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Effectiveness of low dose thyroxine in patients with subclinical hypothyroidism and migraine; systematic review and meta-analysis

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Abstract

Background Subclinical hypothyroidism (SCH) is defined by elevated thyroid-stimulating hormone (TSH) levels alongside normal free thyroxine (T4) and triiodothyronine (T3) levels. Emerging evidence suggests a link between SCH and migraine disorders, including both episodic and chronic migraine. Given this association, researchers have explored whether correcting mild thyroid dysfunction with low-dose levothyroxine could alleviate migraine symptoms in affected individuals. This study investigates the potential efficacy of low-dose thyroid replacement therapy in reducing migraine frequency and severity among patients with comorbid SCH and migraine.

Methods A search was conducted on Cochrane Central, Medline, Embase, Web of Science Core Collection, and Scopus to identify randomized clinical trials (RCTs), case-control studies, and cohort research studies evaluating the use of low-dose thyroxine in patients with subclinical hypothyroidism (SCH).

Results This review analyzed four studies, two of which qualified for meta-analysis. The findings suggest a potential association between (SCH) and migraine. Notably, levothyroxine treatment in hypothyroid patients appeared to correlate with reduced migraine frequency and headache severity. However, while the meta-analysis showed a trend toward migraine reduction with thyroxine therapy, the results did not reach statistical significance - likely due to the limited study sample included in the analysis.

Conclusion The study highlights the importance of thyroid screening in migraine management, due to the link between hypothyroidism and migraines. It recommends routine thyroid function assessments for migraine patients and suggests personalized treatment approaches. Early intervention can minimize migraine episodes and improve quality of life. Adherence to low dose levothyroxine regimens can reduce migraine frequency. Further research is required to elucidate the underlying mechanisms, optimize treatment protocols, and explore potential comorbidities.

Keywords Hypothyroidism, Levothyroxine, Migraine, Headache

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Background

Migraine is the most common type of headache disorder and a leading cause of health impairment worldwide, despite the existence of over 200 known headache conditions [1]. Migraine is a neurological condition characterized by frequent headaches, light and sound sensitivity, nausea, and vomiting. Its pathogenesis is influenced by genetic susceptibility, neurovascular alterations, cortical spreading depression (CSD), and neuronal malfunction [2]. Cortical spreading depression is a main mechanism of migraine, causing depolarization of neurons and glia across the cerebral cortex. Neurovascular changes, such as blood flow changes and inflammatory mediator production, also contribute to migraine. Migraines have a significant economic impact, especially in high-income countries [3]. Hormonal considerations contribute to the higher prevalence of migraine in women compared to males. The interictal stage can be challenging due to lifestyle constraints and fear of future attacks. Migraine episodes can be incapacitating, impairing social, academic, and occupational activities. To improve the quality of life for migraine affected individuals, it is crucial to understand the underlying processes and address their effects through effective therapies and interventions [4].

Although primary headaches (such as migraines, tension-type headaches, and cluster headaches) are more prevalent and affect a large portion of the population, secondary headaches are of considerable clinical concern because they are linked to potentially serious underlying conditions [5, 6]. Nearly all secondary headaches are classified according to their underlying causes, both epidemiologically and medically [7]. Migraine and tension-type headache are the only headache disorders (those without an obvious underlying cause) that are prevalent enough to significantly impact population health [8]. However, given the widespread co-occurrence of migraine and hypothyroidism—particularly subclinical hypothyroidism—it is crucial to examine whether these conditions are merely coincidental or if they share a bidirectional causative relationship [9]. Notably, headache is present in one-third of patients with hypothyroidism, but whether this represents true migraine, tension-type headache, or an overlap of both remains unclear.

Migraine, tension-type headaches, and medication-overuse headaches are the primary causes of most headache-related disorders, with migraine having the greatest impact on population health [10, 11].

Normal thyroxine (T4) and increased thyroid stimulating hormone (TSH) values are hallmarks of subclinical hypothyroidism [12]. Variations in TSH levels are significantly greater than variations in T4 levels [13]. According to studies, the prevalence of subclinical hypothyroidism varies by population and ranges from 3 to 10%, with the incidence rising to 18–20% in elderly patients [14, 15]. Women and elderly people are more likely to have subclinical hypothyroidism [16]. Observational studies have linked subclinical hypothyroidism (defined as TSH ≥ 10 mIU/L) to an increased risk of both coronary artery disease (CAD) events, fatal stroke, and congestive heart failure [17–19].

As more high-sensitivity thyroid function tests become available, the prevalence of this condition is going to increase. In the United States, levothyroxine is the second most often prescribed drug [20]. This could be partially explained by the greater awareness of subclinical hypothyroidism and the subsequent treatment or trials of levothyroxine replacement medication. According to a UK study, the percentage of people with hypothyroidism who receive treatment grew from 2.3 to 3.5% between 2005 and 2014 [21].

Previous studies have associated hypothyroidism to migraines and suggested that treating hypothyroidism may reduce the intensity of migraines [22–25]. Although the role of thyroid replacement medication in managing headaches in these patients is well-established, yet the underlying mechanism remains unclear.

Despite recent research suggesting that migraine is more common in patients with subclinical hypothyroidism, there is uncertainty regarding the effectiveness of thyroid replacement medication in treating migraines in these individuals [26–28]. Additionally, no previous systematic review and meta-analysis have been conducted on this topic. Therefore, this study assessed the effectiveness of low-dose thyroid replacement therapy as a supplemental treatment for individuals who suffer from both migraine and subclinical hypothyroidism.

Materials and methods

Protocol registration and guidelines

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed in the current review [29, 30]. Prior to starting, the International Prospective Register for Systematic Reviews (PROSPERO) received and approved the review protocol with the ID [CRD42024543388].

Eligibility criteria

Randomized clinical trials (RCTs), case-control studies, and cohort research designs evaluating the effectiveness of levothyroxine in adult patients diagnosed with migraine and subclinical hypothyroidism were considered for inclusion.

Search scheme

A systematic electronic database search was conducted from October 15 to 30, 2024, across the Cochrane Central, Medline, Embase, Web of Science Core Collection, pubmed and Scopus databases. The aim was to identify

research studies that evaluated the effectiveness of low-dose thyroid replacement therapy as an adjunct treatment for patients with subclinical hypothyroidism who experience migraines. A controlled search using medical vocabularies (MeSH) was conducted, combining the following: (a) keywords related to the population ("hypothyroidism" OR "hypothyroid" OR "thyroid hypofunction" OR "thyroid dysfunction" OR "subclinical hypothyroidism"), (b) terms for the intervention ("levothyroxine" OR "levothyroxine sodium" OR "L-thyroxine"), and (c) terms related to the outcome of interest ("Migraine" OR "headache"). These elements formed the search strategy.

Screening process

All retrieved literature (n = 456) was imported into EndNote® and Rayyan® software for further screening and removal of duplicates. Two independent reviewers (FAA and DHQ) selected studies based on the eligibility criteria set for this systematic review. The first screening phase involved reviewing titles and abstracts to identify articles that met the inclusion criteria. Selected papers were then read in full before being included in the final dataset.

Any study in which there was a disagreement among the reviewers in the first phase was included and examined in the full-text phase. Any disagreements were settled by consensus or by a third reviewer's involvement (MNN).

Procedure for gathering data

Information was gathered from each included study by two independent members of the research team. A third reviewer's intervention or consensus was used to settle any disputes that occurred during the data collection process. Data were extracted from eligible articles, collecting information on the following variables: study title, first author(s), publication date, sample size, disease course and severity, age, gender, disease duration, intervention details, outcome indicators, adverse events, and risk of bias assessment were all gathered for the baseline description.

Outcomes

The effect of levothyroxine on the frequency of migraine attacks was the primary outcome. This study evaluated outcomes related to changes in migraine severity, improvements in quality of life, and potential side effects or complications of low-dose thyroid replacement therapy, including weight fluctuations, heart rate variations, and other thyroid-related symptoms. It also examined the impact of long-term thyroid replacement therapy on migraine management and thyroid function.

Synthesis and analysis of data

The results provided information about demographic characteristics in a narrative way. To evaluate the impact of levothyroxine against a placebo on reducing the frequency of migraines, a meta-analysis was conducted. When the odds ratio was available for the study, it was used to determine the number of events in the experimental and control groups. R software was used for the meta-analysis. The I2 and Cochran's Q tests were used to assess heterogeneity across studies. When heterogeneity was less than 50%, meta-analysis was carried out using a fixed-effect model. A random-effects model was employed when heterogeneity exceeded 50%.The completed PRISMA checklist is provided as a supplementary file (Supplementary File 1).

Risk of bias in individual studies

Two independent reviewers used the Newcastle Ottawa technique to evaluate the included studies' risk of bias. Each study's primary outcome has its risk of bias evaluated. "Good quality," "satisfactory quality," and "unsatisfactory quality" were the ratings given to the studies. The included RCT was assessed by risk of bias tool of Cochrane (ROB-2).

Results

Search results

A total of 456 records were identified by our search, 28 duplicate records were found, and 364 records were excluded based on title and abstract screening. For determining eligibility, the complete text of the remaining 64 records was retrieved. Four studies were determined to be eligible for consideration following a thorough evaluation (Fig. 1).

Characteristics of the included studies

The general characteristics of the selected studies are shown in Table 1. There were 4 studies involving 322,300 participants in total. Randomized controlled studies (n = 1), case-control (n = 1), and, cohort (n = 2) are examples of diverse study designs.

Characteristics of the studies participants

The studies focused on the relationship between migraines, hypothyroidism, and levothyroxine treatment in different populations. The majority of participants were females, reflecting the higher prevalence of hypothyroidism and migraines in women. The studies targeted specific populations, including episodic/chronic migraine patients, those adhering to levothyroxine therapy, and pregnant women. Exclusion criteria were used to avoid confounding conditions like thyroid cancer, pregnancy complications, or dose instability (Table 2). The two tools that were most specifically stated in the included studies

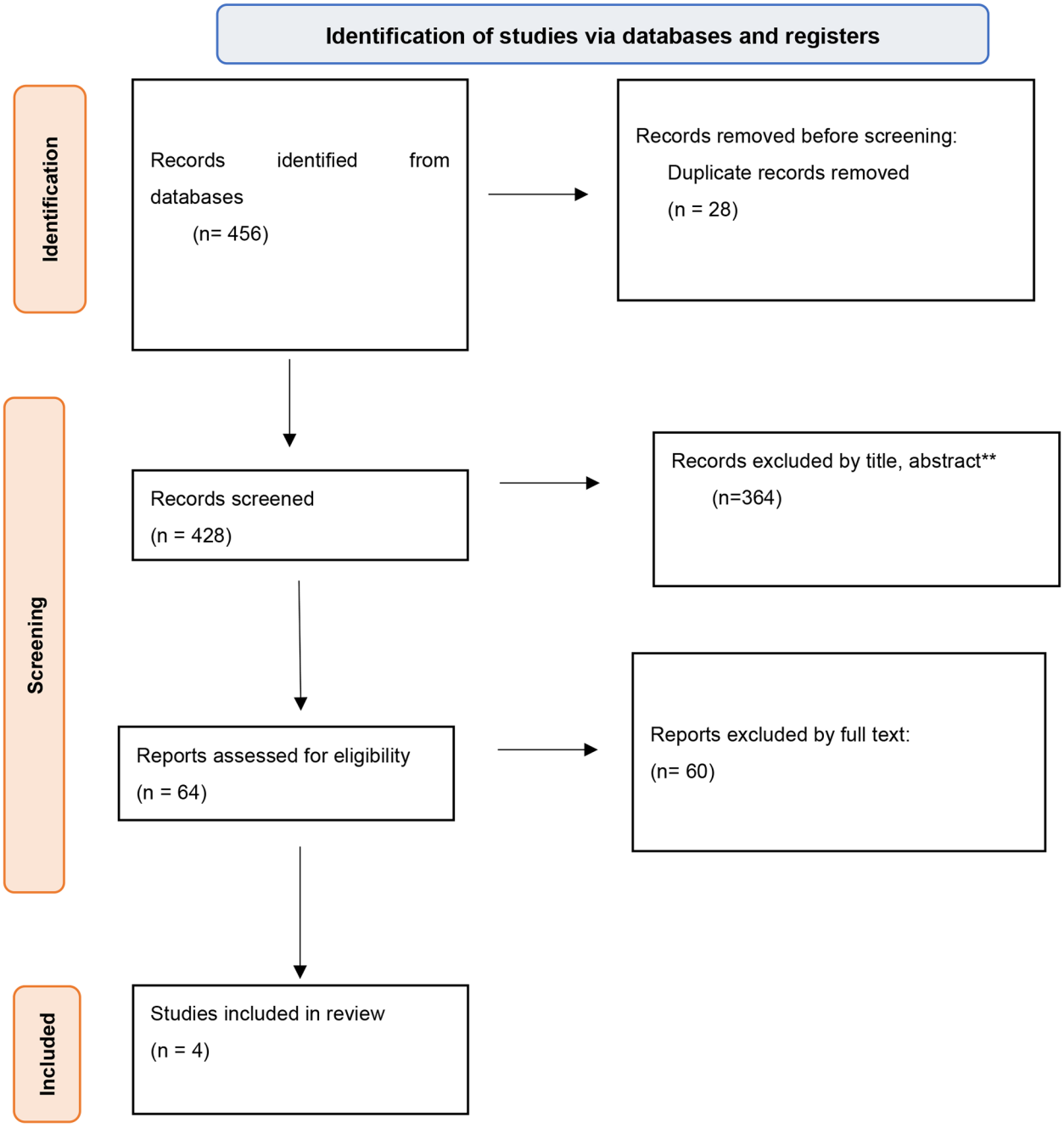

Fig. 1 PRISMA flow diagram

Table 1 General characteristics of the included studies

Study ID	Country of Study	Type of Study	Sample Size	Duration of Follow-Up	Quality assessment
Dev, 2023 [22]	India	A randomized controlled trial	87	3 months	**Some concern**
Filipchuk, 2022 [31]	Argentina	Case control	137	6 months	Satisfactory quality
Hepp, 2018 [32]*	USA	Matched cohort	318,628	1 year	Good quality
Lage, 2020 [33]*	USA	Retrospective cohort	3448	NA	Satisfactory quality

* Included in the meta-analysis

Table 2 Characteristics of the studies participants'

Study ID	Number of Participants	Age	Gender	Inclusion criteria	Exclusion criteria
Dev, 2023 [22]	87 patients	18 to 50 years	5 male – 82 females	The study included patients with episodic migraines diagnosed with subclinical hypothyroidism and negative anti-thyroid peroxidase antibody levels.	Patients with thyroid disease, abnormal neurological examinations, pregnancy, chronic illnesses affecting thyroid hormone levels, and regular drug intake.
Filipchuk, 2022 [31]	111	Mean age of patients with episodic migraine: (36.22 +/- 11.28); mean age of patients with chronic migraine (40.43+/- 11.28)	92.5% females (Episodic migraine), 93.2% females (chronic migraine)	Migraine patients and those receiving a stable dose regimen of levothyroxine for at least 6 months and considered euthyroid (corrected) if hypothyroidism was present	Patients under evaluation for possible hypothyroidism, or those in the dose-titration process, were excluded
Hepp, 2018 [32]	Equal number of adherent and non-adherent to levothyroxine (LT4) (159314)	Equal to and older than 18 years	female adherent"73.9%, non-adherent:75.9%	Patients have two separate claims for hypothyroidism (identified by ICD-9-CM of 243.xx or 244.xx, except 244.2x and 244.3x) between 1 January 2012 and 31 December 2014 and at least one prescription for levothyroxine (LT4) filled over that same time horizon	Patients younger than age 18 as of the index date or if they were diagnosed with thyroid cancer (ICD-9-CM of 193.xx) or pregnancy (ICD-9-CM of 630.xx–679.xx, V22.xx, V23.xx, V30.xx–V39.xx or V72.42) at any time from the start of the pre-period through the end of the post-period.
Lage, 2020 [33]	2340 treated with levothyroxine, 1108 untreated	32.76 ± 4.80 years	All females	Women ages 18–49 years who were identified as both hypothyroid and pregnant in 2014 were included in the study	Patients with thyroid cancer or those without continuous insurance coverage during their pregnancy were excluded from the analyses.

Table 3 Description of Levothyroxine treatment

Study ID	Description of Low Dose Thyroxin	Dosage of Thyroxin Administered	Duration of Treatment	Description of Control Group
Dev, 2023 [22]	Patients take levothyroxine on an empty stomach an hour before food, and avoided medications that interfere with absorption or took it four hours or more after ingestion.	25 mg of levothyroxine supplementation	3 months	Both groups continued or received treatment for migraine prophylaxis.
Filipchuk, 2022 [31]	N/A	N/A	At least 6 months	A post-hoc case-control supplementary; selecting age, gender, and BMI matching controls from the episodic migraine sample database to be compared with the "cases" patients.
Hepp, 2018 [32]	Adherent when they took LT4 at least 80% of the days in the postperiod	NA	1 year	Non-adherent to LT4
Lage, 2020 [33]	NA			Untreated with levothyroxine

to assess the migraine are the MIDAS scale Dev, 2023 [22] and the ICHD-3 criteria Filipchuk, 2022 [31]. Using clinical records and diagnostic codes, migraines were evaluated as a comorbidity in hypothyroidism patients.

A summary of studies regarding the use of low-dose thyroxin treatment is shown Table 3, with particular attention paid to details such dosage, duration, and descriptions of the control group. The studies differ significantly in terms of characteristics. Apart from a few studies that provided information on patient instructions or adherence e.g., majority of studies do not provide a precise description or procedure for low-dose thyroxin administration [22, 32]. Not all studies provide the same dosage information. The recommended dosage was 25 mg [22]. There are studies that show short-term durations of approximately 3 to 6 months [22, 31]. However, studies like Hepp, et al. (2018) suggest long-term durations of 12 months [32]. Control groups getting migraine prophylaxis were included as in Dev, et al. (2023) trial

Table 4 Outcomes of the included studies

Study ID	Primary Outcomes	Secondary Outcomes	Effect Size
Dev, 2023 [22]	Levothyroxine treatment significantly decreased headache frequency and severity compared to the placebo group at three months of follow-up. Additionally, the treatment significantly decreased the MIDAS score, indicating a significant improvement in headache management.		Headache Frequency Mean Difference: 1.61, Headache Severity Mean Difference: 1.15 MIDAS Score Mean Difference: 2.15
Filipchuk, 2022 [31]	Treated hypothyroidism (dose stable) was significantly more prevalent among chronic migraine patients (29.55%) than in episodic migraine patients (8.96%; $\chi = 7{,}937$, $p < 0.01$), with an estimated odds ratio of 4.26 (95% confidence interval = 1.48 to 12.30).	N/A	There were no significant differences regarding age, gender proportions, or BMI between the two groups
Hepp, 2018 [32]	Reduction of migraine frequency. Adherent patients were less likely to be diagnosed with comorbid conditions like Addison's disease, bipolar disorder, chronic kidney disease, depression, migraine, obesity, type 1 or 2 diabetes, and reduced migraine frequency.	Adherent patients had slightly higher drug costs but lower costs in other categories such as total, hospital, ER, outpatient, and laboratory expenses.	OR: 0.94
Lage, 2020 [33]	Pregnant women, pregnant women treated with levothyroxine were significantly younger, had a lower Charlson Comorbidity Index score and had lower rates of comorbid type 2 diabetes and migraines		Migraine % in treated with levothyroxine was 2.7% compared to 4.1% in untreated

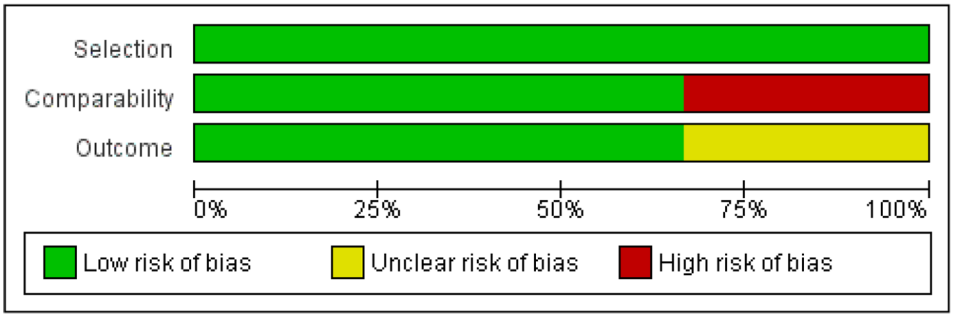

Fig. 2 Risk of bias graph

[22]. Other studies employed untreated or non-adherent groups as controls [32, 33].

Effects of managing hypothyroidism on headache and migraine symptoms

This study demonstrated a significant relationship between migraines, hypothyroidism, and levothyroxine treatment. Levothyroxine substantially decreases the frequency, intensity, and disability scores of migraines. Compared to women who do not receive treatment, pregnant women who take levothyroxine had fewer migraines. Patients with chronic migraines are more likely than those with episodic migraines to experience treatment-stable hypothyroidism. Following a levothyroxine therapy lowers the frequency of migraines and is linked to less comorbid conditions such as depression and diabetes (Table 4).

Quality assessment of the included studies

Figures 2 and 3 provide an overview of the studies' risk of bias evaluations. Each study exhibited a low risk of bias in the selection domain, suggesting that participant allocation and selection were appropriately conducted. However, a substantial risk of bias in the comparability domain was present in about 25% of the studies, suggesting potential issues with group comparability. The risk of outcome bias was low in about 75% of the research, while the remaining studies had an uncertain risk, suggesting that the results may not have been fully or clearly reported.

In the selection and comparability domains, Filipchuk, 2022 [31], Hepp, et al. 2018 [32], and Lage, 2020 [33] all had low risk of bias; nevertheless, their reporting of results varies. In Lage et al. (2020) [33], there was uncertainty, while in Filipchuk, et al. (2022) [31], comparability

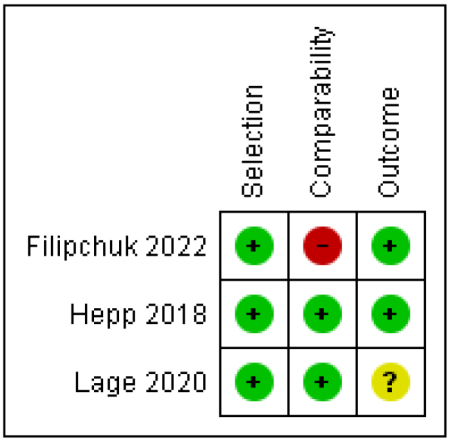

Fig. 3 Risk of bias summary

was a concern. However, Hepp, et al. (2018) seemed to be the most reliable study [32].

Meta-analysis of effect of low dose Levothyroxine on migraine frequency in patients with subclinical hypothyroidism

The fixed-effect model indicated a small but statistically significant reduction in migraine frequency with thyroxine. However, due to considerable heterogeneity, the random-effects model was likely a more suitable approach. In this model, the impact was not statistically significant, implying that the advantage of thyroxine over placebo may vary among studies. Overall, this meta-analysis suggested that although thyroxine may reduce migraine frequency, the effect was not statistically significant (Fig. 4).

Discussion

The findings of this systematic review found that subclinical hypothyroidism (SCH) increased the incidence of migraines. Additionally, the study indicated that hypothyroidism elevated the risk of autoimmune disorders in affected individuals. However, levothyroxine treatment for hypothyroidism reduced the frequency of migraines as well as milder headaches, including tension-type and chronic headaches. Previous studies supported this, demonstrating a significant correlation between hypothyroidism and migraines, and indicating that taking levothyroxine may help alleviate some of the symptoms [34, 35]. Moreover, another study that compared thyroid function in migraineurs to non-migraineurs found a correlation between the pathophysiology of migraines and fluctuations in thyroid-stimulating hormone (TSH) levels [36]. In the same study found that hypothyroidism is a comorbid condition that worsens the discomfort associated with primary headache disorders like migraine [36]. The study by Filipchuk et al. (2022) [31] found that patients with chronic migraines had a significantly higher prevalence of treated hypothyroidism compared to those with episodic migraines, suggesting a potential link between hypothyroidism and the chronicity of migraines [30]. Importantly, in that study found that factors such as body mass index, or age, or gender proportions did not affect this association, emphasizing the need for further research to investigate the mechanisms underlying this connection [31]. However, a prior study explored the relationship between Hashimoto's thyroiditis, an autoimmune disorder associated with hypothyroidism, and migraine, finding that Hashimoto's thyroiditis was common among migraineurs and could influence the intensity of migraines [37].

This study meta-analysis revealed that levothyroxine drug may reduce migraine frequency in people with subclinical hypothyroidism, although the effect was not statistically significant. Previous studies have yielded varying results, with some indicating major gains and others implying a minimal effect [31, 32, 38]. Previous research has indicated that chronic migraine sufferers had a high proportion of treated hypothyroidism, which correlates with a considerable decrease in migraine frequency and intensity. A substantial decrease in migraine frequency and severity in children following levothyroxine medication was revealed [39]. Also, the effect of metabolic status and body composition on the impact of pharmacological migraine treatment was investigated, implying

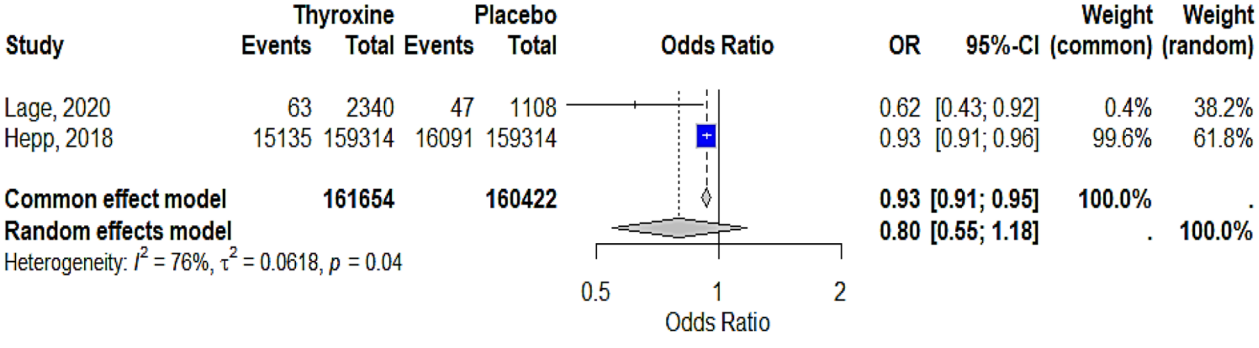

Fig. 4 Forest plot of effect of levothyroxine on migraine frequency

that metabolic diseases, such as thyroid dysfunction, can impair the efficiency of antimigraine medications [40]. People with hypothyroidism had a higher frequency of migraines according to a previous study, and levothyroxine treatment reduced headache frequency in both overt and subclinical hypothyroid patients [24]. These studies support the findings that levothyroxine medication can decrease the frequency and severity of migraines in people with subclinical hypothyroidism.

By controlling thyroid hormone levels, lowering autoimmune activity, restoring neurotransmitter balancing, and enhancing energy metabolism, levothyroxine may assist people with subclinical hypothyroidism experience fewer migraines [41]. Although the exact mechanisms are unknown, levothyroxine may help balance metabolic processes, lower inflammation, and normalize thyroid hormone levels—which in turn might reduce the frequency and intensity of migraines [42]. Levothyroxine may also aid in immune system modulation, lowering autoimmune activity and inflammation that cause migraines. Levothyroxine could improve energy metabolism, which lowers stress levels and could mitigate migraine triggers [43]. These processes demonstrate how levothyroxine may help patients with subclinical hypothyroidism control their migraines.

It is crucial to comprehend psychiatric comorbidities in individuals with headache disorders, or migraine in particular, because of the reciprocal relationship between the two anxiety and depression can actually trigger the onset of headaches, but they can also result from recurrent headache episodes. In therapeutic practice, these factors are crucial: comorbidity with depression and anxiety appears to have little effect on drug use and misuse, but individuals with these comorbidities reported worse satisfaction and efficacy from their treatments. Therefore, it is crucial for diagnosis, therapy, and prognosis to screen for concomitant mental illnesses in headache sufferers, and migraine sufferers in particular [44].

Neuroinflammation, dysregulation of the HPT axis, vascular dysfunction, and neurotransmitter imbalance are among the common pathophysiological processes that are thought to underlie the reciprocal link between migraine and SCH. Understanding the association has significant clinical implications for the detection, tracking, and management of both conditions. Determining the effectiveness of focused therapies and clarifying the underlying processes should be the main goals of future study [45].

This study has certain limitations. Several factors, such as patient characteristics, follow-up duration, dosage and duration variations, sample size, study quality, and heterogeneity, affect the meta-analysis of thyroxine's impact on migraine frequency. These aspects may provide inconsistent results and make it challenging to reach firm conclusions. Although the study offers insightful information on the connection between migraine and subclinical hypothyroidism, the specific characteristics of the study population, clinical context, and methodology may restrict the generalizability of the findings. To gain a better understanding of how thyroxine affects migraine frequency, the study also emphasizes the need for additional large-scale, high-quality randomized controlled studies using consistent methodologies.

Conclusions

This study highlighted the importance of thyroid screening in the management of migraines, especially chronic migraines, due to the association between hypothyroidism and migraines. It recommended that practitioners undertake routine thyroid function assessment for individuals suffering from migraines or chronic headaches. Personalised treatment approaches for both hypothyroidism and migraine symptoms may be effective. Early intervention in patients with chronic migraines may minimize attacks and improve overall quality of life. Although preliminary data indicate that levothyroxine supplementation may alleviate migraine symptoms, methodological constraints and limited statistical power preclude definitive conclusions. These observations justify both the adoption of thyroid screening in clinical practice and the pursuit of rigorous clinical trials to establish optimal therapeutic algorithms, elucidate neuroendocrine pathways, and characterize relevant comorbid conditions that may influence treatment efficacy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04214-4.

Supplementary Material 1

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Author contributions

AO, MNN, RAA, FAA, DHQ, MAS, RKJ and SSH contributed to conceptualization, methodology, data curation, formal analysis. AM wrote the manuscript. All au-thors read and approved the final version of the manuscript.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics of approval and consent to participate

This study did not require ethical approval as it involved the review and synthesis of data from previously published studies, and no new human or animal subjects were involved.

Consent for publication

Not applicable.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no competing interests.

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