ($k = 1$), acupuncture combined with western medication ($k = 1$), and scalp acupuncture combined with western medication ($k = 1$).

The control groups were subjected to various treatments, including western medication ($k = 22$), sham acupuncture ($k = 11$), herbal medicine ($k = 5$), physical exercise ($k = 2$), relaxation training ($k = 1$), sham acupuncture combined with western medication ($k = 1$), usual care ($k = 1$), waiting list ($k = 1$), and acupuncture combined with physical exercise ($k = 1$).

3.3 Risk of bias assessment

In this study, all 42 included trials reported a randomization process. Each study was rated as high risk for bias related to deviations from intended interventions, primarily due to the lack of blinding for both participants and personnel. Missing outcome data bias was consistently assessed as low risk, as dropout numbers and reasons were clearly reported. Outcome assessment bias was rated as low in 8 studies where blinding of outcome assessors was documented; for the remaining 34 studies, the lack of reported outcome assessor blinding led to the some concerns rating. Reporting bias was determined based on whether all anticipated outcomes were reported, with 50% of the studies rated as low risk and the other half as having some concerns. In summary, 17 studies were rated as high risk for overall bias, while the remaining 25 were assessed as having some concerns. Detailed risk of bias assessments for all included studies are illustrated in Figure 2.

3.4 Network meta-analysis results

3.4.1 Headache frequency

Nineteen studies addressing headache frequency were analyzed, encompassing 15 different treatment modalities. The network diagram of these treatments is presented in Figure 3A. The network meta-analysis revealed a closed-loop structure. The inconsistency test for this closed loop indicated $p \geq 0.05$, suggesting no significant evidence of inconsistency; therefore, a consistency model was utilized for the analysis.

According to the NMA results, both MA (manual acupuncture) + PBNT (plum blossom needle tapping) (SMD = −1.76, 95% CI: −3.31 to −0.22) and EA (electro-acupuncture) (SMD = −1.75, 95% CI: −3.30 to −0.20) significantly reduced headache frequency

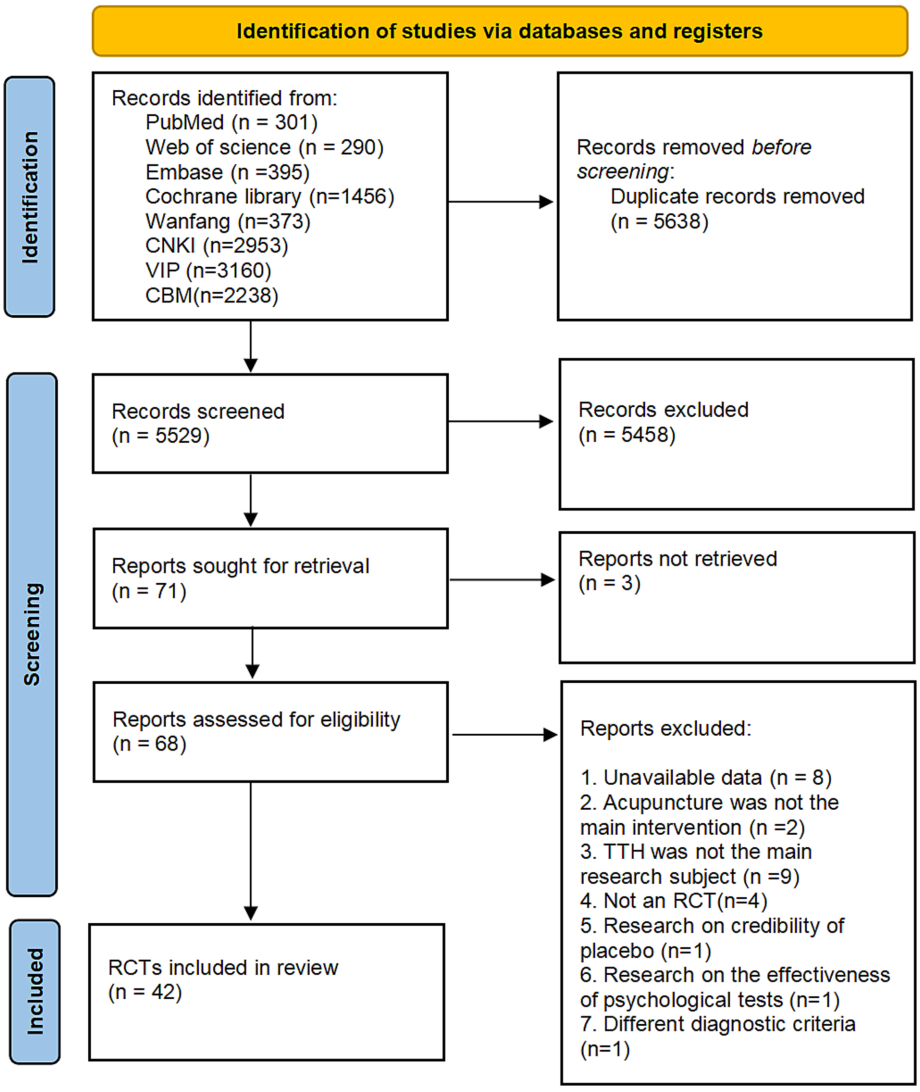

FIGURE 1
Literature screening process.

compared to WM (western medicine). EA demonstrated a significant reduction in headache frequency compared to PT (physical training) (SMD = −1.16, 95% CI: −2.29 to −0.03), MA + HM (herbal medicine) (SMD = −1.34, 95% CI: −2.30 to −0.39), WL (waiting list) (SMD = −2.06, 95% CI: −3.68 to −0.45), and SA (sham acupuncture) + WM (SMD = −2.17, 95% CI: −4.10 to −0.25). No significant differences were observed between the remaining treatment comparisons, as illustrated in Figure 4.

The cumulative probability ranking for effectiveness in reducing headache frequency is as follows: EA (85.9%) > MA + PBNT (80.9%) > MA + WM (78.4%) > RT (relaxation training) (61.5%) > LA (laser acupuncture) (59.1%) > MA + PT (57.0%) > UC (usual care) (55.6%) > MA (47.7%) > PT (47.6%) > PBNT (41.9%) > MA + HM (40.2%) > SA (38.9%) > WM (22.7%) > WL (16.7%) > SA + WM (15.9%), as depicted in Figure 5. The funnel plot analysis, conducted using Stata 17.0 and included in the Supplementary Figure S1, reveals some asymmetry, which may suggest potential publication bias or small-study effects within the research network.

3.4.2 Headache duration

Sixteen studies investigated headache duration across 15 different treatments. The network diagram illustrating these treatments is shown in Figure 3B. The network meta-analysis revealed a closed loop in the network diagram. The inconsistency test for the closed loop yielded $p \geq 0.05$, indicating no significant inconsistency. Therefore, a consistency model was utilized for the analysis. The NMA results indicated no statistically significant differences among the various treatments, suggesting that no single treatment was more effective than the others in reducing headache duration, see Figure 4.

The cumulative probability rankings for reducing headache duration are as follows: EA (83.9%) > MA + WM (73.5%) > LA (68.5%) > MA + PT (61.1%) > RT (57.6%) > MA (54.9%) > SA (50.3%) > PT (50.2%) > UC (48.4%) > PBNT (43.9%) > WL (40.5%) > MA + HM (38.1%) > MA + PBNT (36.4%) > WM (25.6%) > SA + WM (17%), as depicted in Figure 6.

Funnel plot analysis, conducted using Stata 17.0 and provided in the Supplementary Figure S2, reveals that the funnel plot is not

TABLE 1 Characteristics of the included studied.

References	Country	Intervention				Comparison				Outcome
		Treatment	Sample size	Gender (male/female)	Age (mean ± SD)/range	Treatment	Sample size	Gender (male/female)	Age (mean ± SD)/range	
Zheng et al. (31)	China	MA	110	28/82	43 ± 12.5	SA	108	33/75	43.2 ± 12.8	①②④⑤
						UC	24	7/17	38.7 ± 14.6	
Schiller et al. (32)	Germany	MA	24	6/18	39.8 ± 12.2	PT	24	5/18	37 ± 15.3	①②③⑤
						MA + PT	24	2/22	39 ± 11.6	
Jeon and Lee (33)	Korea	EA	15	6/9	40.00 ± 13.11	SA	15	8/7	34.33 ± 11.48	②④
Chassot et al. (34)	Brazil	EA	18	0/18	39.11 ± 10.5	SA	16	0/16	41.44 ± 10.5	④
Endres et al. (25)	Germany	MA	209	46/163	39.2 ± 11.4	SA	200	42/158	38.9 ± 12.2	①②⑤
Wang et al. (35)	Denmark	EA	20	8/10	43.24 ± 6.44	SA	20	10/8	53.39 ± 5.80	②③④
Söderberg et al. (36)	Sweden	MA	30	7/23	35 ± 10.25	PT	3030	7/23	35 ± 9.5	②③④
						RT	30	3/27	43.5 ± 9.25	
Melchart et al. (37)	Germany	MA	132	72/95	42.3 ± 13.5	SA	63	73/46	43.4 ± 12.9	②③
						WL	75	77/58	42.8 ± 13.2	
Ebneshahidi et al. (38)	Iran	LA	25	6/19	33 ± 6.75	SA	25	6/19	38.6 ± 7	②③
Xue et al. (39)	Australia	EA	20	7/13	42.6 ± 1.8	SA	20	7/13	41.5 ± 1.9	②③④
Karst et al. (40)	Germany	MA	34	14/14	47.9 ± 13.8	SA	35	14/21	48.2 ± 14.6	②④
White et al. (41)	England	MA	25	7/18	49.8 ± 2.9	SA	25	5/20	48.2 ± 2.9	②③④⑤
Karst et al. (42)	Germany	MA	21	13/8	50.4 ± 13.5	SA	18	7/11	47.3 ± 16.5	②④
Tong et al. (43)	China	MA + HM	43	16/27	43.4 ± 11.2	WM	43	14/29	42.7 ± 10.4	①②③④
Shi (44)	China	MA + HM	45	19/26	36 ± 10.5	WM	45	16/29	41 ± 8.5	①
Zhou (45)	China	MA + WM	34	22/12	48.21 ± 3.80	WM	34	20/14	47.62 ± 3.11	①②③④
Zhang et al. (46)	China	MA	26	NR	41.5 ± 11.75	SA + WM	20	NR	41.5 ± 11.75	①②③
Peng (47)	China	MA	63	28/35	32.5 ± 5.6	WM	63	26/37	31.3 ± 6.3	①
Li and Liu (48)	China	MA	40	NR	39 ± 10.5	HM	40	NR	39 ± 10.5	①④
Chen et al. (49)	China	MA	34	9/25	32.6 ± 4.5	HM	32	15/17	37.2 ± 6.2	①
Duan (50)	China	MA	48	14/34	42.7 ± 11.5	WM	48	17/31	43.5 ± 11.2	③④
Chen and Feng (51)	China	MA	70	22/48	39.89 ± 9.48	WM	70	18/52	40.36 ± 9.48	①
Guo (52)	China	MA + PBNT	30	13/17	26.5 ± 15.2	WM	30	12/17	24.6 ± 15.4	②③

(Continued)

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TABLE 1 (Continued)

References	Country	Intervention				Comparison				Outcome
		Treatment	Sample size	Gender (male/female)	Age (mean ± SD)/range	Treatment	Sample size	Gender (male/female)	Age (mean ± SD)/range	
Zou et al. (53)	China	MA + BT	30	11/19	36.54 ± 11.60	MA	30	13/17	37.93 ± 11.80	①
						HM	30	16/14	39.23 ± 12.24	
Guo (54)	China	MA + HM	40	25/15	36.5 ± 3.2	WM	40	21/19	38.7 ± 3.8	①④
Wang et al. (55)	China	MA	50	27/23	37.64 ± 3.42	WM	50	23/26	35.17 ± 4.03	②③④
Kang (56)	China	MA + HM	58	20/38	33.5 ± 7.25	HM	33	12/21	30 ± 5	①
Zhang (57)	China	MA + HM	38	16/22	39.3 ± 5.1	WM	38	15/23	39.7 ± 5.2	①
Wu and Sun (58)	China	MA + HM	30	13/17	39 ± 10.5	WM	30	14/16	39 ± 11	①
Gui et al. (59)	China	SPA + WM	30	13/17	38 ± 13	WM	30	19/11	39 ± 11	①
Li et al. (60)	China	MA	30	NR	40 ± 10	WM	25	NR	40 ± 10	①
Jiang (61)	China	MA + HM	40	17/23	39.7 ± 4.3	WM	40	18/22	38.5 ± 4.8	①
Luo et al. (62)	China	MA	42	17/25	45.31 ± 7.58	WM	43	16/27	45.13 ± 8.12	①
Liu and Liu (63)	China	MA + HM	91	68/23	42 ± 12	HM	31	12/19	41.5 ± 11.25	①
Yang et al. (64)	China	MA	41	31/10	40.96 ± 8.23	WM	41	33/8	41.29 ± 8.32	①
Wang et al. (65)	China	MA	150	63/87	44 ± 13	WM	100	42/58	43 ± 13	①③
Chen et al. (49)	China	BT	45	20/25	44 ± 11.5	MA	45	18/27	41 ± 11.5	④
Sun and Guo (66)	China	PBNT	30	11/19	43.5 ± 11.7	WM	30	9/21	42.8 ± 11.3	①②③④
Peng (67)	China	EA + CT	82	38/44	36.23 ± 6.25	WM	81	36/45	34.68 ± 5.27	①
Jin et al. (68)	China	BT	30	12/18	45.3 ± 3.9	WM	30	14/16	43.2 ± 3.2	④
Guo and Shen (69)	China	SPA	50	22/28	33.9 ± 10.2	MA	50	16/34	33.2 ± 10.2	①
						WM	50	19/31	34.0 ± 10.6	
Wang et al. (70)	China	MA	29	8/21	38 ± 10	WM	27	2/20	39 ± 11	①②③④

①, Responder rate (at least 50% reduction of headache days); ②, Headache frequency; ③, Headache duration; ④, Pain intensity; ⑤, Adverse reaction; MA, manual acupuncture; SA, sham acupuncture; PT, physical training; UC, usual care; HM, herbal medicine; WM, western medicine; BT, bloodletting therapy; SPA, scalp acupuncture; PBNT, plum blossom needle tapping; EA, electro-acupuncture; CT, cupping therapy; RT, relaxation training; WL, waiting list; LA, laser acupuncture.

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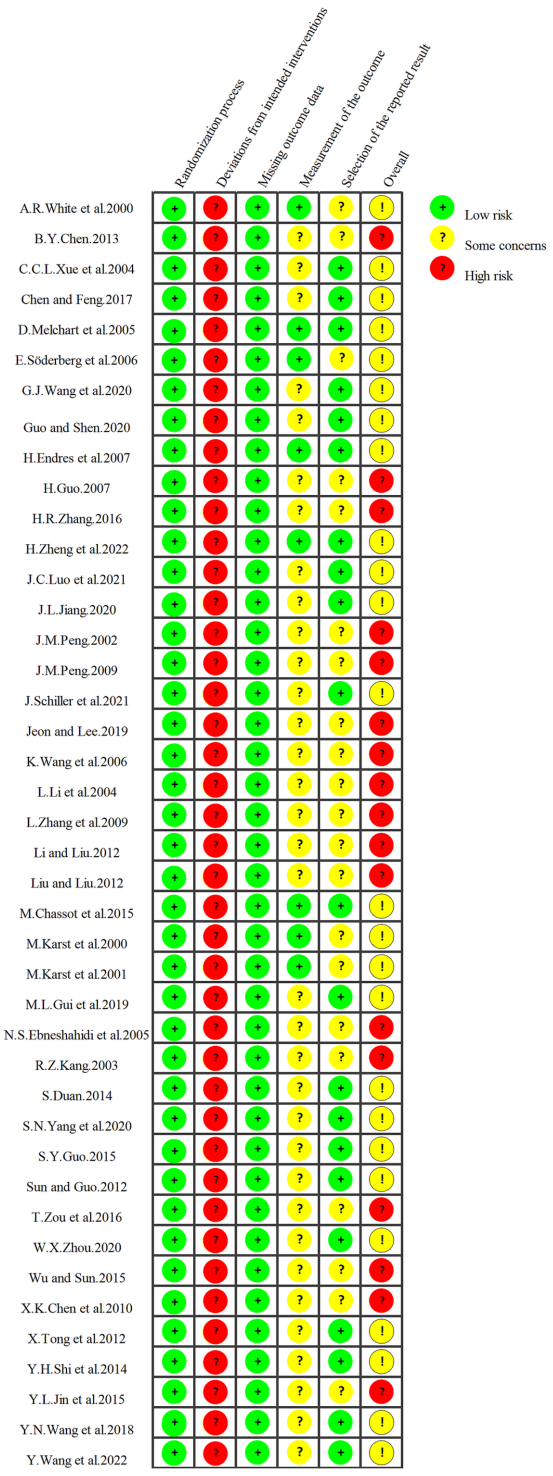

FIGURE 2
Results of the risk of bias evaluation.

perfectly symmetrical. This suggests potential publication bias or small study effects within the research network.

3.4.3 Pain intensity

A total of 22 studies examined pain intensity, involving 12 distinct treatment methods. The network diagram for these treatments is shown in Figure 3C. The network meta-analysis revealed a closed loop within this network. The inconsistency test for the closed loop yielded $p \geq 0.05$, indicating no evidence of inconsistency; thus, a consistency model was employed for the analysis. According to the league table results, both MA + WM (SMD = −2.37, 95% CI: −4.20 to −0.55) and MA (SMD = −1.00, 95% CI: −1.75 to −0.24) significantly reduced pain intensity compared to HM. There were no statistically significant differences observed between other treatment comparisons, as detailed in Figure 7.

The cumulative probability rankings for reducing pain intensity are as follows: MA + WM (89.4%) > SPA + WM (77.7%) > RT (60.5%) > MA (59.4%) > EA (57.3%) > BT (54.9%) > PT (51.6%) > SA (47.1%) > PBNT (38.8%) > MA + HM (27.9%) > HM (17.9%) > WM (17.5%), as shown in Figure 8.

Funnel plot analysis performed with Stata 17.0 is included in the Supplementary Figure S3. The results suggest that the funnel plot is not perfectly symmetrical, which may indicate potential publication bias or small study effects within the research network. The observed absence of studies with large sample sizes, as indicated by the missing top portion of the funnel plot, could suggest a lack of reporting or bias in the results from these studies.

3.4.4 Responder rate

Twenty-six studies assessed the responder rate across 15 distinct treatment methods. The network diagram for these treatments is depicted in Figure 3D. The network meta-analysis revealed a closed loop within the network diagram. The inconsistency test for this closed loop yielded $p \geq 0.05$, indicating no significant inconsistency; thus, a consistency model was applied for the analysis.

The NMA results showed that EA + CT was superior to SA + WM (OR = 41.22, 95% CI: 1.79 to 951.56), HM (OR = 29.75, 95% CI: 1.61 to 550.44), and WM (OR = 28.66, 95% CI: 1.68 to 487.35). MA + BT outperformed SA + WM (OR = 8.73, 95% CI: 1.59 to 48.04), HM (OR = 6.30, 95% CI: 2.03 to 19.52), and WM (OR = 6.07, 95% CI: 1.81 to 20.29). SPA was more effective than SA + WM (OR = 8.47, 95% CI: 1.12 to 63.93), HM (OR = 6.12, 95% CI: 1.16 to 32.34), and WM (OR = 5.89, 95% CI: 1.26 to 27.47). MA was superior to SA + WM (OR = 5.25, 95% CI: 1.48 to 18.66), HM (OR = 3.79, 95% CI: 2.04 to 7.05), and WM (OR = 3.65, 95% CI: 2.29 to 5.83). PBNT was more effective than WM (OR = 3.76, 95% CI: 1.04 to 13.65). MA + HM was more effective than SA + WM (OR = 5.24, 95% CI: 1.26 to 21.73), HM (OR = 3.78, 95% CI: 1.82 to 7.83), and WM (OR = 3.64, 95% CI: 2.16 to 6.14). No significant differences were observed between the remaining treatment comparisons, as illustrated in Figure 7.

The cumulative probability rankings for responder rate are as follows: EA + CT (92.1%) > MA + BT (76.9%) > MA + WM (73.9%) = SPA (73.9%) > SPA + WM (69.3%) > MA (63.5%) > MA + HM (62.4%) > PBNT (61.5%) > MA + PT (43.7%) > SA (40.8%) > PT (36.6%) > WM (17.7%) > HM (17.4%) > SA + WM (12.7%) > UC (7.6%), as shown in Figure 9.

Funnel plot analysis conducted using Stata 17.0 is included in the Supplementary Figure S4. The funnel plot exhibits some asymmetry, which suggests the presence of potential publication bias or small-study effects within the research network.

3.4.5 Adverse reaction

A total of 31 studies evaluated adverse reactions, among which 27 reported no adverse events, while the remaining 4 studies documented related adverse reactions. The most commonly reported

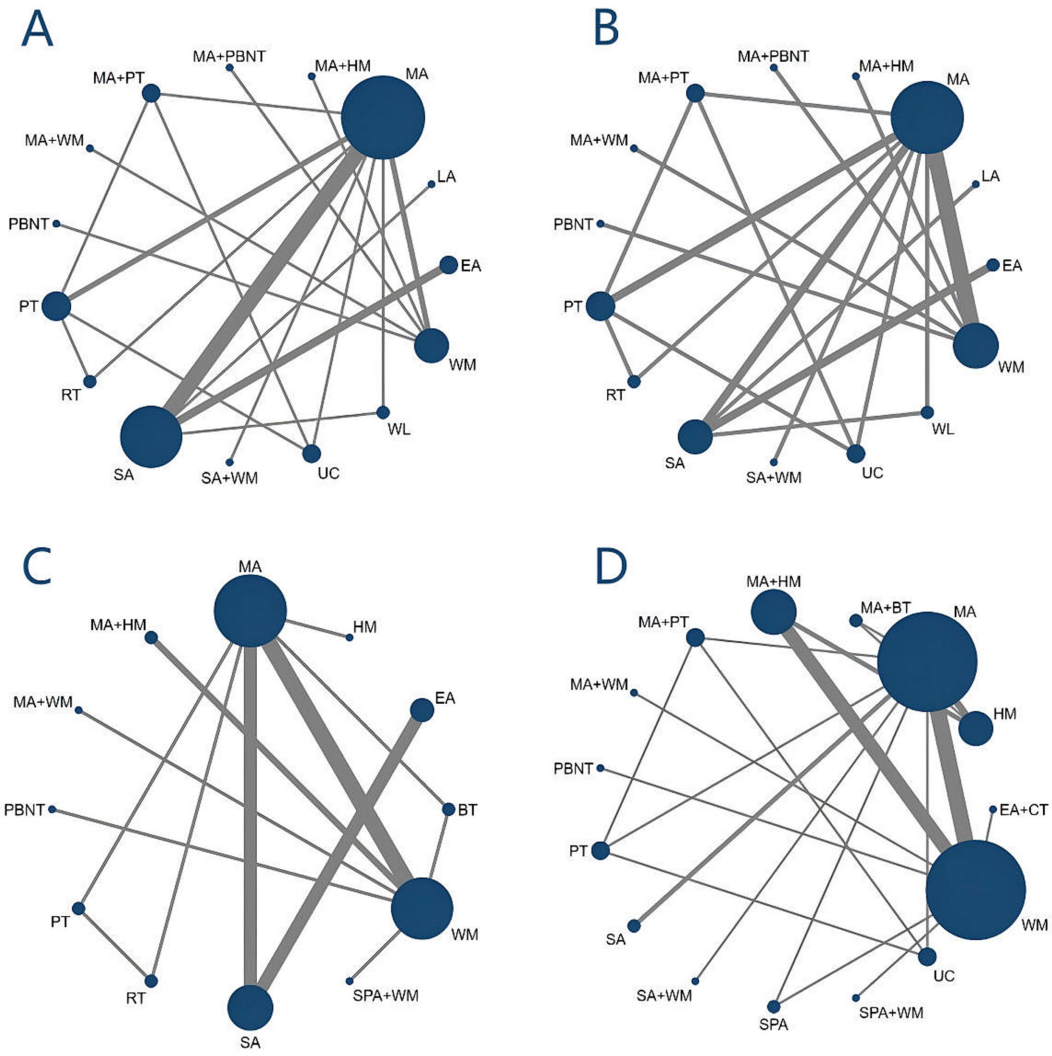

FIGURE 3
Evidence network diagram. **(A)** Headache frequency. **(B)** Headache duration. **(C)** Pain intensity. **(D)** Responder rate.

acupuncture-related adverse effects included subcutaneous hematoma, pain around the needling site, headache exacerbation, temporary headache triggered by needling, and acupuncture-induced syncope.

4 Discussion

The etiology and pathogenesis of chronic TTH remain incompletely understood. Potential contributing factors include persistent muscle tension in the head and neck, leading to local ischemia and the accumulation of metabolic byproducts, which may trigger pain. Other factors involve peripheral and central sensitization, resulting in heightened sensitivity to pain and stress, thus perpetuating headaches. Imbalances in neurotransmitters can lower pain thresholds and amplify pain perception. Psychosocial factors, including negative emotional states and lifestyle habits, may exacerbate headaches indirectly by increasing muscle tension and affecting neurotransmitter levels (1, 24).

In this study, we conducted an extensive literature review and included 42 RCTs that met our inclusion criteria, covering 21 different treatment methods—13 single therapies and 8 combination therapies. Our evaluation of various acupuncture techniques focused on headache frequency, duration, pain intensity, and responder rate, leading to the following conclusions:

1 Responder rate: As a primary outcome, responder rate provides a direct measure of treatment efficacy. Our analysis showed that EA + CT demonstrating the highest efficacy.
2 Headache frequency: EA was found to be the most effective in reducing headache frequency. In addition, combination therapies generally exceeded the efficacy of single treatments with MA, PBNT, or WM.
3 Headache duration: EA emerged as potentially the most effective treatment for shortening headache duration.
4 Pain intensity: The MA + WM combination was superior to other therapies in reducing pain intensity. Combinations of MA with WM or HM were more effective than MA, WM, or HM alone.
5 Adverse reactions: Among the included studies, Endres et al. (25) reported one case of severe headache potentially triggered by sham acupuncture, while no further evidence was provided.

SA+WM	-0.69 (-3.18,1.79)	-0.90 (-4.21,2.41)	-0.98 (-4.28,2.33)	-1.11 (-4.12,1.90)	-1.17 (-4.49,2.14)	-1.38 (-4.42,1.66)	-1.44 (-4.16,1.28)	-1.47 (-4.18,1.25)	-1.54 (-3.78,0.69)	-1.72 (-4.75,1.32)	-1.83 (-4.88,1.21)	-2.20 (-5.70,1.29)	-2.42 (-5.74,0.91)	-2.84 (-5.98,0.29)
Rank 15th	WM	-0.21 (-2.40,1.98)	-0.28 (-2.46,1.89)	-0.42 (-2.71,1.87)	-0.48 (-2.67,1.71)	-0.69 (-3.02,1.65)	-0.75 (-2.65,1.15)	-0.77 (-2.65,1.11)	-0.85 (-1.94,0.24)	-1.02 (-3.35,1.30)	-1.14 (-3.47,1.19)	-1.51 (-4.41,1.39)	-1.72 (-3.93,0.48)	-2.15 (-4.61,0.30)
Rank 14th	MA+PBNT	-0.08 (-3.16,3.01)	-0.21 (-3.38,2.96)	-0.27 (-3.37,2.83)	-0.48 (-3.68,2.72)	-0.54 (-3.44,2.36)	-0.57 (-3.45,2.32)	-0.64 (-3.09,1.80)	-0.82 (-4.01,2.38)	-0.93 (-4.13,2.27)	-1.30 (-4.94,2.33)	-1.52 (-4.63,1.59)	-1.94 (-5.23,1.35)
Rank 1st	Rank 13th	MA+HM	-0.13 (-3.29,3.02)	-0.20 (-3.28,2.89)	-0.40 (-3.59,2.79)	-0.46 (-3.35,2.42)	-0.49 (-3.36,2.38)	-0.57 (-3.00,1.86)	-0.74 (-3.92,2.44)	-0.86 (-4.05,2.33)	-1.23 (-4.85,2.40)	-1.44 (-4.54,1.66)	-1.87 (-5.15,1.41)
MA+PBNT	Rank 2nd	Rank 12th	WL	-0.06 (-3.23,3.11)	-0.27 (-3.15,2.62)	-0.33 (-2.88,2.22)	-0.35 (-2.37,1.67)	-0.43 (-2.45,1.58)	-0.61 (-3.48,2.27)	-0.72 (-3.61,2.16)	-1.09 (-4.09,1.90)	-1.31 (-4.48,1.87)	-1.73 (-4.30,0.84)
-0.01 (-2.20,2.17)	EA	Rank 3rd	Rank 11th	PBNT	-0.21 (-3.41,2.99)	-0.27 (-3.17,2.63)	-0.29 (-3.18,2.59)	-0.37 (-2.82,2.08)	-0.54 (-3.74,2.65)	-0.66 (-3.86,2.54)	-1.03 (-4.67,2.60)	-1.24 (-4.35,1.87)	-1.67 (-4.96,1.62)
-0.13 (-2.30,2.04)	-0.12 (-2.29,2.06)	MA+WM	Rank 4th	Rank 10th	UC	-0.06 (-2.12,2.00)	-0.09 (-2.66,2.48)	-0.17 (-2.23,1.90)	-0.34 (-3.03,2.36)	-0.45 (-2.66,1.75)	-0.82 (-4.21,2.56)	-1.04 (-4.25,2.17)	-1.47 (-4.48,1.55)
-0.78 (-3.13,1.57)	-0.77 (-2.58,1.04)	-0.65 (-2.99,1.69)	RT	Rank 5th	Rank 9th	PT	-0.02 (-2.21,2.16)	-0.10 (-1.66,1.45)	-0.28 (-2.33,1.78)	-0.39 (-2.46,1.67)	-0.76 (-3.87,2.34)	-0.98 (-3.89,1.93)	-1.40 (-4.10,1.29)
-0.84 (-3.33,1.65)	-0.83 (-2.63,0.98)	-0.71 (-3.19,1.77)	-0.06 (-2.23,2.11)	LA	Rank 6th	Rank 8th	SA	-0.08 (-1.61,1.46)	-0.25 (-2.81,2.31)	-0.37 (-2.94,2.20)	-0.74 (-2.95,1.47)	-0.95 (-3.85,1.95)	-1.38 (-2.97,0.21)
-0.91 (-3.27,1.45)	-0.90 (-2.72,0.93)	-0.78 (-3.12,1.57)	-0.13 (-1.99,1.74)	-0.07 (-2.25,2.11)	MA+PT	Rank 7th	Rank 7th	MA	-0.17 (-2.22,1.88)	-0.29 (-2.35,1.77)	-0.66 (-3.35,2.03)	-0.87 (-3.33,1.59)	-1.30 (-3.50,0.90)
-0.95 (-3.31,1.41)	-0.94 (-2.76,0.89)	-0.82 (-3.16,1.53)	-0.17 (-2.03,1.70)	-0.11 (-2.29,2.07)	-0.04 (-1.57,1.49)	UC	Rank 8th	Rank 6th	RT	-0.12 (-2.81,2.58)	-0.49 (-3.87,2.89)	-0.70 (-3.90,2.50)	-1.13 (-4.14,1.88)
-1.17 (-3.05,0.70)	-1.16 (-2.29,-0.03)	-1.04 (-2.90,0.82)	-0.39 (-1.81,1.02)	-0.33 (-1.98,1.31)	-0.26 (-1.69,1.17)	-0.22 (-1.65,1.21)	PT	Rank 9th	Rank 5th	MA+PT	-0.37 (-3.76,3.02)	-0.58 (-3.79,2.63)	-1.01 (-4.03,2.01)
-1.14 (-3.31,1.02)	-1.13 (-2.69,0.43)	-1.01 (-3.16,1.13)	-0.36 (-1.78,1.05)	-0.30 (-2.27,1.66)	-0.23 (-1.67,1.20)	-0.19 (-1.63,1.24)	-0.03 (-1.10,1.05)	MA	Rank 10th	Rank 4th	LA	-0.21 (-3.85,3.43)	-0.64 (-3.36,2.08)
-1.33 (-3.49,0.84)	-1.31 (-3.48,0.85)	-1.19 (-3.34,0.96)	-0.54 (-2.87,1.78)	-0.49 (-2.96,1.99)	-0.42 (-2.75,1.92)	-0.38 (-2.71,1.96)	-0.18 (-2.32,1.96)	-0.15 (-2.00,1.69)	PBNT	Rank 11th	Rank 3rd	MA+WM	-0.43 (-3.73,2.87)
-1.37 (-3.52,0.77)	-1.36 (-3.51,0.79)	-1.24 (-3.37,0.89)	-0.59 (-2.90,1.72)	-0.53 (-2.99,1.92)	-0.46 (-2.78,1.86)	-0.42 (-2.74,1.90)	-0.23 (-2.35,1.89)	-0.20 (-2.03,1.62)	-0.05 (-2.17,2.07)	SA	Rank 12th	Rank 2nd	EA
-1.36 (-3.32,0.61)	-1.34 (-2.30,-0.39)	-1.22 (-3.18,0.73)	-0.57 (-2.11,0.97)	-0.52 (-2.05,1.02)	-0.45 (-2.00,1.11)	-0.41 (-1.96,1.15)	-0.21 (-1.45,1.02)	-0.18 (-0.79,0.42)	-0.03 (-1.97,1.91)	-0.02 (-1.94,1.91)	MA+HM	Rank 13th	Rank 1st
-1.76 (-3.31,-0.22)	-1.75 (-3.30,-0.20)	-1.63 (-3.16,-0.10)	-0.98 (-2.75,0.79)	-0.92 (-2.88,1.03)	-0.85 (-2.63,0.93)	-0.81 (-2.59,0.97)	-0.62 (-2.13,0.89)	-0.59 (-1.65,0.47)	-0.44 (-1.95,1.08)	-0.41 (-1.63,0.81)	-0.39 (-1.88,1.10)	WM	Rank 14th
-2.08 (-4.36,0.20)	-2.06 (-3.68,-0.45)	-1.94 (-4.21,0.32)	-1.29 (-3.22,0.63)	-1.24 (-3.25,0.77)	-1.17 (-3.10,0.77)	-1.13 (-3.06,0.81)	-0.93 (-2.62,0.75)	-0.90 (-2.20,0.40)	-0.75 (-3.01,1.51)	-0.72 (-2.02,0.58)	-0.70 (-2.94,1.54)	-0.31 (-1.99,1.36)	WL	Rank 15th
-2.19 (-4.62,0.25)	-2.17 (-4.10,-0.25)	-2.05 (-4.48,0.37)	-1.41 (-3.51,0.70)	-1.35 (-3.61,0.92)	-1.28 (-3.39,0.84)	-1.24 (-3.35,0.88)	-1.04 (-2.93,0.85)	-1.01 (-2.57,0.54)	-0.86 (-3.27,1.55)	-0.83 (-2.50,0.84)	-0.81 (-3.21,1.58)	-0.42 (-2.30,1.46)	-0.11 (-2.14,1.91)	SA+WM

FIGURE 4
Forest plot comparing the efficacy of various acupuncture treatments in headache frequency and headache duration of TTH based on Bayesian network meta-analysis. SMD and 95% CIs for headache frequency (depicted by the yellow lower triangle area) and headache duration (depicted by the blue upper triangle area). 95% CIs <0.00 indicates a statistically significant difference between two treatments.

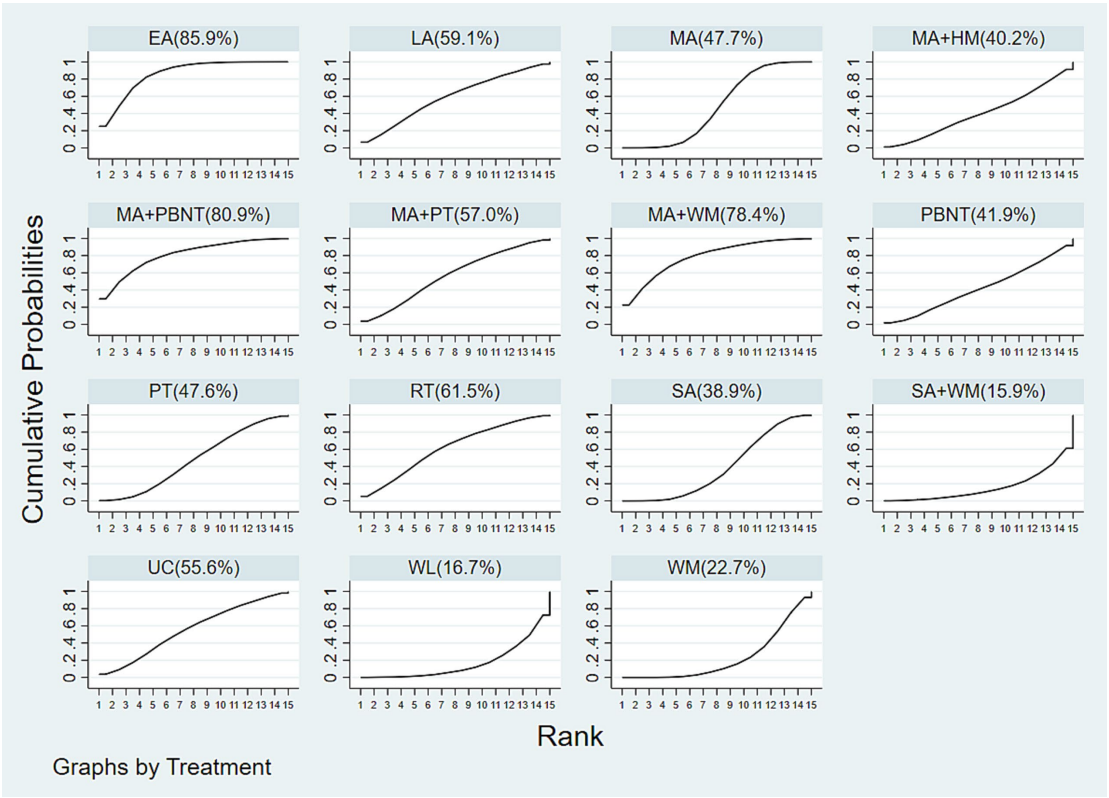

FIGURE 5
Cumulative probability ranking results of headache frequency.

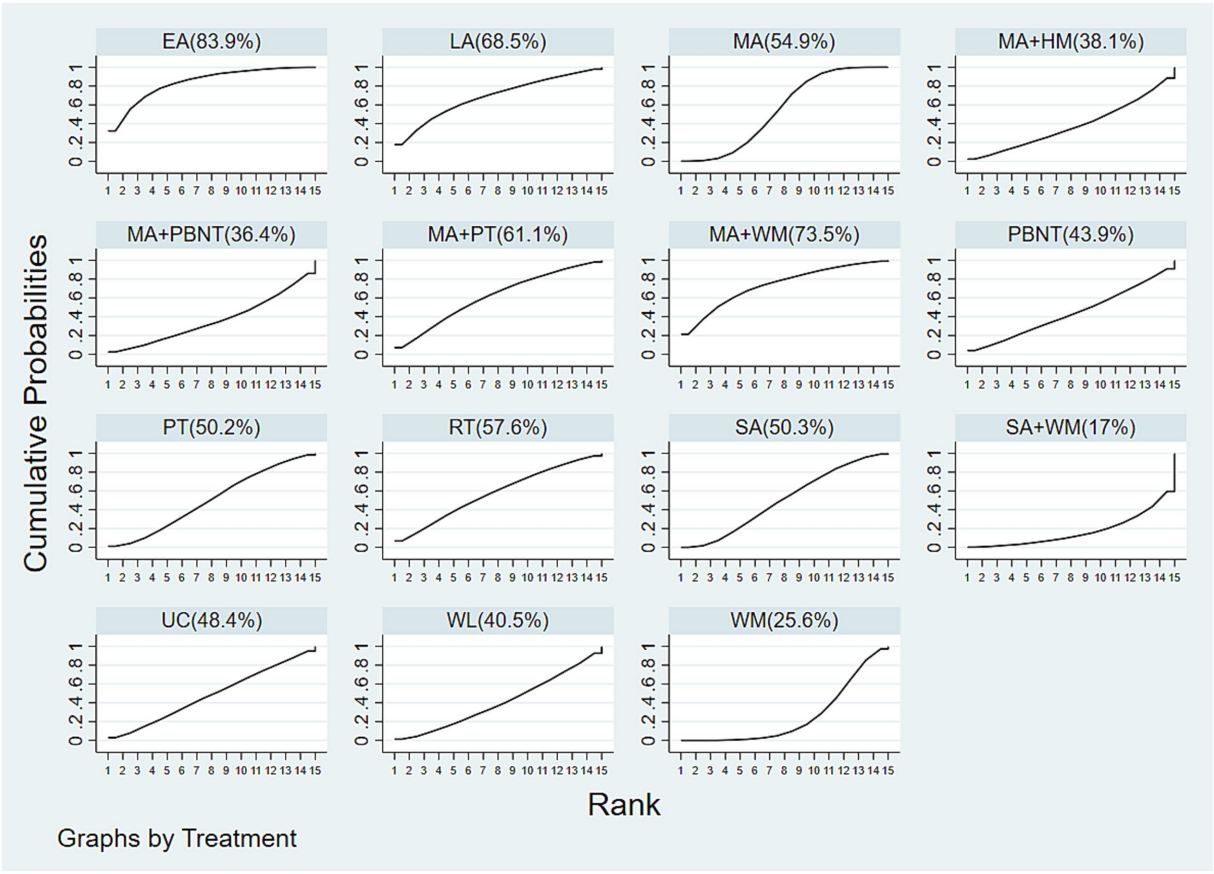

FIGURE 6
Cumulative probability ranking results of headache duration.

Regarding the other three studies reported adverse events, the typical ones include localized pain, bruising, and acupuncture syncope, which usually resolve quickly without further intervention. Therefore, the relatively low incidence and mild effects of the adverse reactions reported in included studies reveals that the safety profile of acupuncture is generally favorable.

EA frequently appeared in our results, particularly as it achieved the best outcomes in responder rate. The mechanism behind EA combined with CT may involve its synergy with cupping therapy. EA applies mild electrical currents to specific acupoints, enhancing local blood circulation and regulating the nervous system. Research indicates that EA increases endogenous opioid release, inhibits pain signal transmission, and alleviates headaches (15). Additionally, EA can balance sympathetic and parasympathetic nervous systems, reducing muscle tension and anxiety, which in turn improves headache symptoms (26). Cupping therapy, through negative pressure, promotes blood and lymphatic circulation, reducing local muscle tension and inflammatory responses. Its mechanical stimulation enhances tissue oxygenation and metabolism and facilitates the removal of harmful substances. Furthermore, cupping therapy stimulates skin and muscle nerve endings, modulating central nervous system functions and alleviating pain and discomfort (27).

EA integrates electrical stimulation with traditional acupuncture needling, providing a more standardized and reproducible approach compared to manual manipulation. Key EA parameters include waveform, frequency, and intensity, with waveform being one of the most critical factors. Commonly used waveforms are the dense-sparse (alternating dense and sparse pulses) and continuous waveforms. The dense-sparse waveform alternates between rapid and slower pulses, effectively promoting rhythmic muscle contraction and relaxation, which enhances circulation, reduces edema, and provides analgesic effects.

Although clinical studies specifically examining the impact of EA waveforms on TTH are limited, existing literature suggests the dense-sparse waveform demonstrates promising results in pain and edema reduction across various conditions. For instance, Wu et al. (28) explored the efficacy of different EA waveforms in treating primary dysmenorrhea and found no significant difference in short- and long-term pain relief or reduction in analgesic use across waveforms, although the dense-sparse waveform showed a slight advantage in immediate pain relief. In a RCT of EA waveform effects on 60 patients with cervical spondylosis, Hu et al. (29) reported that the dense-sparse waveform significantly alleviated dizziness and headaches compared to the continuous wave, highlighting its potential benefits.

These findings suggest that the dense-sparse waveform may facilitate rhythmic contraction and relaxation of cranio-cervical muscles, thereby improving blood and lymphatic circulation and potentially relieving TTH. However, further studies are necessary to verify this hypothesis and establish optimal parameters for clinical efficacy.

When comparing our findings with those of Hu et al. (30), we noted discrepancies. Hu et al. identified SPA + WM as most

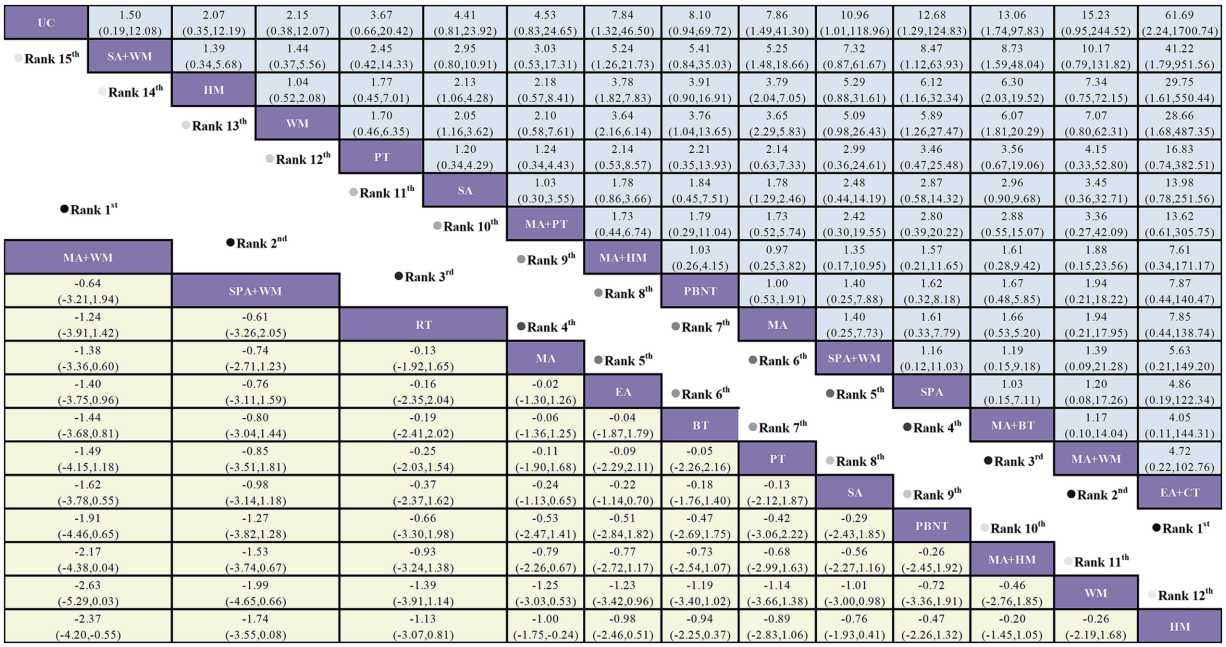

FIGURE 7
Forest plot comparing the efficacy of various acupuncture treatments in pain intensity and responder rate of TTH based on Bayesian network meta-analysis. SMD and 95% CIs for pain intensity (depicted by the yellow lower triangle area). 95% CIs <0.00 indicates a statistically significant difference between two treatments; OR and 95% CIs for responder rate (depicted by the blue upper triangle area). 95% CIs <1.00 or >1.00 indicates a statistically significant difference between two treatments.

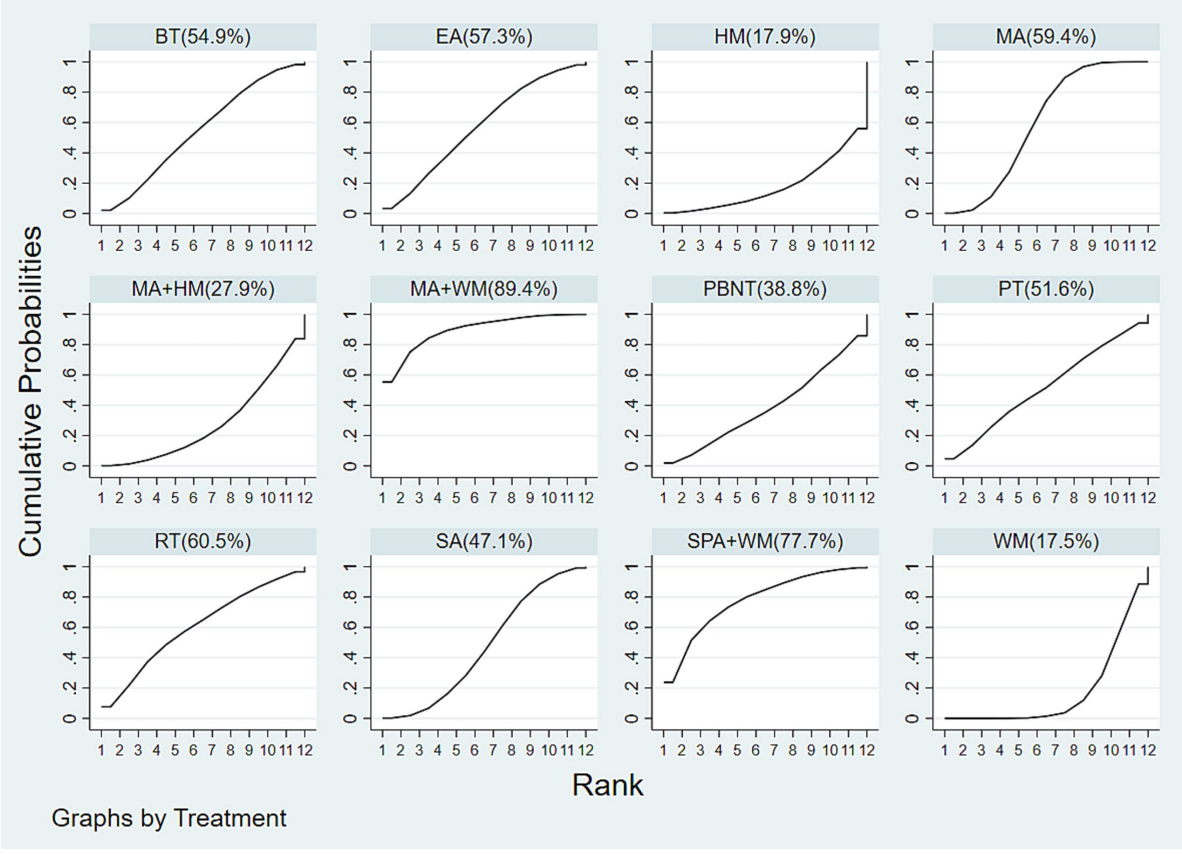

FIGURE 8
Cumulative probability ranking results of pain intensity.

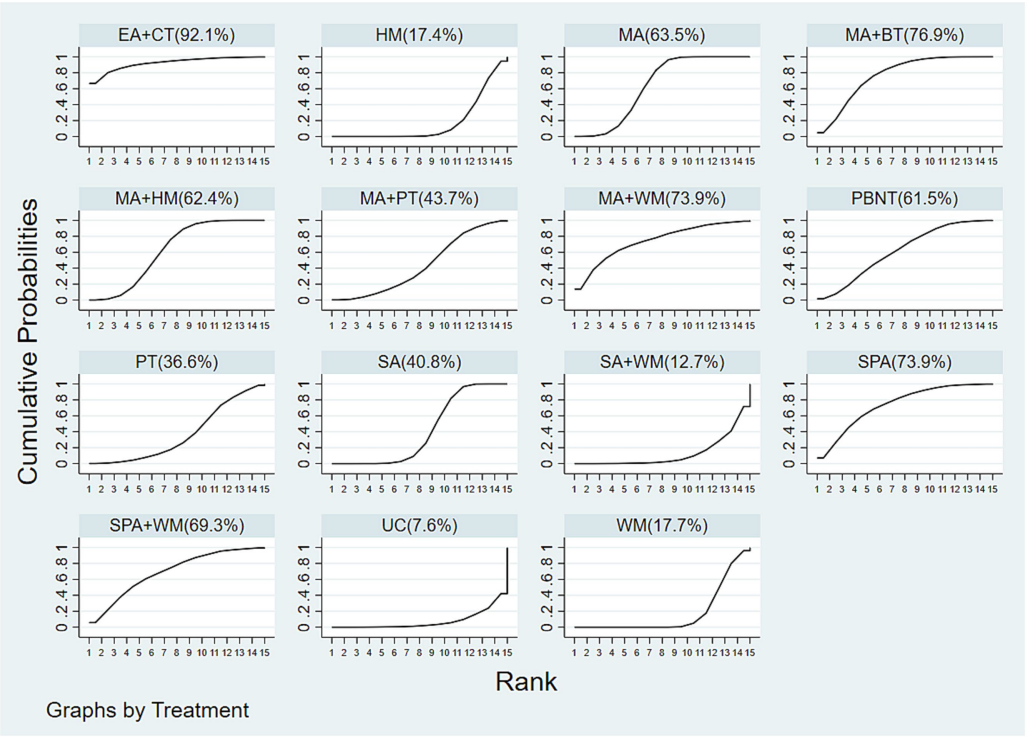

FIGURE 9
Cumulative probability ranking results of responder rate.

effective for reducing pain intensity, whereas our study found MA + WM to be optimal. They reported MA + HM as effective in reducing headache frequency, while EA was found to be superior in our analysis. For responder rate, Hu et al. favored BT, while EA + CT was most effective in our study. Possible reasons for these differences include sample size variations—Hu et al. included 27 studies primarily from China and Asia, while our study incorporated 42 studies featuring a diverse range of research teams from nine different countries, including China, Germany, Sweden, and others. The majority of the populations studied were from Asia, while the research also encompassed data from Europe, North America, and the Middle East. Additionally, there is a broader range of treatments in our study, including LA, RT, and PT, which were not covered by Hu et al.

Through comprehensive search of 8 databases, this study represents the latest network meta-analysis evaluating various acupuncture methods for TTH, incorporating the highest number of studies, the most recent data, and a wide array of treatment modalities.

Despite the valuable insights provided, this study has limitations. Firstly, some included studies did not report on allocation concealment, blinding, or selective reporting biases, which may introduce bias. Secondly, smaller sample sizes in some studies might affect result accuracy. Lastly, although the study involved global research teams, a substantial proportion of participants were Asian, which may impact the generalizability of the findings to other ethnic groups.

In conclusion, our study demonstrates that among the 21 treatments assessed, EA is most effective in reducing headache frequency and duration, while EA + CT and MA + WM are the most effective for improving responder rate and reducing pain intensity, respectively. However, clinical decisions should consider individual patient circumstances. Given the current limitations in literature, further multi-center, large-scale, and prospective RCTs are necessary to confirm these findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YiW: Conceptualization, Data curation, Formal analysis, Software, Validation, Writing – original draft, Writing – review & editing. WL: Funding acquisition, Investigation, Supervision, Writing – original draft. YoW: Project administration, Supervision, Validation, Writing – review & editing. WC: Formal analysis, Software, Validation, Writing – review & editing. HZ: Conceptualization, Funding acquisition, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Coordinates-based meta-analysis for vestibular migraine and the underlying mechanisms behind it

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Background: Vestibular migraine (VM) is a leading cause of recurrent vertigo episodes. Voxel-based morphometry (VBM) is a reliable technique to analyze structural changes, particularly in gray matter (GM) volume, across various neurological conditions. Despite the growing amount of neuroimaging data in recent decades, a comprehensive review of GM alterations in VM remains lacking.

Methods: We conducted a systematic review of three English-language databases (PubMed, Embase, and Web of Science) and two Chinese-language databases (China National Knowledge Infrastructure and Wanfang) to evaluate existing neuroimaging data on GM volume in VM patients. A coordinate-based meta-analysis (CBMA) was performed using the latest algorithm, seed-based d mapping with permutation of subject images (SDM-PSI), to identify brain alterations across individual studies.

Results: Five studies (103 VM patients, 107 HCs) were included. The CBMA demonstrated a significant reduction in GM volume in VM patients compared to HCs, with peak convergence in the left rolandic operculum (SDM-Z = −3.68, *p*-corrected = 0.004, voxels = 629; Brodmann area 48), extending to the posterior insula. Heterogeneity across studies was low (I^2 = 19.35%), and no publication bias was detected (Egger's test: p = 0.826).

Conclusion: This meta-analysis confirms reliable GM volume alterations in the posterior insula–operculum region of VM patients. Longitudinal studies with standardized imaging protocols are needed to clarify whether these changes are causes or consequences of VM.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42021277684.

KEYWORDS

coordinate-based meta-analysis, gray matter, vestibular migraine, voxel-based morphometry, insula

Introduction

Vestibular migraine (VM), which is a common neurological disorder characterized by recurrent episodes of vestibular and migraine-related symptoms, is one of the most common causes of vertigo with a prevalence of 1–2.7% among the adult population (1, 2). Despite established diagnostic criteria for VM from the International Headache Society (IHS) and the Barany Society (3, 4), the pathogenesis of VM is not fully understood. The existing hypotheses are derived from migraine pathophysiology (5). There are anatomical connections between

the nociceptive and vestibular systems at the brainstem and cortical level (6–9). Impairment to these regions is thought to be responsible for the generation of migraine headache and vertigo. Thus, brain structure alterations in the vestibular and nociceptive pathways are important for exploring the pathogenesis of VM.

Voxel-based morphometry (VBM) is a common magnetic resonance imaging (MRI)-based technique that can be used to investigate structural abnormalities, including differences in brain gray matter (GM) volumes, between different populations (10). While several VBM studies of VM patients have been conducted, their results are inconsistent (11–14). For instance, one study found decreased GM volume in the temporal and occipital lobes (11), while another study suggested increased GM volume in the same brain regions (12). Given this variability, further analysis is needed to confirm reliable cerebral GM alterations in VM patients in order to inform potential pathogenesis and clinical treatments.

We hypothesized that VM patients exhibit spatially convergent GM alterations in brain regions critical for integrating vestibular and nociceptive signals, as suggested by their anatomical and functional connectivity. Identifying such alterations may provide a structural basis for the shared pathophysiology of vestibular and migraine symptoms in VM.

One approach to reconcile inconsistent results in imaging studies is coordinate based meta-analysis (CBMA) (15). Notably, this method has been previously applied to analyze voxel-based neuroimaging studies (16, 17). The latest version of CBMA is seed-based d mapping with a permutation of subject images (SDM-PSI) and shows increased accuracy relative to the former versions (18, 19).

This study aimed to explore whether VM patients show convergent GM alterations by conducting a CBMA via SDM-PSI of prior VBM studies comparing VM patient and healthy control (HC) groups. Overall, this work aims to shed light on the underlying neurophysiological mechanisms of this disease.

Methods

Study design

This study complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and follows the guidelines and recommendations of neuroimaging meta-analyses (20). It was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42021277684).

Literature search

We searched the PubMed, Embase, and Web of Science databases using the following free-text terms: ("vestibular migraine") AND ("MRI" OR "voxel-based" OR "morphometry" OR "morphometric" OR "structural" OR "cortical"). We also searched two Chinese databases (China National Knowledge Infrastructure and Wanfang) for studies published in Chinese. The reference lists of the included articles and relevant review articles were manually reviewed to identify other potentially eligible studies. We also searched bioRxiv[1] for unpublished preprints eligible for inclusion. All searches were completed on 6 April 2024.

Study selection

The inclusion criteria are as follows: (1) patients must meet the diagnostic criteria for VM in the International Classification of Headache Disorders 3rd version (ICHD-3); (2) studies must perform a VBM comparison between VM patients and healthy controls; (3) results are reported using Montreal Neurological Institute (MNI) or Talairach coordinates; and (4) studies are published in Chinese or English. The exclusion criteria are as follows: (1) articles that were not original research studies, such as reviews, case reports, reviews, editorial letters, conference reports, etc.; (2) studies without a healthy control group; (3) studies in which analysis was limited to defined regions of interest (ROIs); and (4) studies for which essential neuroimaging data were not available.

Data extraction

Two researchers (DL and LH) independently reviewed the abstracts of the studied identified by the initial search to determine if they met the criteria. If a consensus could not be reached, a third expert was consulted. For all studies that met the inclusion and exclusion criteria, the following information was extracted: (1) publication information (first author's name, title, journal, year of publication); (2) demographic information (number of participants per group, gender distribution, mean age); (3) clinical information [course of migraine, headache frequency, visual analog scale (VAS)]; (4) information about the MRI protocol (scanner manufacturer and platform, field strength, head coil, scan sequence, repetition time (TR), echo time (TE), voxel size); (5) information about data processing (imaging processing software package, smooth kernel, covariates, statistical threshold); and (6) main results (brain region, voxels, peak coordinates (x, y, and z), and corresponding t-statistics). Note that SDM-PSI can transform different statistical values; in this study, results are standardized as *t*-values.

Quality assessment

The quality of each included study was assessed using a 10-point checklist based on a previous neuroimaging CBMA (21). This checklist

Abbreviations: VM, Vestibular migraine; VBM, Voxel-based morphometry; GM, Gray matter; CBMA, Coordinate based meta-analysis; SDM-PSI, Seed-based d mapping with a permutation of subject images; MRI, Magnetic resonance imaging; HC, Healthy control; CI, Confidence interval; MNI, Montreal Neurological Institute; VAS, Visual analog scale; DHI, Dizziness Handicap Inventory; TR, Repetition time; TE, Echo time; TFCE-FWER, Threshold-free cluster enhancement family-wise error rate; BA, Brodmann area; EM, Episodic migraine; CM, Chronic migraine; PIVC, Parieto-insular vestibular cortex; CGRP, Calcitonin gene-related peptides.

1 https://www.biorxiv.org/

primarily assesses the quality of the participants, methods, results, and conclusions (for further details, see Supplementary Table S1).

Meta-analysis

Meta-analysis was performed using SDM-PSI software 6.21.[2] SDM is a voxel-based meta-analysis method that allows researchers to integrate neuroimaging studies reporting peak coordinates (18, 19). This method has been previously applied to study a variety of neurological diseases.

The peak coordinates of significant GM differences in studies comparing VM patients and HCs were collected and organized. The standard SDM-PSI pipeline was then followed. Firstly, the maps of lower and upper bounds of possible effect sizes within a GM mask were calculated for each study after peak coordinates and effect sizes are entered into software. The effect sizes were then analyzed using MetaNSUE based on multiple imputations algorithms. Rubin's rules were applied to integrate results across multiple imputations, combining within-imputation precision and between-imputation variance to generate pooled effect size estimates (18, 22). Finally, we used the default recommended preprocessing parameters [full width at half maximum (FWHM) = 20 mm, mask = gray matter] and performed 1,000 permutations. Voxel-wise results were determined using a threshold-free cluster enhancement family-wise error rate (TFCE-FWER) of $p < 0.05$ corrected for multiple comparisons and an extent threshold ≥10 voxels.

Sensitivity analysis

Sensitivity analyses were conducted to confirm the stability of the CBMA results by excluding one study each time and repeating the analysis.

Heterogeneity and potential publication bias analysis

Analysis of heterogeneity between studies was assessed using the I^2 statistic; $I^2 > 50\%$ was considered to reflect significant heterogeneity. The risk of potential publication bias was assessed by extracting significant values for the main CBMA peak using Egger's test (23) with a threshold of $p < 0.05$.

Meta-regression analysis

Meta-regression analyses were planned to investigate the potential effects of clinical variables (e.g., headache frequency, disease duration) on GM alterations. These analyses would have been conducted using the SDM-PSI framework, with statistical significance assessed at $p < 0.05$ (TFCE-based FWER correction) and a cluster extent threshold of ≥10 voxels.

2 www.sdmproject.com

Interpretation with coordinated based databases

To further elucidate the cognitive functions associated with the brain regions identified in our meta-analysis (the coordinates [−44, −12, 16] and [48, −12, 8]), we conducted a post-hoc systematic functional decoding analysis using the Neurosynth and BrainMap databases. It was performed to provide a more comprehensive interpretation of our findings by linking the observed activation patterns to established neurocognitive domains. Specifically, the coordinates were queried in both databases to retrieve statistically significant associations with cognitive terms and activation profiles derived from a large corpus of neuroimaging studies. This approach, which has been validated in previous research (24), allowed us to contextualize the identified regions within a broader framework of cognitive function, thereby enhancing the interpretability and translational potential of our results.

Results

Study selection and characteristics

In our study, we conducted a comprehensive literature search using both English (Figure 1) and Chinese databases (Figure 2). In Figures 1, 2, we detail the process of literature screening and exclusion. In English databases, a total of 333 studies were screened, with 152 remaining after removing duplicates. Ultimately, 4 studies were included for CBMA analysis. The reasons for exclusion include: 140 studies excluded due to title and abstract not meeting research standards, 4 MRI-related studies, 1 surface-based morphometry (SBM) study, 1 whole-brain GMV comparison study, and 2 other types of structural studies. In Chinese databases, 49 articles were screened, with 29 remaining after removing duplicates. Ultimately, 1 study was included for CBMA analysis. The reasons for exclusion include: 19 studies excluded due to title and abstract not meeting research standards, 6 MRI-related studies, 1 SBM study, 1 study with unavailable coordinate data, and 1 study not involving whole-brain gray matter volume comparison.

Hence, five eligible studies were identified and their datasets were included in this study, which contained a total of 103 VM patients (83 female) and 107 HCs (82 female) (11–14, 25). Among the five included studies, four were identified from English databases and 1 from Chinese databases. The mean age did not differ significantly between the VM and HC groups [standardized mean difference = 0.23; 95% confidence interval (CI) = −0.04–0.50, z = 1.67, $p = 0.094$]. No significant difference in gender distribution was observed between VM patients and healthy controls ($\chi^2 = 0.05$, df = 1, $p = 0.823$), with comparable proportions of males [VM: 19.4% (20/103) vs. HC: 20.6% (22/107)] and females [VM: 80.6% (83/103) vs. HC: 79.4% (85/107)]. Of the five datasets, four reported headache frequency (mean frequency: 6.32 ± 4.04 days/month), four datasets reported VAS (mean score: 5.57 ± 2.06), and two reported DHI scores (mean scores: 47.83 ± 13.50). Paired comparisons confirmed no significant difference in sample sizes between VM and HC groups across studies [$t(4) = -1.37$, $p = 0.241$]. Additional details are provided in Tables 1, 2.

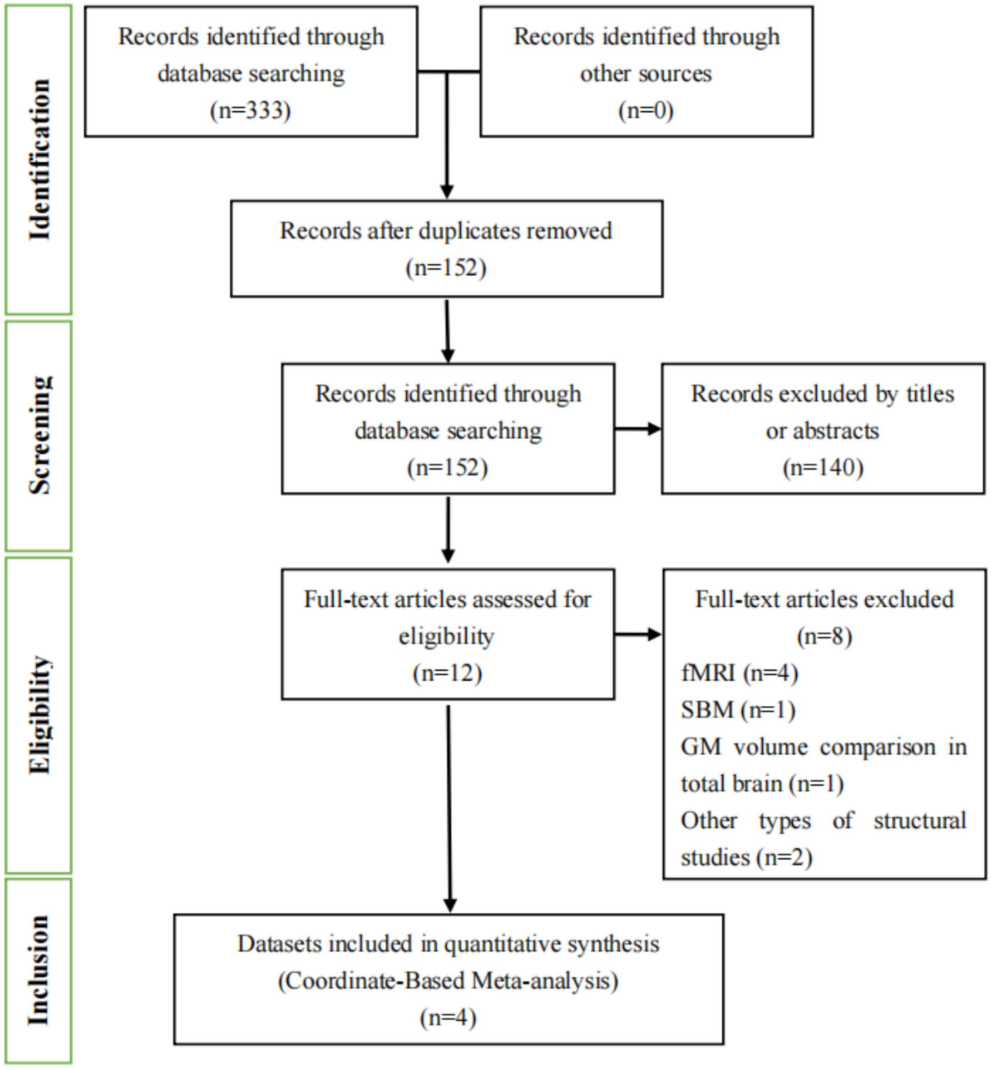

FIGURE 1
Flowchart of the literature selection process for the meta-analysis in English databases. fMRI, functional magnetic resonance imaging; SBM, surface-based morphometry; GM, gray matter.

Main CBMA results

The CBMA results revealed a significant decreased GM volume in patients with VM compared with HCs in the left rolandic operculum (SDM-Z = −3.68 $p = 0.004$, voxels = 629) with the peak MNI coordinate [−44, −12, 16] located in Brodmann area (BA) 48. The two largest clusters belong to the insula (voxels = 126) and rolandic operculum (voxels = 173) (Figure 3a and Table 3).

Sensitivity analysis

We performed a total of five analyses. Even using TFCE-based FWER correction ($p < 0.05$), the left rolandic operculum region was present in 3 of 5 results. During these analyses, we incidentally observed that excluding Zhe et al. (13)—where 14/20 patients had left-sided headaches—resulted in GM reductions in the right Heschel's gyrus (SDM-Z = −3.83 $p = 0.003$, voxels = 504) with the peak MNI coordinate [48, −12, 8] located in BA 48 (Figure 3b and Table 3). It is worth noting that the two largest clusters also belong to the insula (voxels = 243) and rolandic operculum (voxels = 173).

Heterogeneity analysis and publication bias analysis

The I^2 value obtained in this study was 19.35%, suggesting low heterogeneity between studies. The funnel plot showed no significant asymmetry in the left rolandic operculum. This result was confirmed by the Egger's test ($p = 0.826$) (Supplementary Figure S1).

Meta-regression analysis

Planned meta-regression analyses to explore the effects of clinical variables (e.g., headache frequency, disease duration) were not performed. The limited number of included studies ($n = 5$) falls below the recommended threshold for reliable meta-regression, which

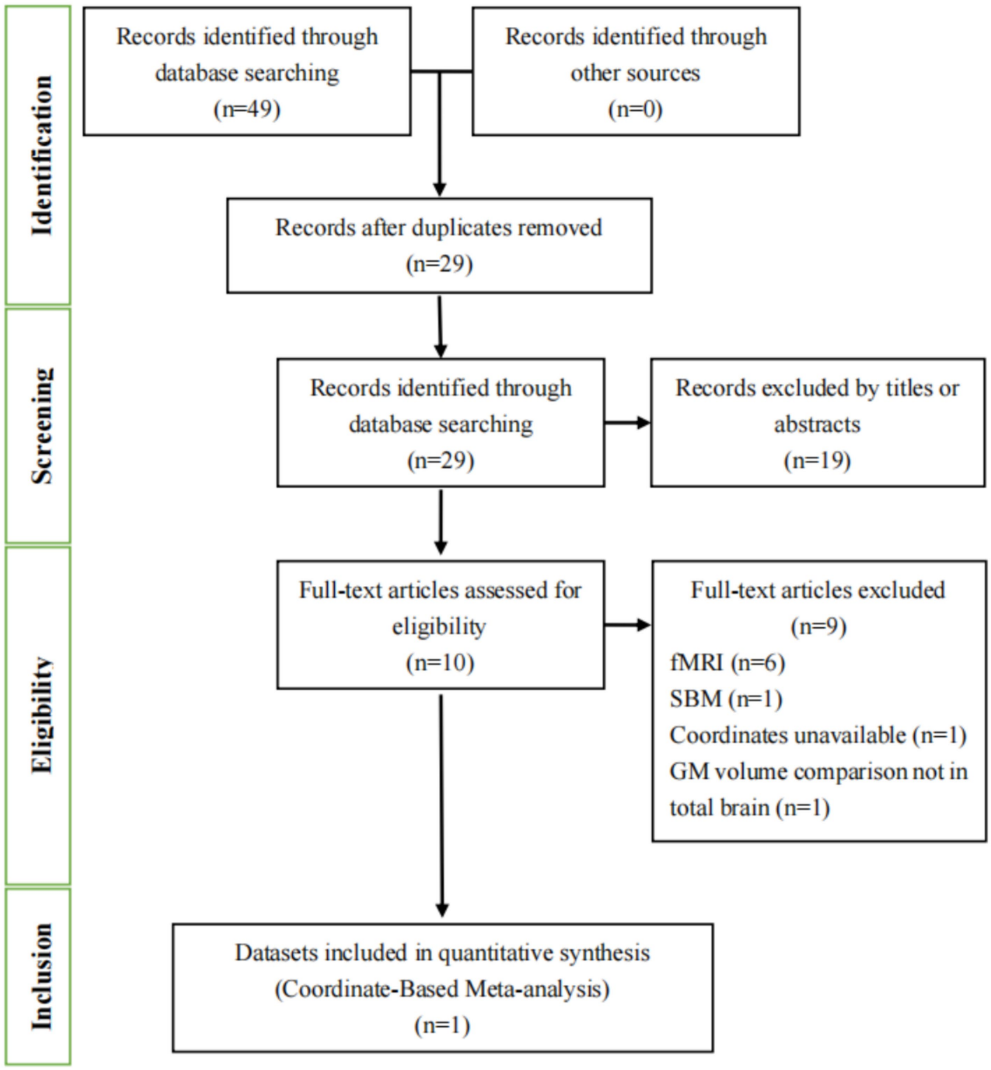

FIGURE 2
Flowchart of the literature selection process for the meta-analysis in Chinese databases. fMRI, functional magnetic resonance imaging; SBM, surface-based morphometry; GM, gray matter.

TABLE 1 Demographic and clinical characteristics of VBM studies were included in the meta-analysis.

Study	Sample (*n*)	Gender (Male /Female)	Age (Years ± SD)	Migraine history (Years ± SD)	Headache frequency (Days/month)	VAS (Mean, SD)
Obermann et al. (11)	VM = 17	3/14	42.71 ± 10.05	6.17 ± 4.51	6 ± 3.02	6.41 ± 1.88
	HC = 17	3/14	42.17 ± 9.26	–	–	–
Messina et al. (12)	VM = 19	7/12	40 ± 11.10*	15.7 ± 5.11*	6 (NA)	NA
	HC = 20	7/13	36.9 ± 9.6*	–	–	–
Zhe et al. (13)	VM = 20	2/18	38.60 ± 11.10	6.50 ± 6.27	6.90 ± 5.32	5.35 ± 1.84
	HC = 20	3/17	37.60 ± 11.84	–	–	–
Zhe et al. (14)	VM = 30	3/27	39.67 ± 11.10	8.39 ± 7.17	6.33 ± 4.89	5.23 ± 2.33
	HC = 30	4/26	37.67 ± 12.14	–	–	–
Wang et al. (25)	VM = 17	5/12	50.94 ± 12.13	5.62 ± 2.48	NA	5.60 ± 1.87
	HC = 20	5/12	45.50 ± 5.17	–	–	–

*The original text does not explicitly mention the standard deviation, based on the results of Furukawa et al. (60), the mean of the standard deviation of similar studies is taken instead.

TABLE 2 Imaging characteristics of the VBM studies were included in the meta-analysis.

Study	Scanner	Field	Head coil	Sequence	TR/TE (ms)	Voxel size (mm^3)	Software	FWHM (mm)	Threshold	Quality score*
Obermann et al. (11)	Siemens Avanto	1.5 T	8 channel	MPRAGE	2400/3.53	1*1*1	SPM 8	10	$p < 0.001$ uncorrected	9
Messina et al. (12)	Philips	3.0 T	NA	3D-FFE	25/4.6	0.89*0.89*0.8	SPM 12	8	$p < 0.05$ (FWE) and $p < 0.001$ uncorrected	9
Zhe et al. (13)	Philips Ingenia	3.0 T	16 channel	MPRAGE	1900/2.26	1*1*1	SPM 12	8	$p < 0.05$ (FDR)	9
Zhe et al. (14)	Philips Ingenia	3.0 T	16 channel	MPRAGE	1900/2.26	1*1*1	SPM 12	8	$p < 0.05$ (FDR)	9
Wang et al. (25)	Philips	3.0 T	8 channel	3D-FFE	7.7/3.7	1*1*1	FSL	4	$p < 0.001$ (FWE)	8.5

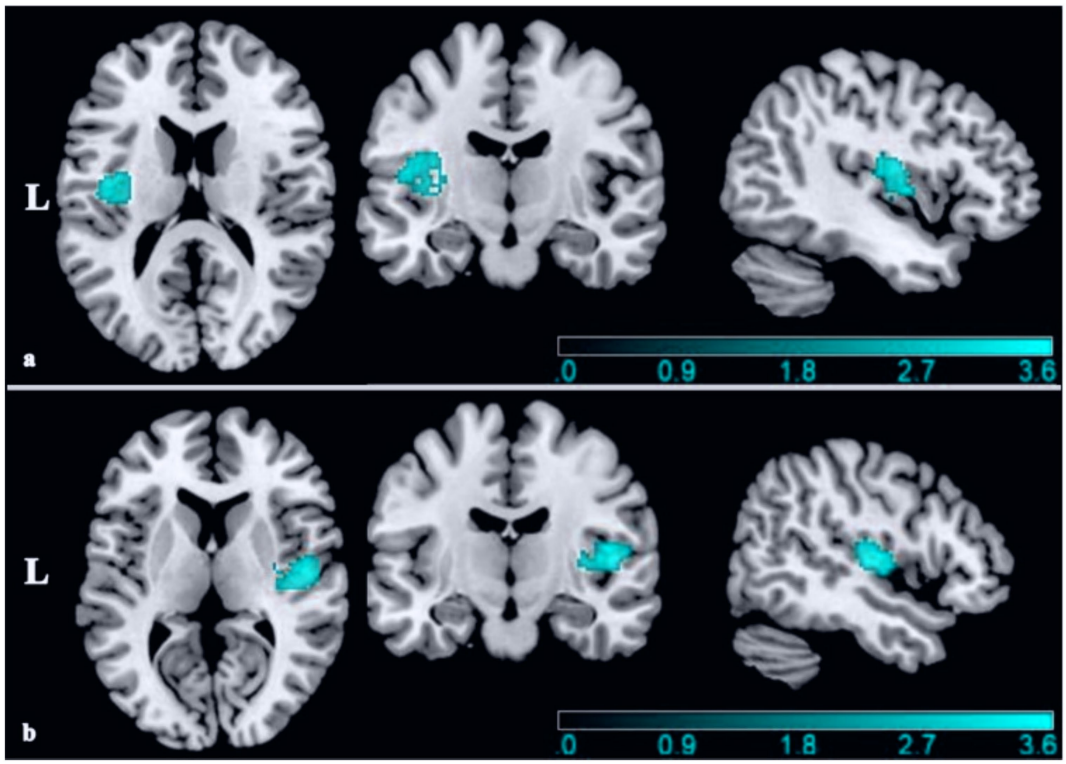

FIGURE 3
(a) The GM volume alterations in this meta-analysis when all datasets included (MNI coordinate: −44, −12, 16, SDM-Z = −3.68, TFCE corrected $p = 0.004$, Voxels = 629); **(b)** the GM volume alterations in this meta-analysis when Zhe 1 excluded (Exploratory finding after excluding a study with left-sided headache predominance) (MNI coordinate: 48, −12, 8, SDM-Z = −3.83, TFCE corrected $p = 0.003$ Voxels = 504). The bule color bar indicates the Z-value of the decreased GM volume. L, left; MNI, Montreal Neurological Institute; SDM, seed-based d mapping; TFCE, threshold-free cluster enhancement.

typically requires data from at least 10 studies to ensure sufficient statistical power and avoid overfitting.

Cognitive function of the coordinates

In an effort to delve deeper into the cognitive functions associated with the coordinates we found, a comprehensive meta-analysis was conducted, utilizing both Neurosynth and BrainMap databases for the exploration of the specific sets of brain coordinates ([−44, −12, 16], [48, −12, 8]).

Within the Neurosynth database, analysis of the coordinate [−44, −12, 16] resulted in the identification of 190 studies within a 6 mm radius. A manual review of these studies highlighted key articles related to the operculo-insular cortex, emphasizing interoceptive and multimodal functions pertaining to tactile, nociceptive, and vestibular representations (26), including studies on cold allodynia (27) and the functional connectivity of the

TABLE 3 Regional differences in GM volume between patients with VM and healthy controls in the meta-analysis.

Condition	Brain regions	Peak MNI coordinate	SDM-Z value	TFCE *p*-value	Numbers of Voxels	Cluster breakdown
All datasets included	Left rolandic operculum	−44, −12, 16	−3.68	0.004	629	Left insula, BA 48 Left rolandic operculum, BA 48 Left lenticular nucleus, putamen, BA 48 Left Heschel gyrus, BA 48 Left superior temporal gyrus, BA 48 Left superior longitudinal fasciculus III Left fronto-insular tract 4 and 5 Left striatum
When Zhe 1 excluded	Right Heschel gyrus	48, −12, 8	−3.83	0.003	504	Right insula, BA 48 Right rolandic operculum, BA 48 Right heschl gyrus, BA 48 Right superior temporal gyrus, BA 48 Right lenticular nucleus, putamen, BA 48 Right fronto-insular tract 5 Corpus callosum

MNI, Montreal Neurological Institute; SDM, seed-based d mapping; TFCE, threshold-free cluster enhancement; BA, Brodmann area.

vestibular cortex (28). Dominant cognitive terms associated with this coordinate were notably centered around "noxious" sensations and pain, as shown in Figure 4A.

Further insights were garnered through the Mango's paradigm analysis, which did not reveal significant findings within a 6 mm radius but unfolded critical associations within larger radius: at 9 mm, associations with pain monitoring/discrimination were observed (Z-score = 3.504); expanding to a 12 mm radius further included vestibular stimulation (Z-score = 4.001), chewing/swallowing (Z-score = 3.869), and overt reading tasks (Z-score = 3.352), as shown in Figure 4C. Moreover, a notable association with schizophrenia was identified (Z-score = 3.79), alongside behavioral perceptions related to somesthetic pain (Z = 3.312).

The investigation of the coordinate [48, −12, 8] brought to light cognitive associations within a 6 mm radius, specifically related to music comprehension and passive listening, marking a stark contrast to the primarily pain-related findings of the previous coordinate. The related terms obtained from neurosynth are shown in Figure 4B. When the radius was increased, findings expanded to include pain monitoring/discrimination and vestibular stimulation, similar to the [−44, −12, 16] coordinate. Within broader radius, additional diseases such as schizophrenia (Z-score = 3.374), multiple sclerosis (Z-score = 3.242), and migraine (Z-score = 2.192, not significant) were correlated, underlining the multifaceted cognitive implications of these regions.

Discussion

Gray matter reductions in vestibular-migraine

In this study, we used an improved SDM-PSI method to quantify GM volume alterations in VM patients compared to HCs. This meta-analysis comprised 5 whole-brain VBM studies including 103 VM patients and 107 HCs. VM patients showed significantly decreased GM volumes in the BA 48 region, including the left insula and left rolandic operculum, compared to HCs. The left rolandic operculum GM reduction remained significant in 3/5 sensitivity analysis. Overall, these findings support that GM volume alterations do occur in VM patients, which may help us to further explore the pathophysiological mechanisms of VM.

In the five datasets included in this study, the finding of a reduction in GM volume in the left posterior insula–operculum region (left insula and left rolandic operculum) was present in three studies; similar brain regions were not reported in the other two studies (12, 25). Notably, Messina et al. (12) reported that VM patients had increased GM volume in frontal and occipital regions compared to HC, which was not found in other VBM studies. The following factors may have contributed to this result. Firstly, there are ethnic differences: the population in three of the five studies was Asian. Secondly, over half (11/19) of VM patients included in Messina et al.'s (12) study were taking anti-migraine medication. In addition, patients were required to be free of headache for 1 month prior to scanning, whereas other studies generally required 1–3 days free of headache before and after scanning, which may reflect GM volume alterations after treatment.

Previous VBM studies have shown that a wide range of brain regions are affected by VM, such as occipital, thalamic, and cerebellar regions (11–14, 25). In contrast, the GM volume alterations in this study were relatively concentrated in anatomically and spatially nearby brain regions. This difference may relate to the fact that some previous studies adopted more lenient statistical thresholds, such as not correcting for multiple comparisons ($p < 0.001$). The present study used a TFCE-based FWER correction ($p < 0.05$), which may have led to fewer positive findings. Different scanners, field strengths, sequences, TR/TE, data processing methods, and covariates in regressions may also have affected the results (29, 30). The clinical characteristics of the patients, such as the primary side of the headache attack, may also have affected the results. This is discussed in more detail below.

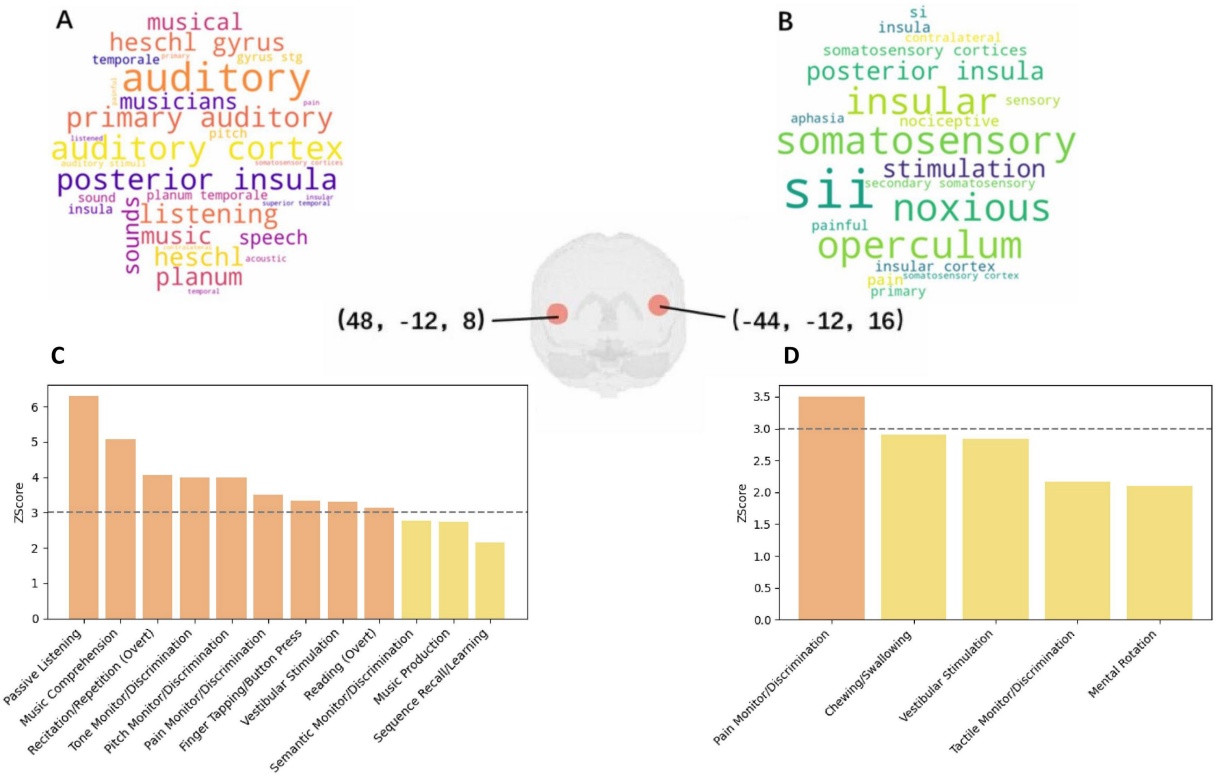

FIGURE 4
(a) Word Cloud for Coordinate [48, –12, 8] from Neurosynth; **(b)** Word Cloud for Coordinate [–44, –12, 16] from Neurosynth; **(c)** Paradigm Analysis for Coordinate [48, –12, 8] at nine radius; **(d)** Paradigm Analysis for Coordinate [–44, –12, 16] at nine radius.

Lateralization and pathophysiological implications

The observed GM alterations were predominantly localized to the left hemisphere, particularly in the rolandic operculum and posterior insula. This lateralization aligns with evidence of asymmetric vestibular processing, where the right hemisphere typically dominates vestibular function in right-handed individuals (31, 32). Notably, 4/5 studies explicitly recruited right-handed participants, and the left-lateralized findings persisted even when excluding Obermann et al. (11), which did not report handedness. While the incidental observation of right-lateralized GM reductions after excluding Zhe et al. (13) in sensitivity analysis suggested a potential association between headache laterality and GM asymmetry. The link to headache lateralization is exploratory, as laterality data were inconsistently reported. Obermann et al.'s (11) study did not mention the patients' habitual hand, but the GM volume alterations remained localized to the left hemisphere when Obermann et al.'s (11) study was excluded in the sensitivity analysis. The relationship between headache laterality and structural changes remains unresolved. A prior study in migraine with aura found no GM differences tied to headache side (33), while others report contralateral cortical thinning in typical migraine. These discrepancies highlight the need for prospective studies with standardized laterality assessments. Our findings should not be overinterpreted to suggest a causal link between headache side and ipsilateral GM changes. Rather, they underscore the necessity of controlling for laterality in future VM imaging studies.

Pathophysiological implications

The brain regions showing decreased GM volume in the present study were mainly part of the posterior insula and operculum regions, which both belong to the parieto-insular vestibular cortex (PIVC) (34). The PIVC is thought to be the core of the vestibular information processing center in macaque monkeys and is composed of the posterior insula, retroinsular region, and parietal operculum (35, 36); in humans, the equivalent brain regions might be the cytoarchitectonic area OP2 in the parietal operculum (28). Abnormalities in these regions have been reported in other types of neuroimaging studies of VM. A positron-emission tomography (PET) study reported increased metabolism in the posterior insula during the ictal phase compared to the interictal phase (37). A functional magnetic resonance imaging (fMRI) study revealed an altered blood oxygen level-dependent (BOLD) signal in this region (38). Our study supports these findings and suggests consistency between structural and functional alterations in these regions. Structural and functional alterations in PIVC regions can also be observed in other vestibular disorders, such as bilateral vestibulopathy (39) and chronic subjective dizziness (40). A VBM study of a stroke population also showed that structural damage in PIVC regions was closely associated with the development of

vestibular symptoms (41). Therefore, it is reasonable to think that impairments to these brain regions cause vestibular symptoms.

More importantly, the posterior insula and operculum regions are also involved in processing of nociceptive information (42, 43). The posterior insula receives nociceptive afferents from the thalamic nucleus and interacts with brain regions such as the somatosensory cortex and cingulate gyrus, and the operculum is functionally analogous to the insula (9, 44–46). Structural and functional alterations in this region have also been reported in studies of episodic migraine (EM) and chronic migraine (CM) (47–51), which further confirm the findings of our study. Maleki et al. (49) showed decreased GM volume and functional activation in the insula in high-frequency migraineurs compared with low-frequency migraineurs, potentially implying that attack frequency leads to brain alterations. Schwedt et al. (52) constructed classifiers consisting of multiple structural MRIs that were highly accurate at identifying if patients had CM. Another study found that migraine duration may further increase the accuracy of classifiers (53). Taken together, these studies suggest that GM atrophy in the insula and its surrounding region correlate with the burden of migraine attack. Interestingly, vestibular syndrome often begins several years after typical migraine and is more common in CM (5). Given the heterogeneity of VM, we suggest that, for a subsample of VM patients, GM atrophy may be the result of recurrent headache attacks. The correlation between the headache side and GM atrophy side also suggests this possibility.

Clinical applications

Regarding clinical applications, previous studies have shown that the regions around the insula may play an important role in migraine treatment (54–56). Triptans were shown to decrease activation in the posterior insular cortex compared with saline control (55). Moreover, it has been shown that the GM volume of the PIVC is negatively correlated with the Dizziness Handicap Inventory (DHI) score in VM patients (14). Considering the response of brain regions to anti-migraine treatments and its correlation with clinical indicators, it may serve as a target assessing the effects of treatment. Most importantly, we need to reduce headache attacks to reduce vertigo attacks.

Overall, the existing evidence is insufficient for causal deduction. It is not clear whether structural alteration in the PIVC region is the cause of vertigo or a compensatory response to impairment of the rest of the vestibular network. Although studies suggest GM atrophy to be hypofunctional (49, 57), this warrants further confirmation. The development of a multicenter imaging database of migraine patients and long-term follow-up studies will be important for elucidating these questions.

Limitations

The primary limitations of this study stem from the scarcity of available neuroimaging data on vestibular migraine (VM), with only five studies meeting inclusion criteria. The small sample size (103 VM patients and 107 HCs across all datasets) precludes meta-regression analyses to evaluate the influence of clinical variables such as headache frequency, vertigo severity, or pain intensity, limiting our ability to disentangle migraine-specific contributions from vestibular-related GM alterations. Notably, all included studies had modest per-group sample sizes (<40 participants), which may amplify random error and reduce the stability of effect size estimates. Technical heterogeneity across studies—including variability in MRI protocols (1.5 T vs. 3.0 T scanners), statistical thresholds (uncorrected vs. FWE-corrected), and software pipelines (SPM vs. FSL)—further complicates the interpretation of spatially convergent findings, despite our use of TFCE-FWER correction to minimize false positives. While the SDM-PSI algorithm improves sensitivity over traditional CBMA methods, it relies on assumptions of unbiased reporting, potentially excluding studies with one-tailed statistical approaches. Additionally, post-hoc explorations of headache lateralization were limited by inconsistent reporting of symptom laterality in original studies and were not pre-specified in the PROSPERO protocol, necessitating cautious interpretation. Finally, the cross-sectional design precludes causal inferences regarding whether GM reductions in the posterior insula–operculum complex represent a predisposing neural vulnerability or a consequence of recurrent nociceptive-vestibular network activation, underscoring the need for longitudinal multimodal investigations (58, 59).

Conclusion

CBMA confirmed a significantly reduced GM volume in VM patients. The GM volume alterations are mainly located in the posterior insula–operculum region, which is involved in both the nociceptive and vestibular networks system. Exploratory observations regarding headache lateralization warrant further investigation. Given that the causal relationship between structural alterations and the development of vestibular symptoms remains unclear, further structural and functional imaging paradigms, as well as longitudinal studies, are necessary to draw more precise conclusions. Furthermore, the headache side of the patient should be taken into account when designing migraine-related neuroimaging studies in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

XF: Writing – original draft, Writing – review & editing. LD: Writing – original draft, Writing – review & editing. HL: Conceptualization, Software, Writing – review & editing. KW: Supervision, Writing – review & editing. JZ: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1495423/full#supplementary-material

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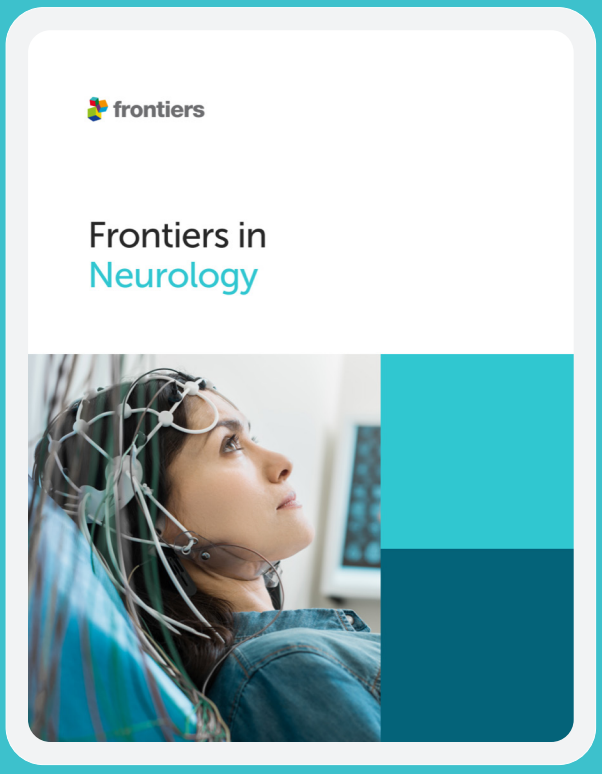

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