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SYSTEMATIC REVIEW

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Risk of dry eye in headache patients: a systematic review and meta-analysis

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ABSTRACT

Objectives: The objective of this meta-analysis was to identify whether headache increase the risk of dry eye disease (DED).

Methods: PubMed, Web of Science, Cochrane Library and EMBASE databases were searched for relevant studies. The odds ratio (OR) of DED in all-cause headache was calculated *via* Stata software. To explore the source of heterogeneity, subgroup and sensitivity analyses were conducted. Funnel plots and Egger's test were performed to assess publication bias.

Results: This meta-analysis included 11 studies. Pooled analysis indicated that all-cause headache was related to a higher risk of DED (OR = 1.586, 95% CI:1.409–1.785, I^2 = 89.3%, $p < .001$). Migraine headache, tension headache and cluster headache were all related to a higher risk of DED (OR = 1.503, 95% CI: 1.369–1.650, I^2 = 81.8%, $p < .001$; OR = 1.610, 95% CI: 1.585–1.635, $p < .001$; OR = 2.120, 95% CI: 1.104–4.073, $p = .024$), respectively. The risk of DED in case–control studies was slightly higher than in cross-sectional studies and cohort study (OR = 1.707, 95% CI: 1.291–2.258, I^2 = 85.0%, $p < .001$; OR = 1.600, 95% CI: 1.590–1.610, I^2 = 0.0%, $p < .001$; OR = 1.440, 95% CI: 1.096–1.893, $p = .009$), respectively. Subgroup analysis in territory type showed that all-cause headache in America, Europe, Asia and Oceania were all related to a higher risk of DED.

Conclusions: This study indicates that headache is related to a higher risk of DED, especially in the migraine patients. These results suggest that headaches should be regarded as an independent risk factor for DED.

KEY MESSAGES

- In this meta-analysis, 11 studies (one cohort study, four case–control studies and six cross-sectional studies) covering 3,575,957 individuals were included.
- Pooled analysis indicated that all-cause headache was related to a higher risk of dry eye (OR = 1.586, 95% CI: 1.409–1.785, I^2 = 89.3%, $p < .001$).
- These results suggest that headaches should be regarded as an independent risk factor for dry eye.

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Headache; migraine; dry eye disease; meta-analysis; systematic review

Introduction

Dry eye disease (DED) is the most prevalent chronic ocular surface disorder in clinical practice, with constant or intermittent symptoms of ocular dryness or pain, foreign body or burning sensation, photophobia and visual impairment [1–3]. The incidence of DED ranged from 5% to 50%, significantly in association with public health and financial burden worldwide [4,5]. The pathogenesis of DED is complex and multifactorial, but typically involves the production reduction or excessive evaporation loss from the tear film [6]. In recent years, there has been a rising awareness of the prevention strategy in DED, such as risk factor management, may be more cost-effective than disease treatment at the population level [7]. Several previous studies have explored the risk factors, such as gender, age, smoking, diabetes, contact lens use, ocular surgery history, psychiatric disorders [8–12]. The impact of headache on DED is easily neglected in clinical practice.

Headache has arisen as a public health burden, ranked as the second leading cause of disability worldwide. Headache is characterized as a lower life quality, reduced productivity and increased economic expenses [13,14]. Several observational studies have

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explored the risk for DED in headache that patients with headache are more prone to have DED than those without [15,16]. However, the precise nature is still unknown. Therefore, we carried out a study to identify whether headache is related to a higher risk of DED.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [17], and the protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO) platform (CRD42022333038).

Data sources and searches

We systematically searched the databases including PubMed, Cochrane Library, EMBASE and Web of Science until 12 May 2022. The literature searches were restricted to English language publications and without restriction of countries or study type. The search strategy utilized both medical subject headings (MeSH) and keywords. The terms included 'Dry Eye Syndromes', 'Headache' and 'Migraine Disorders'. We manually reviewed the references of the included studies as well as other published systematic reviews for seeking additional relevant studies. The detailed search strategy was presented in Supplementary Materials 1.

Inclusion criteria

The eligible studies had to meet the criteria as follows: (1) case-control, cross-sectional or cohort study; (2) investigations of the association of all-cause headache with the risk of DED; (3) the risk of DED as the outcome, and presented as an adjusted odds ratio (OR) and its corresponding 95% confidence interval (CI). In our study, 'all-cause headache' was characterized as 'patients suffered from any form of primary headache in the history', such as migraine, cluster headache or tension headache and others. We selected the study with the longest follow-up or the largest number of individuals when more than one study reported data based on the same population.

Exclusion criteria

Exclusion criteria was as follows: conference abstract, study protocol, duplicate publication or study without interested outcomes.

Study selection

Based on predefined criteria, two authors (SY Liu and LJ Zhang) independently selected the titles and abstracts of all records. After the initial screening, duplicate records and unrelated articles were excluded. Following that, we downloaded the full texts of these articles and conducted a thorough review to identify all eligible articles. Discussions were performed with SF Fang if there was a divergence.

Data extraction

SY Liu and LJ Zhang independently extracted the relevant data as follows: first author, publication year, country or region, study type, sample size, study period, age, diagnosis of DED and headache, headache type and confounders adjusted. SF Fang checked the data. Discussions were performed with SF Fang if there was a divergence.

Risk of bias assessment

We assessed the quality of a cohort or a case-control study with the Newcastle-Ottawa Quality Assessment Scale (NOS) [18] from three aspects: selection, comparability and outcome (cohort study) or exposure (case–control study). And we scored according to the following criteria: low quality (0–3), moderate quality (4–6) and high quality (7–9).

We assessed the quality of a cross-sectional study with the American Agency for Health Care Quality and Research's (AHRQ) cross-sectional study quality evaluation items [19]. We assessed an item as '1' if the answer was 'YES', or as '0' if the answer was 'UNCLEAR' or 'NO'. And we scored according to the following criteria: low quality (0–3), moderate quality (4–7) and high quality (8–11).

Statistical analysis

We used the Stata software (version 14.0) to perform the analysis. The adjusted OR and its 95% CI were extracted from the included studies to calculate the relation between headache and the risk of DED. Heterogeneity was calculated *via* the Chi-square test and I^2 value and a random-effects model was used considering the clinical heterogeneity. The sensitivity analysis was conducted to ascertain the reliability of the overall effects. The funnel plots and egger's regression test was conducted to explore the bias of publication [20,21]. Finally, we performed subgroup

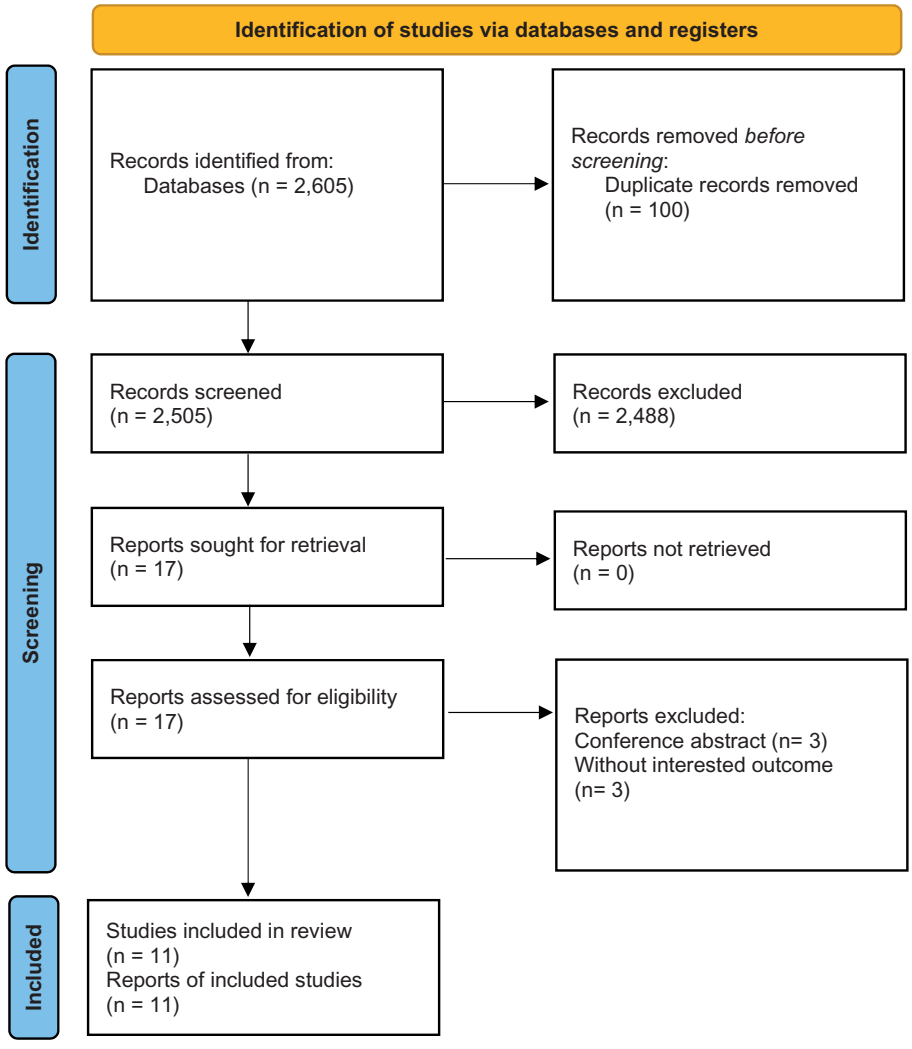

Figure 1. Literature screening flowchart.

analyses according to the headache type, study type and territory type.

Results

Search results

We collected 2605 articles before 12 May 2022 from the systematic search, and 100 duplicate articles were first excluded. A total of 2488 articles were also excluded after screening the title and abstract. Then six articles were excluded after reading the full-text, of which three conference abstracts, and three articles without interested outcomes [22–24]. Eleven studies [25–35] were finally included in this systematic review. The selection strategy is shown in Figure 1.

Study characteristics

This meta-analysis included 11 studies [25–35] covering 3,575,957 individuals. Of these studies, one study [26] was cohort study, four studies [25,30,32,33] were case–control studies and six studies [27–29,31,34,35] were cross-sectional studies. The publication year of these studies was 2010–2020. The sample size of the included studies was ranged from 99 to 3,265,894 participants. The diagnostic criteria for DED or headache in four studies [25,31–33] was the International Classification of Diseases-9 or 10 (ICD-9 or 10) diagnostic codes. The adjusted estimates were presented in most studies except two studies [31,34], and the adjusted confounders in the included studies were slightly distinct. The characteristics of the 11 studies are presented in Table 1.

Risk of bias assessment

We assessed the quality of the eleven studies *via* the NOS and AHRQ, and the scores are presented in Table 1. And the details are presented in Supplementary Tables 2 and 3, respectively. Four studies [25,26,32,33]

Table 1. Characteristics of studies included in the review.

Author	Year	Country	Study type	Sample Size	Study period	Age (years)	Diagnosis of DED	Diagnosis of headache
Tsung-Jen Wang	2010	China (Taiwan)	Case–control	Total: 48,028; DED: 12,007; No DED: 36,021	2005–2006	52.4 ± 17.5	ICD-9-CM	ICD-9-CM
Adam J. Paulsen	2014	America	Cohort	Total: 3275; DED: 475; No DED: 2800	2005–2008	49 (range 21–84)	Questionnaire	Questionnaire
Jelle Vehof	2014	England	Cross-sectional	Total: 3538; DED: 367; No DED: 3171	2012	57.1 ± 13.1 (20–87)	Questionnaire	Structured postal questionnaire
Asuman Celikbilek	2014	Turkey	Cross-sectional	Total: 99; DED: 42; No DED: 57	2013	18–50	A complete ophthalmologic examination	International Classification of Headache Disorders II diagnostic criteria
Soonwon Yang	2016	Korea	Cross-sectional	Total: 14,329; DED: 1390; No DED: 12,939	2010–2012	Over 19	Full ocular examinations	Questionnaire
Victoria S. Chang	2018	America	Case–control	Total: 233; DED: 94; No DED: 139	2016	46.3 ± 13.0 (19–77)	DED questionnaire 5 (DEQ5)	A numerical rating scale questionnaire
Charity J. Lee	2017	America	Cross-sectional	Total: 3,265,894; DED (tear film dysfunction, ocular pain): 959,881; No DED: 2,306,013	2010–2014	DED: 69.4 ± 12.9, 63.4 ± 15.3, respectively; No DED: 64.5 ± 14.3	ICD-9	ICD-9
Omar M. Ismail	2019	America	Case–control	Total: 72,969; DED: 9638; No DED: 63,331	2008–2018	Over 18	ICD-9 and10	ICD-9 and 10
Karel Kostev	2019	Germany	Case–control	Total: 87,354; DED: 102; No DED: 87,252	2018	Over 18	ICD-10	ICD-10
Michael T.M. Wang	2020	New Zealand	Cross-sectional	Total: 372; DED: 109; No DED: 263	2018–2019	39 ± 22 (21–85)	TFOS DEWS II	Not reported
Jelle Vehof	2020	England	Cross-sectional	Total: 79,866; DED: 7230; No DED: 72,636	2014–2017	50.4 (20–94)	Women's Health Study dry eye questionnaire	A self-administered questionnaire

Author	Headache type	Confounders adjusted	Adjusted OR	Scores
Tsung-Jen Wang	Headache Migraine	Gender, age, monthly income and level of the community	Headaches: 1.30 (1.24–1.36) Migraine: 1.76 (1.57–1.98)	9
Adam J. Paulsen	Migraine headache	Sex and age	Migraine headache: 1.44 (1.10–1.90)	7
Jelle Vehof	Migraine	Sex and age	Migraine: 1.47 (1.15–1.88)	6
Asuman Celikbilek	Migraine	Sex and age	Migraine: 1.56 (0.69–3.50)	8
Soonwon Yang	Migraine	Age, sex, BMI, current smoking, heavy drinking, regular exercise, metabolic syndrome, dyslipidemia, stress perception, and diagnosis of depression	Migraine: 1.58 (1.34–1.86)	9
Victoria S. Chang	Headache Migraine	Diet, environmental factors	Headaches: 2.14 (1.16–3.95) Migraine: 1.70 (0.84–3.45)	6
Charity J. Lee	Headaches Tension headache Migraine	Not reported	Headaches: 1.60 (1.59–1.61) Tension headache: 1.61 (1.58–1.63) Migraine: 1.31 (1.30–1.32)	6
Omar M. Ismail	Migraine headache	Age, sex, use of specific medications, a history of rheumatoid arthritis, Sjögren disease or lupus, a history of cataract or refractive surgery	Migraine headache: 1.42 (1.20–1.68)	8
Karel Kostev	Migraine	Age, sex and relevant codiagnoses (rheumatoid arthritis, Sjögren syndrome, lupus and cataract)	Migraine: 3.45 (2.16–5.47)	8
Michael T.M. Wang	Migraine headaches	Not reported	Migraine headache: 2.96 (1.38–6.37)	6
Jelle Vehof	Cluster headache Migraine	Sex and age	Cluster headache: 2.12 (1.10–4.06) Migraine: 1.27 (1.20–1.34)	8

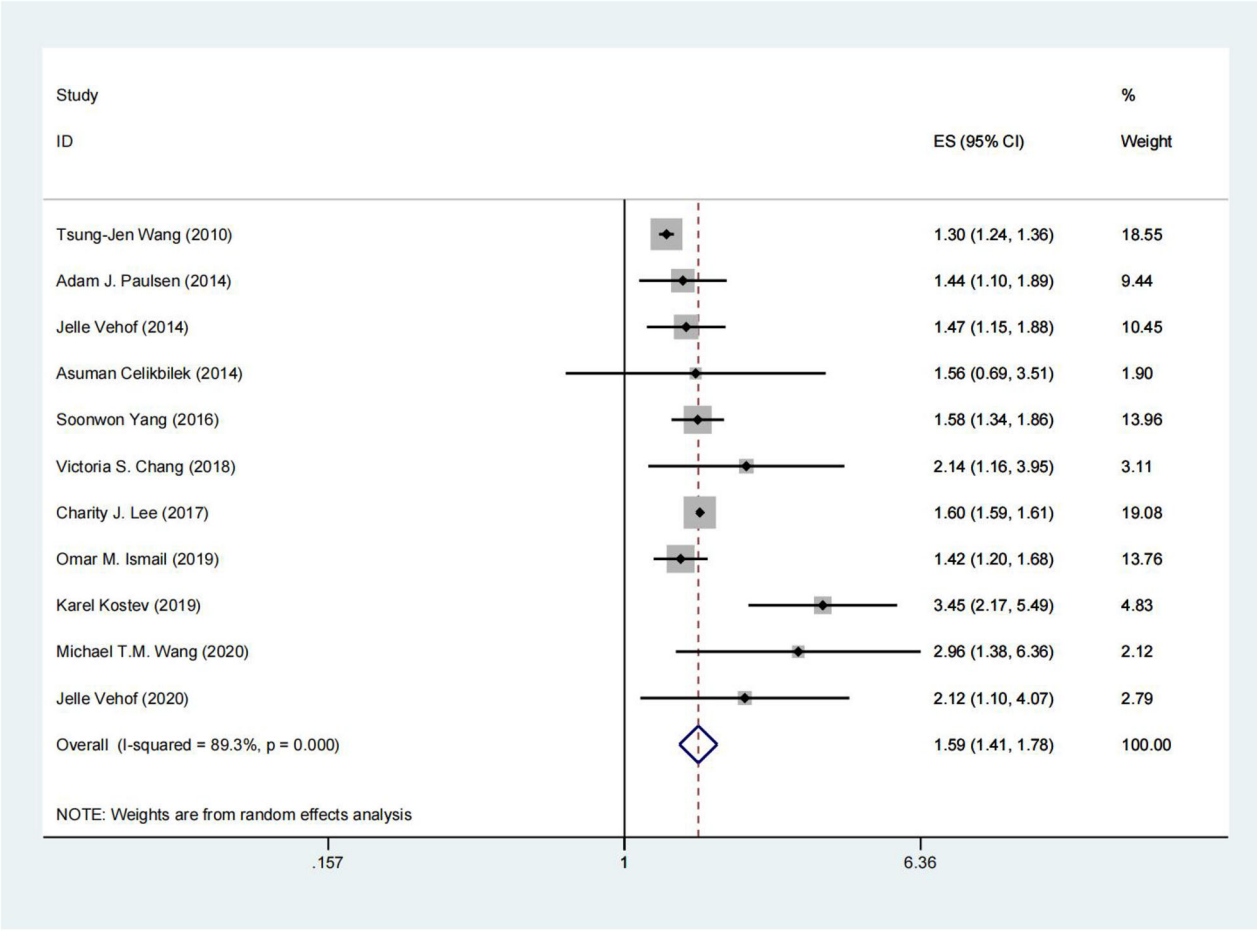

Figure 2. Forest plot showing the effect of all-cause headache on DED.

were scored as ≥7 (high quality) and one study [30] was scored as 6 (moderate quality) according to the NOS criteria. The average score of these five studies was 7.6, representing an overall high quality. Three studies [28,29,35] were scored as ≥7 (high quality) and three studies [27,31,34] were scored as 6 (moderate quality) according to the AHRQ criteria. The average score of these six studies was 7.2, representing an overall high quality.

All-cause headache and risk of DED

Eleven studies [25–35] assessed the relation between all-cause headache history and the risk of DED. The pooling analysis indicated that all-cause headache was related with a higher risk of DED (OR = 1.586, 95% CI: 1.409–1.785, I^2 = 89.3%, $p < .001$; Figure 2). Owing to the significant heterogeneity, we also performed a sensitivity analysis to identify the heterogeneity source. Sensitivity analysis revealed that none of the included studies altered the pooled-effect size, demonstrating the robustness of the overall findings and the result is shown in Supplementary Figure A. A visual examination of the funnel plot revealed that there was no evidence of a significant publication bias (Figure 3). And the Egger's regression tests ($p = .714$) revealed that the bias of publication was negligible in analysis.

Types of headache and risk of DED

Eleven studies [25–35] assessed the relation between migraine and the risk of DED and found that migraine had a higher risk of DED (OR = 1.503, 95% CI: 1.369–1.650, I^2 = 81.8%, $p < .001$; Figure 4). One included study (P29392243) showed that tension headache was associated with an increased risk of DED (OR = 1.610, 95% CI: 1.585–1.635, $p < .001$; Figure 4); and another included study (P32376389) showed that cluster headache was related to a higher risk of DED (OR = 2.120, 95% CI: 1.104–4.073, $p = .024$; Figure 4).

Study type and risk of DED

Subgroup analysis in the study type indicated that the risk of DED in case–control studies was slightly higher

than in the cross-sectional studies and the cohort study (OR = 1.707, 95% CI: 1.291–2.258, I^2 = 85.0%, $p < .001$; OR = 1.600, 95% CI: 1.590–1.610, I^2 = 0.0%, $p < .001$; OR = 1.440, 95% CI: 1.096–1.893, $p = .009$; respectively; Figure 5).

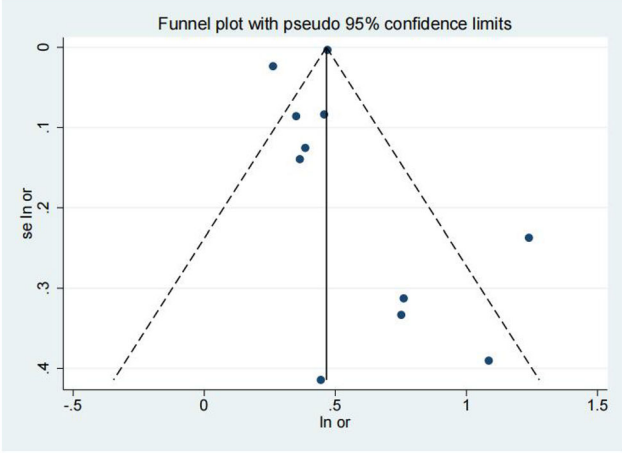

Figure 3. Funnel figure showing the effect of all-cause headache on DED.

Types of territory and risk of DED

Subgroup analysis in the territory type showed that the all-cause headache in America, Europe, Asia and Oceania were all related to a higher risk of DED (OR = 1.579, 95% CI: 1.493–1.669, I^2 = 10.9%, $p < .001$; OR = 2.158, 95% CI: 1.214–3.836, I^2 = 80.7%, $p = .009$; OR = 1.410, 95% CI: 1.196–1.663, I^2 = 61.6%, $p < .001$; OR = 2.960, 95% CI: 1.378–6.359, $p = .005$, respectively; Figure 6).

Discussion

Main findings

In this study, we investigated the relation between headache and the risk of DED in 3,575,957 individuals

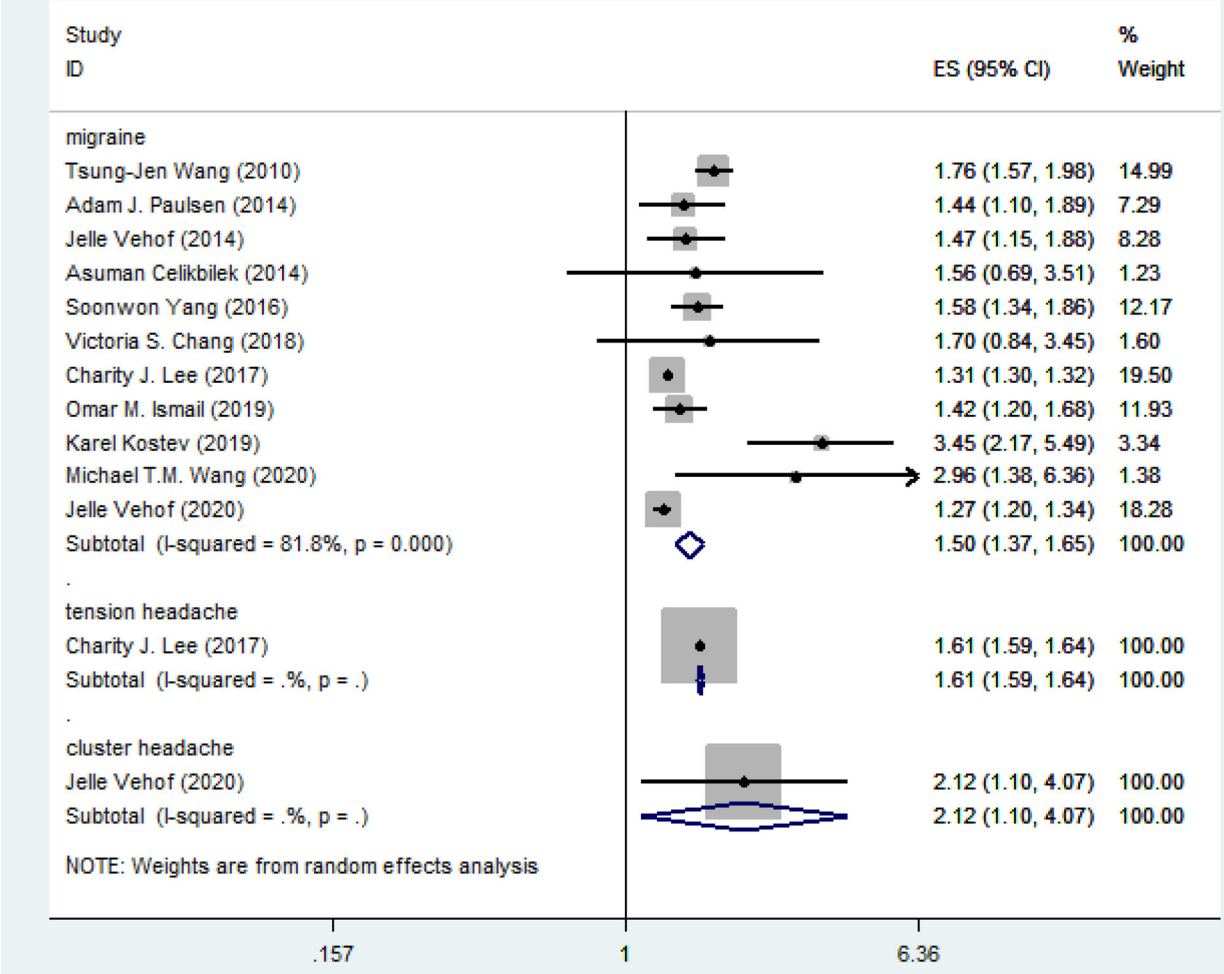

Figure 4. Forest plot showing the types of headache and risk of DED.

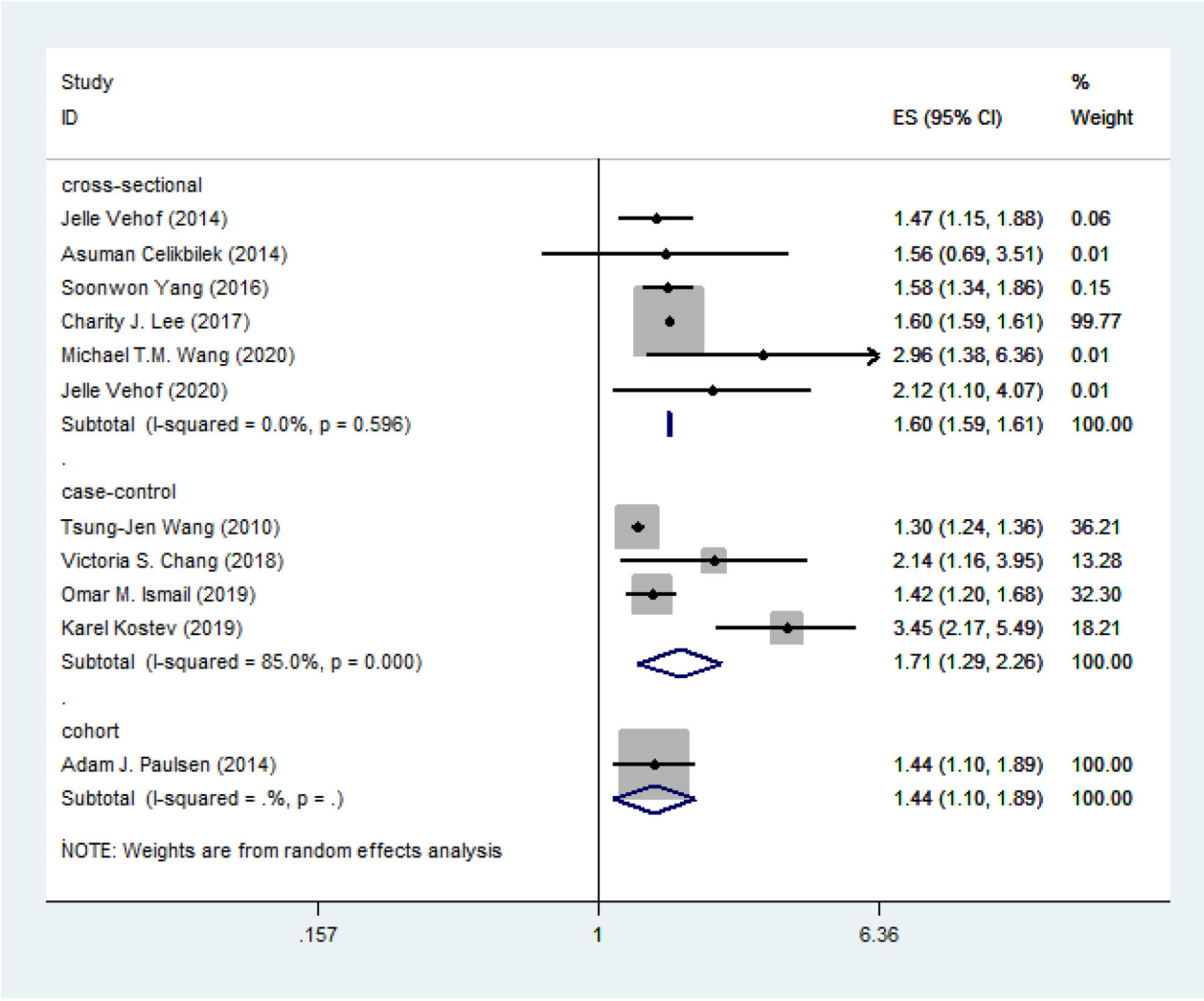

Figure 5. Forest plot showing the study type and risk of DED.

from eleven studies [25–35]. We discovered that compared with the controls without all-cause headache, there was a 1.586-fold increased incidence of DED among individuals with all-cause headache. Subgroup analyses showed that headache type (migraine, tension headache or cluster headache), study type (case–control, cohort or cross-sectional) and territory type (America, Europe, Asia or Oceania) were all related to a higher risk of DED. These results suggest that headaches should be regarded as an independent risk factor for DED.

Findings interpretation

Consistent with the findings of previous review [36], our study revealed that headache might increase the risk of DED. Chen et al. showed that migraine was related to a 1.55-fold increased incidence of DED [36], which was similar that observed in our study. Furthermore, subgroup analysis indicated that the incidence of DED was higher in hospital-based studies (OR = 1.97, $p = .036$) compared with population-based studies (OR = 1.42, $p < .001$). However, it did not mean that any type of the headache was related to a higher risk of DED. Moreover, their study showed that there was no relation between geographic location and DED, which may be reasonably associated with only seven published studies included. In our current analysis, we included more relevant and recent published studies and performed subgroup analysis according to the headache type, study type and territory type, providing reliable evidence regarding the relationship between headache and the risk of DED.

Several studies have been reported that headache was related to the inflammatory connective tissue diseases (Sjögren's syndrome, systemic lupus erythematosus, etc.) [37–40]. So far, the exact pathophysiological mechanism of the relation between headache and DED was not yet fully understood. However, it is well established that the underlying inflammatory

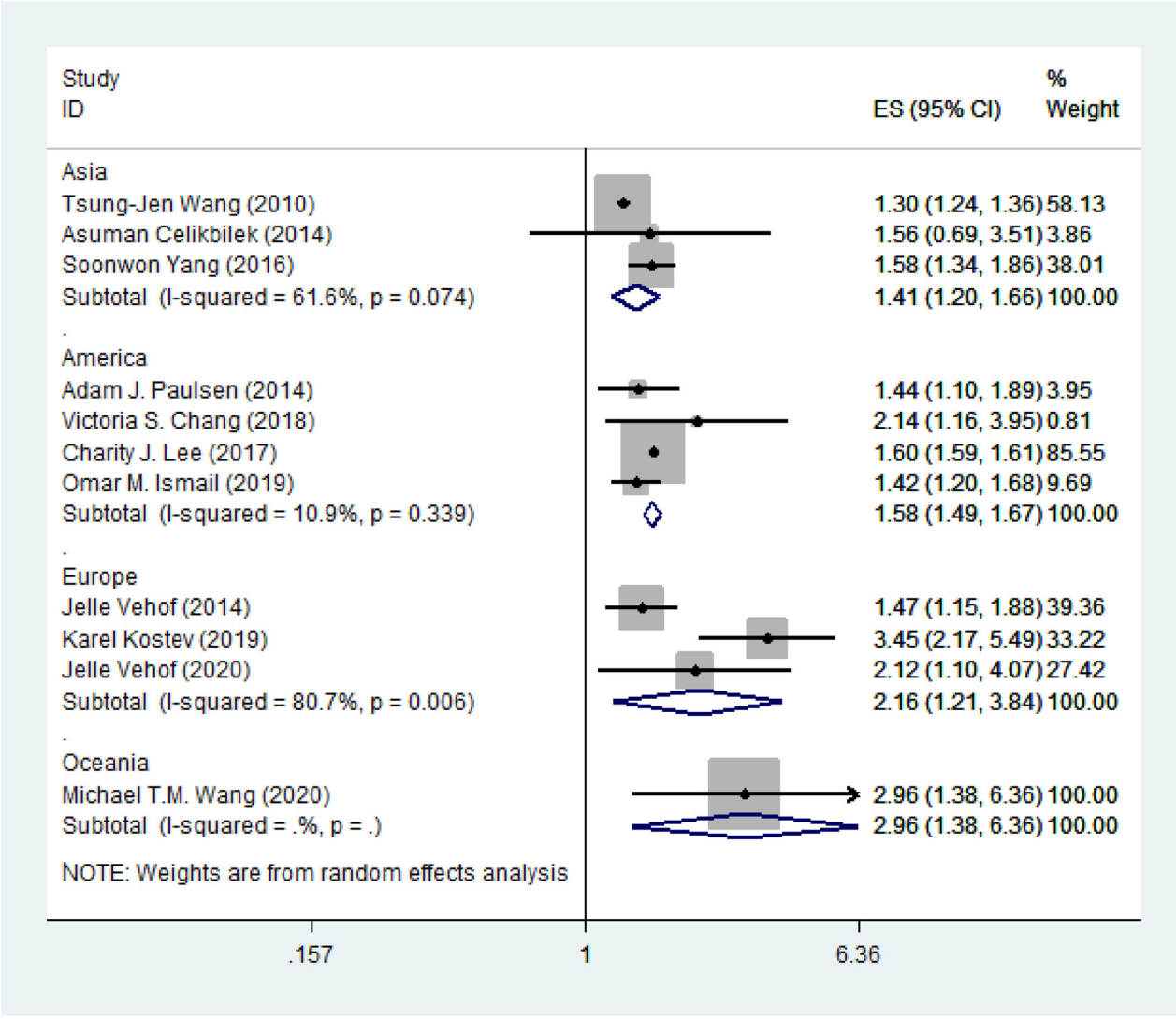

Figure 6. Forest plot showing the types of territory and risk of DED.

processes may play a major role in the pathophysiology of headache and DED [23]. The density of corneal nerve fibre was markedly lower in the patients with migraine than the controls, which indicates that cornea was a preferred target for neurogenic inflammation and structural changes in the trigeminal nerve might participant the pathophysiology of headache [2,15]. Since there was a close relation between the trigeminal nerve and the secretion of lacrimal gland, neurogenic inflammation might provide an environment that accelerates DED development [41,42]. Neurogenic inflammatory mediators and cytokines (neuropeptides, C-reactive protein, etc.) have been thought to trigger the process of plasma extravasation and trigeminal ganglion hypersensitivity in headache development [43–46]. Meanwhile, the inflammatory changes and hyperosmolarity environment in ocular surface also led to the development and propagation of headache [23,47,48].

We noticed that the heterogeneity of the eleven studies was significant, which could be related to the following factors. First, the sample size in three included studies were relatively small, which may have affected the results accuracy [28,30,34]. Therefore, more studies with larger sample sizes are required to identify the relation. Second, there were discrepancies in the diagnostic standards for headache and DED in the included studies, such as ICD-9/10, examination or questionnaire. Additionally, the diagnosis was mainly according to electronic health records in most included studies, which may also have affected the outcomes. Third, the included studies were performed in the America, Europe, Asia and Oceania, where regional bias is a valid possibility. As the subgroup analysis in the territory type showed that the risk of DED varied in different areas, more studies with the same area were required to identify the relation. Last, study design of the included studies was different, which may also have affected the

outcomes. As the subgroup analysis in the study type indicated that the risk of DED in the case–control studies was slightly higher than in the cross-sectional studies and the cohort study, more studies with the same study design are needed to clarify the association.

Implications and limitations

Our study reviewed the research findings concerning the relation between all-cause headache history and the risk of DED, demonstrating that headache should be regarded as an independent risk factor for DED. It emphasizes that we should pay greater attention to the incidence of DED among headache patients.

However, our study also has some limitations. First, there were only 11 relevant studies included. So, we could not conduct subgroup analysis on more types of headache. Second, we did not conduct co-variate analysis in our study. However, most of the included studies mentioned their adjusted confounders, making the confounding bias well-controlled. So, the results of our study were convincing and of clinical value. Finally, and most importantly, since the diagnostic criteria of DED varied in the included studies, we cannot deny the possibility of misdiagnosing neuropathic corneal pain (NCP) to DED. Particularly, in two included studies, the diagnosis of DED was determined by self-report, which might increase the misdiagnosis rate [26,27]. Therefore, ophthalmologists should pay more attention to differentiate the patients presenting with dry eye-like symptoms into DED or NCP and select the appropriate treatment strategies [49,50].

Conclusions

Our study indicates that headache increases the risk of DED, especially in migraine patients. However, more relevant studies are still required to identify the exact pathophysiological process behind this clinical phenomenon. The findings of our study can be meaningful in the prevention and treatment of DED.

Author contributions

L.J.Z. conceived the study. L.J.Z., S.Y.L. and S.F.F. collected the data. S.Y.L. conducted analysis and drafted the manuscript. S.F.F. and H.D. contributed to data interpretation and revised the manuscript. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The data sets in the study are presented in the article or supplementary material, and further information can be directed to the authors.

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