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ORIGINAL ARTICLE

Comorbidities as risk factors for migraine onset: A systematic review and three-level meta-analysis

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Abstract

Introduction: Migraine is a debilitating neurological disease with a multifaceted pathophysiology. Pre-existing comorbidities may influence the risk of developing migraine. This review and meta-analysis aim to present a comprehensive overview of the known comorbidities predisposing individuals to new migraine onset, thereby improving our understanding of the respective diseases' interactions.

Methods: A systematic search of PubMed and EMBASE identified studies on pre-existing comorbidities as risk factors for new migraine onset. We performed three-level meta-analyses employing restricted maximum likelihood estimation to calculate pooled risk ratios (pRR). Subgroup and sensitivity analyses were conducted to assess the robustness of the data. Risk of bias (RoB) was assessed with the Quality in Prognostic Studies Tool. This review was pre-registered on Prospero (CRD42024501140).

Results: From a total of 17,330 records, we identified 38 studies, encompassing 124 effect sizes from 58 exposures. Most studies ($n = 28$, 74%) had a low RoB. Heterogeneity was high (>90%), primarily due to within-study differences (>50%), and was not significantly impacted by moderator tests or the exclusion of outliers. We found significantly increased risks for migraine onset associated with prior atopic conditions [pRR = 1.53 (1.15, 2.03)], psychiatric or psychological disorders [pRR = 2.63 (1.79, 3.85)], sleep disorders [pRR = 1.89 (1.26, 2.85)], and cardiovascular conditions [pRR = 1.72 (1.07, 2.76)].

Conclusions: Pre-existing atopic, psychiatric, sleep, and cardiovascular conditions are significantly associated with new migraine onset, likely due to shared genetic predisposition and mediating factors like stress and inflammation. Future research should focus on these associations to advance targeted prevention and treatment strategies.

KEYWORDS
comorbidities, meta-analysis, migraine, prediction, risk factors

Maria Terhart and Lucas Hendrik Overeem contributed equally to this work and share first authorship.

INTRODUCTION

Migraine is a highly prevalent and disabling neurological disorder, characterized by recurrent headache episodes often accompanied by photophobia, phonophobia, nausea, and vomiting [1]. Despite substantial research efforts over recent decades, the etiology of migraine remains incompletely understood.

Twin and family studies from the 1990s provided initial insights into the genetic underpinnings of migraine, revealing heritability estimates from 35% to 60% and indicating that first-degree relatives of migraine patients have a 1.5- to 4-fold increased risk compared to the general population [2]. While the genetic component of the disease is undisputed [2], genetic analyses are not suitable for determining the individual risk for migraine in clinical practice and genetics are not the sole factor influencing it. The factors not purely explained by the genetic component are the subject of intensive research. These include comorbidities [3, 4], environmental influences [5], and lifestyle factors [6], all of which were also referenced in a recent comprehensive publication [7].

In this context, the interplay between comorbidities and subsequent migraine onset warrants particular attention. A deeper understanding of these interactions could inform the development of targeted therapeutic strategies for patients with particular risk profiles. Early intervention strategies could reduce the overall burden of the disease, decrease healthcare costs, and improve patient outcomes. Moreover, insights into these comorbid risk factors could enhance our understanding of migraine pathophysiology and guide future research and treatment strategies.

Previous systematic reviews have established an elevated risk of various comorbidities among migraine patients [3,4,8]. However, these reviews have often neglected to focus on the exact chronological order between the onset of these comorbidities and migraine. This makes it difficult to draw definitive conclusions regarding the directionality and nature of these associations.

Despite significant research efforts, a comprehensive synthesis of studies focusing specifically on pre-existing comorbidities and migraine is lacking. Therefore, this work aims to conduct a systematic review and meta-analysis of longitudinal studies examining comorbidities as predictive factors for migraine. By integrating these findings, we strive to identify patterns within the literature that may enhance our understanding of the shared pathophysiology of these conditions and suggest novel avenues for therapeutic intervention.

METHODS

Standard protocol approvals, registrations, and patient consents

The study was pre-registered on Prospero (CRD42024501140) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Since this study does not involve direct human or animal subjects, and all data were extracted from previously published studies, ethical approval or informed consent were not required.

Search strategy, selection, and inclusion criteria

Our primary objective was to identify pre-existing comorbidities that might serve as risk factors for migraine. To achieve this, we first identified observational studies on migraine risk factors and screened full texts to select those specifically addressing comorbidities. To synthesize the findings, we conducted a systematic review with a multilevel, multivariate meta-analysis.

We included all eligible studies published between 1960 and 2023. We performed a systematic literature search on November 28, 2023 on PubMed and Embase. Duplicates were removed using EndNote 21.3. The keywords we used for our systematic search were:

PubMed: "susceptib*"[Title/Abstract] OR "predispos*"[Title/Abstract] OR "risk"[Title/Abstract] OR "predict*"([Title/Abstract]) AND "migrain*"[Title/Abstract].

Embase: (1) predispos*.mp. (2) susceptib*.mp. (3) predict*.mp. (4) risk.mp. (5) migrain*.mp. (6) (1 or 2 or 3 or 4) and 5 (7) limit 6 to article.

After the initial search, two reviewers (MT, JBH) screened titles and abstracts against inclusion criteria. All articles were screened by both reviewers independently. Any discrepancies were discussed between all reviewers until a consensus was reached. Thereafter, full-texts were assessed by MT, JBH, LHO, and BR.

Inclusion criteria

Studies were included if they either (1) were cohort studies where any predictive factors were collected at baseline and participants were followed over time to observe the incidence of migraine, or where the presence or absence of any predictive factors was retrospectively assessed, including studies based on databases (e.g., insurance data) and registry data; or (2) used case–control designs to compare individuals with and without migraine, with retrospective collection of predictive factors.

Exclusion criteria

We excluded studies that: (1) were not published in English, German, or Dutch; (2) were not full-text articles, for example, letters or conference theses; (3) did not contain original data, such as various types of reviews and meta-analyses; (4) included less than 100 study participants; (5) lacked information on the presence of exposure before migraine on-set; (6) did not distinguish between migraine headache and non-migraine headache. Migraine diagnosis in the meta-analysis was defined like it was in the original study; (7) did not report raw-data or data transformable to risk ratios; (8) did not specifically report comorbidities as risk factors.

Data extraction

Data from each study were independently extracted and coded by two researchers (LHO and BR) to minimize errors. Any discrepancies were resolved by consensus. The following descriptive and methodological variables were coded from the studies: first author, title, publication year, study location, country, geographical region, study design, study cohort, sample size, proportion of female participants, follow-up duration in years, definition of migraine diagnosis and type of migraine as reported in the original study, presence of aura, age at migraine onset assessment, and used diagnostic classification system. Additionally, variables for predicting factors were extracted in a 2×2 table format as follows: (a) exposed with event; (b) exposed without event; (c) unexposed with event; and (d) unexposed without event. In the case of multiple outcomes, the reference group served as the non-exposed group for estimating binary effect sizes.

Effect sizes and their corresponding variances were estimated for all endpoints predicting migraine at a later age. In the case that the raw data were not reported, we attempted to estimate effect sizes based on the reported information according to the Cochrane guidelines for systematic reviews [9]. These effect sizes were organized into a hierarchical structure to allow effect sizes to vary on three levels:

- Level 1 (sampling variance): Sampling variance of the extracted effect sizes.
- Level 2 (within-study variance): Variance between effect sizes extracted from the same study.
- Level 3 (between-study variance): Variance between studies. In short, this model allows effect sizes to vary between participants (level 1), outcomes (level 2), and studies (level 3).

Risk of bias (RoB) assessment

We used the Quality in Prognosis Studies (QUIPS) tool to assess study quality by evaluating potential sources of bias across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis/reporting [10]. Each domain was rated to determine the overall RoB. Studies were classified as having low, moderate, or high RoB based on these ratings. Low risk indicates high reliability, moderate risk suggests some potential bias but reasonable trustworthiness, and high risk indicates significant bias concerns and less reliable findings.

Assessment of heterogeneity

Due to the variety of predictive factors, we anticipated high heterogeneity among estimates. The three-level model decomposes heterogeneity into three distinct levels. By calculating the I^2 statistic at each level, the model quantifies the proportion of variability attributable to heterogeneity. A multivariate Q test was employed to detect statistically significant heterogeneity across studies and outcomes. This approach allows for a more precise estimation of effect sizes and their confidence intervals, as it accounts for the nested structure of the data. To explore potential sources of heterogeneity, we conducted a multivariable meta-regression analysis. The model included the following moderators at study and cohort level:

1. Study design: Prospective Cohort Study, Retrospective Cohort Study, Retrospective Case–Control Study
2. Publication year: year 1964–2014, year 2015–2016, year 2017–2019, year 2020–2021, year 2022–2023
3. Study quality: Low RoB, Moderate RoB, High RoB
4. Type of used data: Cohort Data, Insurance/Register Data
5. Age at migraine onset: Childhood, Adolescence, Adulthood
6. Location of the study: East Asia, Europe, North America, Oceania

Sensitivity analysis

We conducted sensitivity analyses to evaluate the robustness of the results. We performed a moderator analysis using meta-regression to explore the influence of potential moderators on the effect sizes. An outlier analysis identified and assessed the impact of extreme values on the overall findings using Cook's Distance. We assessed publication bias using funnel plots, sunrise plots, and Egger's test. These comprehensive sensitivity analyses aimed to ensure the reliability and stability of the meta-analytic conclusions.

Meta-analytic model

A three-level random-effects meta-analysis model was employed to account for the dependency structure inherent in the data at the three levels. All exposures with two or more effect sizes were pooled. The model was fitted using restricted maximum likelihood (REML) estimation. Analyses were carried out in groups to examine the consistency of results across different exposures and to explore potential sources of heterogeneity. Exposure categorization into different subgroups was done in consensus between BR and LHO. A detailed summary of the categorization of the comorbidities, as named in the original studies, is provided in Table 1. Statistical analyses were performed using R Studio software (version 2024.04.0). The three-level meta-analysis and meta-regression models were conducted using the *metafor* package, which allows for the fitting of complex random-effects models.

RESULTS

Search results and sample characteristics of studies

Our initial search identified 17,330 records published between January 1, 1964, and November 28, 2023. After removing duplicates, 12,790 records were screened based on title and abstract, resulting

TABLE 1 Classification of comorbidities into subgroups.

Subgroup	Specific Comorbidity as described in the original study
Atopic conditions/ disorders	Allergic conjunctivitis
	Allergic rhinitis
	Atopic dermatitis
	Asthma
	Food allergy
Psychiatric and psychological conditions/ disorders	Depression
	Anxiety
	Anxiety and depression
	ADHD
	Autism spectrum disorder
	Low sense of coherence
Sleep conditions/ disorders	Pavor nocturnus
	Sleepwalking
	Sleep-related breathing disorders
	Insomnia
	Sleep disorder
	Sleep duration <3.5 h or 3–5 h
Cardiovascular conditions/ disorders	Incomplete circle of Willis: any/anterior/ posterior
	Fetal configuration circle of Willis
	Coronary artery disease
	Hypertension
	Stroke
	Diastolic blood pressure (increments)
	Systolic blood pressure (increments)
Autoimmune and inflammatory conditions/ disorders	Chronic osteomyelitis
	Autoimmune disease
	Rosacea
	Chronic periodontitis
	Psoriasis
	Fibromyalgia
	High C-Reactive Protein (CRP)[a]
Metabolic conditions/ disorders	Recurrent gastrointestinal disturbance
	Gallbladder stone disease
	Chronic kidney disease
	Diabetes mellitus
	Hyperlipidemia
Other conditions/ disorders	Abdominal migraine
	Benign paroxysmal vertigo
	Bruxism
	Cyclic vomiting
	Chronic obstructive pulmonary disease
	Neck/back/head injury
	Osteoporosis
	Marfan syndrome
	Nasal septum deviation
	Back pain
	Infantile colic
	Asphyxia, retinopathy of prematurity or bronchopulmonary dysplasia
	Neurological problems

[a]While elevated CRP levels are not a comorbidity per se, they have been included in the inflammatory group due to their role as a biomarker of systemic inflammation.

in 141 records for eligibility assessment. Ultimately, we included 38 studies in our analysis based on eligibility, Figure 1.

These 38 studies reported a total of 124 effect sizes from 58 exposures. Table 2 provides an overview of the study characteristics. Regarding migraine type, only two studies reported on episodic vs. chronic migraine, with 95% and 93% of migraine cases being episodic migraine [11] [12]. Aura was reported in 10 of the studies [11–20], with a mean percentage of migraine with aura of 38% (±13.5). Table S1 gives a detailed summary of all included exposures with the respective effect sizes and e-references. We categorized 8 studies as atopic, 20 studies as psychiatric and psychological, 6 studies as sleep-related, 7 studies as cardiovascular, 6 studies as metabolic, 6 studies as autoimmune and inflammatory, and 9 studies as other disorders. We opted for these categories to give a comprehensive and easily accessible overview of our findings. More granular results can be found in the supplemental material.

Pooled risk ratios (pRRs)

The overall pooled risk ratio for pre-existing comorbidities and the risk of developing migraine was pRR = 1.46 (95% CI [1.11, 1.92], $p = 0.007$). Figure 2 summarizes the pRR from all comorbidity subgroups. Stratified forestplots can be found in Figures S3–9.

Subgroup analyses detected increased pooled risks of developing migraine later in life for individuals with atopic (pRR = 1.53 [1.15, 2.03]), psychiatric (pRR = 2.63 [1.79, 3.85]), sleep (pRR = 1.89 [1.26, 2.85]), and cardiovascular conditions or disorders (pRR = 1.72 [1.07, 2.76]). Pooled autoimmune and inflammatory, metabolic and other disorders were not found to increase the risk of developing migraine later in life.

In the model fit assessment, the three-level model was found to have the best fit, Table S2. There was significant overall heterogeneity ($I^2 = 98.9\%$, Q(124) = 10,893.74, $p < 0.001$), 0.1% of which could be attributed to Level 1 (sampling error), 61.1% to Level 2 (within-studies), and 38.5% to Level 3 (between-studies), Table S2. Further details including heterogeneity estimates and effect sizes for each subgroup can be found in Table S3.

Assessing RoB

The majority of the included studies had a low RoB ($n = 28$, 74%). Six studies (16%) had an overall high RoB. Bias due to confounding was found to be the factor inducing the most RoB. Figure S1 and Figure S2 display the QUIPS Traffic Light Plot and QUIPS Summary Plot.

Moderator analysis

The moderator analysis revealed that study design influenced the pooled risk of migraine, F(2, 121) = 3.41, $p = 0.036$. However, substantial heterogeneity remained unexplained by study design,

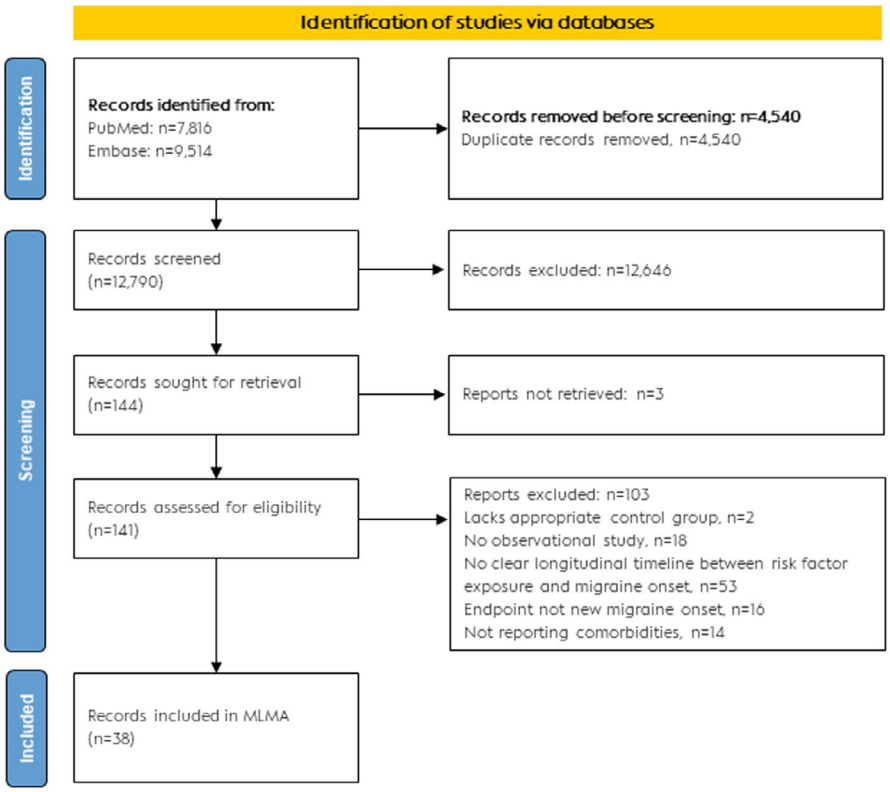

FIGURE 1 PRISMA flow diagram of study selection. MLMA = multilevel meta-analysis.

QE(122) = 7767.80, $p < 0.001$. Compared to studies with a prospective design, studies with a retrospective design reported higher risk ratios for migraine, with pRR = 1.09 [0.74, 1.58] and pRR = 1.94 [0.86, 4.36], respectively. This effect was further confirmed when testing data type as a moderator, F(1, 122) = 5.11, $p = 0.026$. Studies based on insurance or registry data (all retrospectively collected) reported higher overall risks for migraine compared to studies based on cohort data, with pRR = 1.08 [0.75, 1.59] and pRR = 1.77 [0.79, 3.96], respectively. Substantial heterogeneity remained unexplained by data type, QE(122) = 10879.81, $p < 0.001$.

The location of the studies also affected the overall risk of migraine, F(3, 120) = 3.17, $p = 0.027$, though substantial heterogeneity persisted, QE(120) = 7654.1093, $p < 0.001$. Studies conducted in Europe reported lower risks for migraine (pRR = 1.08 [0.49, 2.37]) compared to those conducted in East Asia (pRR = 2.07 [1.47, 2.91]).

The factors "age of assessed migraine onset," "study quality", and "publication year" did not significantly affect the pRR for migraine due to comorbidities, Table 3.

Analysis of outliers

We identified six outliers based on the 4/n cut-off of Cook's distance from four studies [21–24]. Five outlies came from Taiwan's National Health Insurance Research Database (NHIRD) registry reporting effect sizes for depression[21 22], cerebrovascular accident [21], autoimmune disease [21], and benign paroxysmal vertigo [24]. The reported RR ranged from 3.2 to 50.3. The heterogeneity including outliers was Q(123) = 10889.66, $p < 0.001$ and changed to Q(118) = 8850.16, $p < 0.001$ after adjustment. The pRR decreased from pRR = 1.49 [1.13, 1.95] to $pRR_{adj} = 1.35$ [1.05, 1.75], remaining statistically significant.

Publication bias

Egger's test did not identify asymmetry in the funnel plot (t(122) = 1.446, $p = 0.151$). However, after adjusting for publication bias using the Trim and Fill method, moderate funnel plot asymmetry was detected (t(156) = 2.298, $p = 0.023$). This adjustment suggests that the original analysis may have underestimated the extent of publication bias. The significant result from the Egger's test after applying the Trim and Fill method indicates the possibility of missing studies due to publication bias. The studies included in our meta-analysis of comorbid risk factors appear to be well-powered (median power = 96.8%) and highly replicable (R-Index = 100%), with a slight indication of fewer significant findings than expected. The high replicability and median power suggest that the overall evidence is strong and reliable, as shown in Figure 3.

DISCUSSION

This systematic review and meta-analysis identified associations between atopic, psychiatric, sleep-associated, and cardiovascular disorders (CVD) and subsequent migraine onset.

A particularly robust association was observed between atopic disorders and migraine. Diseases analyzed in multiple studies

TABLE 2 Summary of the study characteristics.

Study characteristic	No. of studies, $N = 38$
Study sample	
<1000 participants	9 (24)
1000–9999 participants	4 (11)
10,000–99,999 participants	9 (24)
≥100,000 participants	16 (42)
Proportion of women	
>75% of the sample	2 (5)
25%–75% of the sample	34 (89)
<25% of the sample	2 (5)
Participant age at migraine onset	
Childhood	3 (8)
Childhood & adolescence	7 (18)
Adolescence & adulthood	3 (8)
Adulthood	25 (66)
Migraine diagnosis according to	
ICHD-1	4 (11)
ICHD-2	5 (13)
ICHD-3	4 (11)
ICD-9	12 (32)
ICD-10	5 (13)
Self-reported	5 (16)
Other	3 (8)
Maximum follow-up duration in years:	
<10	9 (24)
10–20	24 (63)
>20	5 (13)
Study design	
Prospective cohort	14 (37)
Retrospective cohort	17 (45)
Retrospective case–control	7 (18)
Data Type	
Insurance/Registry Data	24 (63)
Cohort Data	14 (37)
Region	
Europe	14 (37)
North America	4 (11)
East Asia	18 (47)
Oceania	2 (5)
Publication year	
Year 1964–2014	10 (26)
Year 2015–2016	4 (11)
Year 2017–2019	11 (29)
Year 2020–2021	6 (16)
Year 2022–2023	7 (1)
Risk of bias	
Low	28 (74)
Moderate	4 (11)
High	6 (16)

Note: Values are given in *n* (%). Values might not add-up to 100% due to rounding.

included asthma [11,14,20,25,26] allergic conjunctivitis [11,19,20] allergic rhinitis, [11,18,20,25] and atopic dermatitis [11,20,25]. Notably, asthma demonstrated a bidirectional relationship with migraine, with comparable odds ratios observed in both directions [14]. The strong association between atopic diseases and migraine has been a focus of research for decades, primarily based on the hypothesis of overactive mast cells as a common denominator. Mast cells in the dura mater can be activated by allergens and pro-inflammatory agents, including calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide [27]. Degranulation of mast cells in the dura is associated with sustained activation of trigeminal afferents [28] suggesting that heightened mast cell activity and sensitivity in individuals with atopic disorders may elevate migraine risk. Additionally, broader pro-inflammatory mediators, such as tumor necrosis factor-alpha and interleukin-1 beta, may also play a role in this association [29].

Specific anti-inflammatory treatments might modulate mast cell activity in the dura and thereby potentially reduce the migraine risk. In line with this hypothesis, children with atopic diseases who were treated with nasal or inhaled corticosteroids or antihistamines were less likely to have migraine compared to those who were not treated in this way [11]. Furthermore, a cross-sectional analysis of patients with allergic rhinitis revealed that immunotherapy was associated with a reduced prevalence of migraine [30]. These findings underscore the potential for targeted anti-inflammatory treatments to mitigate migraine risk in individuals with atopic disorders.

Another group of comorbidities highly associated with new-onset migraine includes psychiatric disorders. Ten studies included data on the relationship between prior depression and migraine, all of which reported a positive association [22, 31–39]. The relationship between depression and migraine appears to be bidirectional, with studies reporting new-onset depression in migraine patients at rates comparable to the development of new-onset migraine in patients with depression [22,32,37–39].

Several theoretical frameworks might explain this association. One possibility is a shared genetic predisposition [41, 42]. A recently published pooled analysis from several genome-wide association studies identified 14 gene loci associated with both conditions [40]. Another critical theory posits that external factors, particularly stress, mediate the relationship between psychiatric illnesses and new-onset migraine [32,34]. In some studies, the association between migraine and depression was no longer significant after adjusting for stressors [34] suggesting that stress may play a crucial role in linking these two conditions.

The genetic and stress hypotheses are not mutually exclusive but rather complementary. Genetic vulnerability may shape an individual's stress response and resilience, rendering those with certain genetic profiles more susceptible to physical conditions exacerbated by stress, such as depression and migraine. Another significant comorbidity was anxiety, which is often comorbid with depression and shares a lot of pathophysiological considerations [41]. Further psychiatric exposures included attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder.

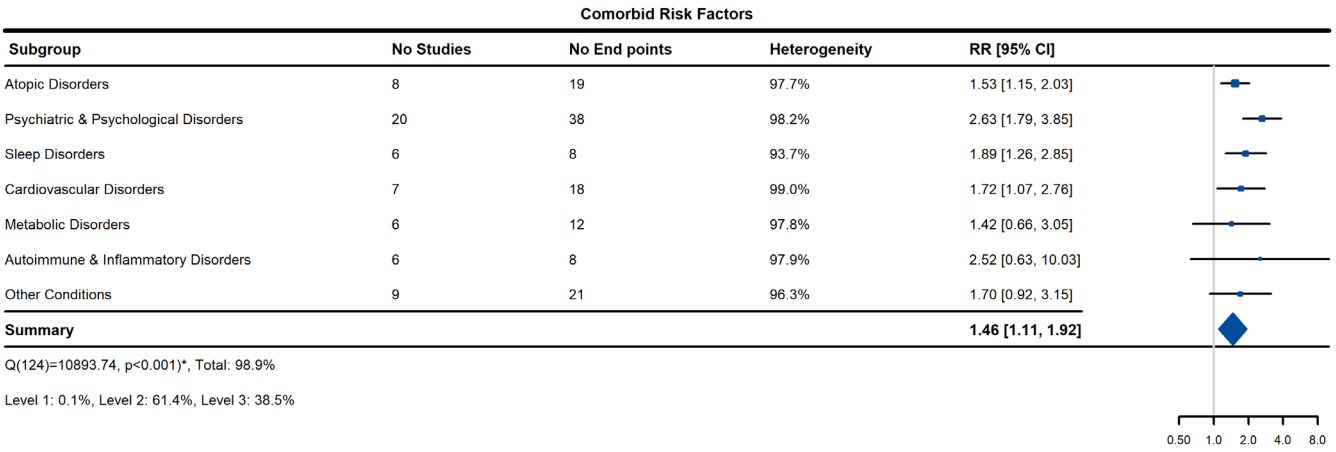

FIGURE 2 Summary forest plot of the pooled risk ratios for the comorbid subgroups.

TABLE 3 Moderator analysis of comorbid risk factors.

Moderator Variable	Nº Studies	Nº effect sizes	Risk ratio (95% CI)	β (95% CI)
Study design				
Prospective cohort	14	43	1.09 (0.75, 1.58)	–
Retrospective cohort	17	64	1.94 (0.86, 4.36)	0.575 (0.137, 1.013)*
Retrospective case–control	7	17	1.47 (0.56, 3.86)	0.296 (−0.301, 0.892)
Meta regression *F*-test	$F(2, 121) = 3.41$, $p = 0.036$*			
Test for residual heterogeneity	QE (121) = 7767.80, $p < 0.001$*			
	I^2_t: 98.4% (I^2_{L1}: 0.1%, I^2_{L2}: 65.4%, I^2_{L3}: 34.5%)			
Type of Data				
Cohort Data	14	40	1.09 (0.75, 1.59)	–
Insurance/Register Data	24	48	1.77 (0.79, 3.96)	0.485 (0.061, 0.91)*
Meta regression *F*-test	$F(1, 122) = 5.11$, $p = 0.026$*			
Test for residual heterogeneity	QE (122) = 10879.81, $p < 0.001$*			
	I^2_t: 98.9% (I^2_{L1}: 0.1%, I^2_{L2}: 64.7%, I^2_{L3}: 35.1%)			
Age at migraine onset				
Adolescence & adulthood	3	3	1.22 (0.57, 2.61)	–
Adulthood	25	83	1.45 (0.31, 6.82)	0.176 (−0.612, 0.963)
Childhood	3	12	1.49 (0.25, 8.8)	0.207 (−0.804, 1.218)
Childhood & adolescence	7	26	1.74 (0.34, 8.96)	0.358 (−0.519, 1.235)
Meta regression *F*-test	$F(3, 120) = 0.25$, $p = 0.863$			
Test for residual heterogeneity	QE (120) = 10730.21, $p < 0.001$*			
	I^2_t: 98.9% (I^2_{L1}: 0.1%, I^2_{L2}: 59.9%, I^2_{L3}: 39.9%)			
Study Quality				
High RoB	6	17	1.47 (0.83, 2.62)	–
Low RoB	28	89	1.42 (0.44, 4.65)	−0.035 (−0.645, 0.574)
Moderate RoB	4	18	1.92 (0.48, 7.68)	0.263 (−0.549, 1.075)
Meta regression *F*-test	$F(2, 121) = 0.43$, $p = 0.650$			
Test for residual heterogeneity	QE (121) = 10549.87, $p < 0.001$*			
	I^2_t: 98.9% (I^2_{L1}: 0.1%, I^2_{L2}: 60.3%, I^2_{L3}: 39.6%)			
Study origin				
East Asia	18	61	2.07 (1.47, 2.91)	–
Europe	14	43	1.08 (0.49, 2.37)	−0.648 (−1.091, −0.205)*

(Continues)

TABLE 3 (Continued)

Moderator Variable	Nº Studies	Nº effect sizes	Risk ratio (95% CI)	β (95% CI)
North America	4	9	1.16 (0.44, 3.06)	−0.579 (−1.210, 0.052)
Oceania	2	11	1.57 (0.49, 5.08)	−0.274 (−1.106, 0.558)
Meta regression *F*-test	$F(3, 120) = 3.17$, $p = 0.027$*			
Test for residual heterogeneity	QE (120) = 7654.1093, $p < 0.001$*			
	I^2_t: 98.4% (I^2_{L1}: 0.1%, I^2_{L2}: 66.7%, I^2_{L3}: 33.2%)			
Publication year				
1964–2014	10	27	1.23 (0.78, 1.93)	–
2015–2016	4	14	2.19 (0.67, 7.19)	0.577 (−0.158, 1.312)
2017–2019	11	33	1.29 (0.45, 3.68)	0.048 (−0.548, 0.643)
2020–2021	6	17	1.66 (0.51, 5.42)	0.301 (−0.429, 1.030)
2022–2023	7	33	1.72 (0.60, 4.98)	0.336 (−0.273, 0.944)
Meta regression *F*-test	$F(4, 119) = 0.90$, $p = 0.468$			
Test for residual heterogeneity	QE (119) = 8772.76, $p < 0.001$*			
	I^2_t: 98.6% (I^2_{L1}: 0.1%, I^2_{L2}: 61.3%, I^2_{L3}: 38.5%)			

Note: I^2_{L1}: Level 1 (sampling variance): Sampling variance of the extracted effect sizes. I^2_{L2}: Level 2 (within-study variance): Variance between effect sizes extracted from the same study. I^2_{L3}: Level 3 (between-study variance): Variance between studies. RoB, risk of bias. * denotes statistically significant.

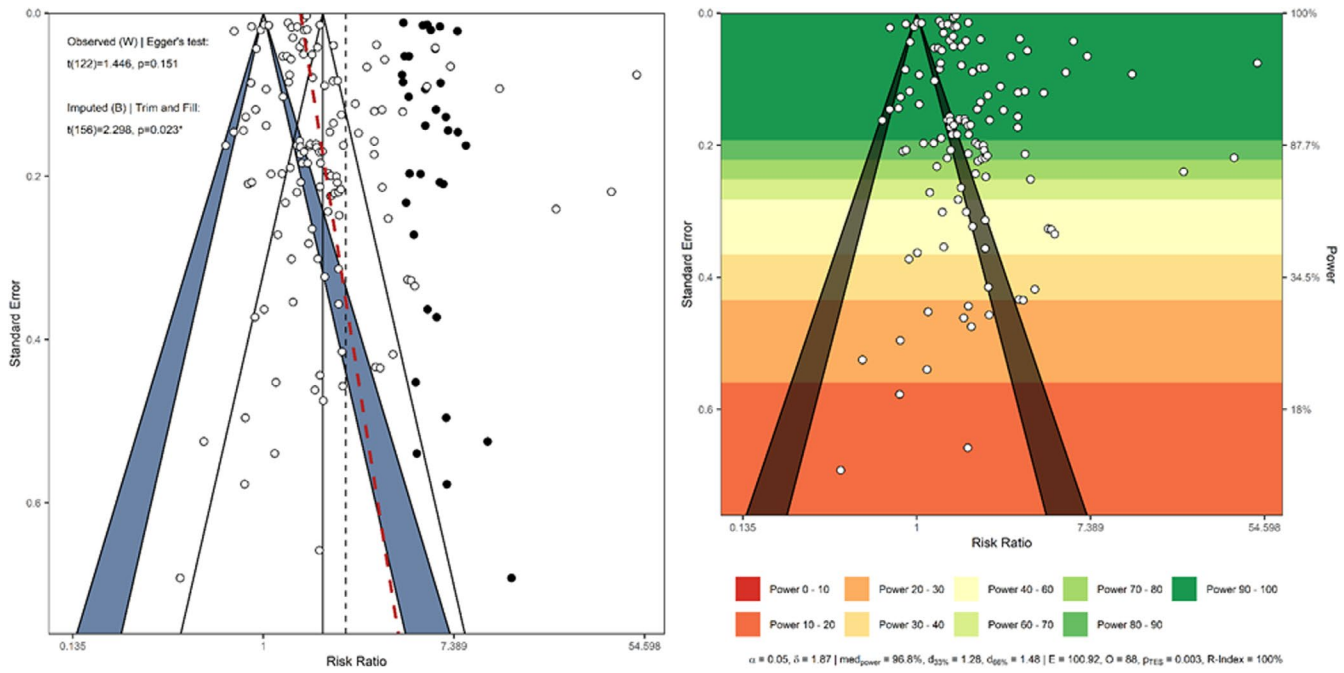

FIGURE 3 Funnel plot and sunrise plot for comorbid diseases.

This meta-analysis also identified a significant association between pre-existing sleep disorders and new-onset migraine. This finding aligns with prior reviews that have demonstrated a bidirectional relationship between different sleep disorders and migraine, independent of comorbid anxiety and depression [42–44]. Proposed explanations for this relationship include dysfunctions in the hypothalamus and brainstem and the orexinergic system—areas implicated in both sleep physiology and pain modulation [42–44].

Finally, our analysis revealed an association between CVD and the development of migraine. It is already well-established that migraine, especially migraine with aura, increases the subsequent risk of CVD [45]. Our analysis expands upon this knowledge by suggesting that CVD also increases the risk of subsequent migraine. Current theories propose common disease mechanisms, such as endothelial dysfunction, to explain the association [45]. It is relevant to mention that the exposures categorized as CVD in this meta-analysis were all secondary endpoints of the respective studies, derived from insurance or registry

data. This introduces the possibility of bias in our results. Therefore, our findings regarding the relationship between migraine and CVD should be assessed in future studies for validation.

Our focus on migraine onset might have several clinical and scientific implications. Future studies could use the herein produced data to estimate the proportion of migraine prevented by the elimination of these risk factors and thus the reduction of migraine burden and its associated individual and societal cost. Health practitioners who work primarily with patients with atopic or psychiatric disorders could provide information on the associated migraine risk and instruct patients on potential protective approaches like stress management, thereby sensitizing the patients and leading to earlier medical consultations in the event of migraine onset. Health politicians on the other side could also help to spread the knowledge about the heightened migraine risk with the mentioned conditions. This could help to raise awareness around migraine manifestation as a multifaceted neurological disease in the general population.

The studies included in our review generally exhibited a high level of quality. A three-level multivariate meta-analysis allowed for the simultaneous assessment of multiple correlated outcomes, offering greater statistical power and a nuanced understanding of the effects. Nonetheless, several limitations of our study should be acknowledged. The included studies encompass both registry-based and clinical datasets as well as adult and pediatric populations. In addition, we have only sparse data on migraine type (episodic vs. chronic) and on the presence of aura, because most of the original studies have not reported this information. Our emphasis was on providing a comprehensive overview of pre-existing comorbidities as predictors of migraine rather than an in-depth focus on each individual effect. The high heterogeneity in the meta-analysis arises from a range of factors, including variations in study designs, populations, comorbidities, and age groups. Despite using a multilevel approach that accounts for such variability, the heterogeneity remained substantial. Additionally, the categorization of comorbidities into subgroups involved some degree of subjectivity; alternative categorizations by different authors could yield slightly different numerical results. However, our overarching conclusions are robust and align well with existing literature. Another limitation arises from the challenges in controlling for potential confounders in some studies, which could introduce bias. For instance, studies utilizing health insurance data often lacked information on important variables such as family history of migraine, a well-established confounder in migraine research. Including such variables in future study designs could improve the accuracy of risk assessments for new-onset migraine. While no strict guidelines exist for the minimum number of effect sizes required for analysis [46,47], interpreting subgroups with fewer than 10 effect sizes should be approached with caution. It is also worth noting that purely genetic risk factors were not considered in this review, as they have been thoroughly evaluated in other targeted studies and reviews. Finally, our review evaluated comorbidities for their association with migraine onset and not for its chronification. Risk factors for chronification might overlap but should be studied in a different review.

CONCLUSION

In conclusion, this systematic review and meta-analysis detected significant associations between atopic disorders, psychiatric conditions, sleep disorders, and CVD and new onset migraine. Future research should focus on developing screening programs that incorporate known risk factors, facilitating early interventions tailored to vulnerable populations.

AUTHOR CONTRIBUTIONS

Maria Terhart: Conceptualization; writing – original draft; methodology; data curation; investigation. **Lucas Hendrik Overeem:** Investigation; methodology; visualization; formal analysis; data curation; writing – original draft. **Ja Bin Hong:** Investigation; methodology; writing – review and editing; formal analysis. **Uwe Reuter:** Writing – review and editing. **Bianca Raffaelli:** Conceptualization; methodology; validation; writing – review and editing; supervision; project administration.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data used in this meta-analysis are available from the corresponding author, BR, upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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