Title: The prevalence of headache disorders in Postural Tachycardia Syndrome: A systematic review and meta-analysis of the literature

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Abstract

Background

Headache is a common presentation of postural tachycardia syndrome (POTS), yet robust prevalence data is lacking.

Objectives

To undertake a systematic review and meta-analysis to estimate the prevalence of headache disorders in POTS, and to explore the potential shared pathophysiological mechanisms that underpin these conditions as well as treatment options.

Methods

Three databases were searched for publications evaluating prevalence of migraine (primary outcome) and general and orthostatic headache (secondary outcomes) in patients with POTS. Two independent reviewers selected studies and extracted data. A random-effects meta-analysis calculated the pooled prevalence of migraine in POTS. A narrative literature review explored the pathophysiology and treatment options for concurrent headache disorders and POTS.

Results

Twenty-three articles met inclusion criteria. Estimated pooled prevalence of migraine in POTS was 36.8% (95% CI 2.9-70.7%). Various shared pathophysiological pathways for these conditions, as well as proposed treatment strategies, were identified.

Limitations

Heterogeneity of study design, populations, and methodology for identifying headache disorders and POTS limited the generalisability of results.

Conclusions

Migraine is a common comorbidity in POTS, with prevalence exceeding that of the general population. Further studies are required to assess this comorbidity and investigate the underlying mechanisms, as well as identify effective treatment strategies.

Introduction

Postural tachycardia syndrome (POTS) and migraine are both disabling conditions that predominantly affect females of working age. POTS is characterised by symptoms of orthostatic intolerance of ≥6 months duration associated with an increase in heart rate by ≥30 beats per minute within 10 minutes of transitioning to a standing posture, without an accompanying fall in blood pressure of >20/10mmHg(1). International epidemiological studies are lacking, but POTS is estimated to affect approximately 0.2-1% of the population in developed countries.(2) POTS-related disability is significant, rendering up to 25% of people unable to work.(3) POTS affects females 4-5 times more often than males.(3)

Migraine is a common and disabling condition that presents with recurrent moderate to severe headache attacks and associated neurological and systemic manifestations(4). Worldwide, migraine is the leading cause of reversible disability in people under 50 years of age, affecting 1.3 billion people(4–6), with females affected two to three times more often than males(7). Although “headache” is considered to be a common presentation of POTS, it remains a poorly understood symptomatology in this cohort with respects to exact headache subtype, prevalence, pathophysiology, and optimal management strategies.

While there have been several studies reporting the prevalence of migraine and other headache disorders in POTS, there has been no attempt to systematically review these data and derive a robust prevalence estimate of migraine in POTS. Further, the common pathophysiological mechanisms underpinning these conditions warrant further exploration.

The aim of this study was to undertake a systematic review and meta-analysis of the existing literature to ascertain the prevalence of migraine and other headache disorders in POTS, and to conduct a narrative literature review to explore these conditions' potential shared pathophysiology.

Methods

Study design

A systematic review and meta-analysis of the existing literature were performed. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42020196608). In addition, a narrative review of the included articles and other highly relevant articles was undertaken to explore the

pathophysiology underpinning headache disorders and POTS, as well as treatment options.

Eligibility criteria

All cohort, case-control, or cross-sectional publications that reported the prevalence of headache in a clearly defined population of patients with POTS were included. Adult and paediatric populations were both included. Reviews, letters without original data, publications with limited methodological details, and non-English language studies were excluded. The primary outcome was the prevalence of migraine in POTS cohorts. Secondary outcomes were the prevalence of any headache disorder or orthostatic headache in this population.

Search strategy

A systematic literature review was performed of three electronic databases (Ovid MEDLINE and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions; Embase Classic+Embase and Cochrane Central Register of Controlled Trials) from inception until 6 July 2020 utilising a search strategy combining key words and related database-specific subject terms (supplementary attachment 1). Two authors (JR and XP) independently evaluated the identified publications for eligibility

on Covidence(8), performing two screening reviews of abstract evaluation followed by full-text evaluation. Discrepancies in screening results were resolved by a third author (EF). A repeat search of the literature was performed on 4th January 2022 and identified no further articles for inclusion.

Risk of bias assessment

Articles selected in the study were assessed for risk of bias using the Joanna Briggs Institute (JBI) for Critical Appraisal tool (supplementary attachment 1)(9,10). The JBI critical appraisal checklist for qualitative research was chosen as an appraisal tool for studies assessing prevalence. Risk of bias analysis was performed independently by two reviewers (JR and XP). Discrepancies were resolved by discussion between reviewers.

Data extraction

A data extraction form was utilised to extract equivalent information from each included study. Data extracted included name of the first author, year of study, country of study cohort, study design, sample size, age of cohort, duration of POTS, diagnostic criteria of POTS (if stated), prevalence of headache, prevalence of each headache type (if stated), diagnostic criteria of headache (if stated). Prevalence figures

and 95% confidence intervals were extracted or calculated from the available data using Wilson's method(11).

Two independent reviewers performed the data extraction (JR and XP). Discrepancies were discussed between the reviewers and a third reviewer arbitrated any unresolved issues.

Analysis

An initial descriptive analysis was undertaken for the included studies which reported the primary and/or secondary outcomes. Meta-analysis was undertaken of the primary outcome using a random-effects model, and a pooled prevalence figure was calculated with a 95% confidence interval. Heterogeneity between studies was assessed using the I^2 statistic, with an I^2 value above 75% indicating high heterogeneity(12). A sub-group analysis was undertaken to assess how the method of establishing migraine diagnosis affected prevalence. Sensitivity analyses were performed to evaluate the robustness of the results. Data analysis was performed in SPSS statistics (v27.0) and Microsoft Excel.

Results

Search results

The search strategy identified 504 studies for title and abstract screening, of which 23 studies fulfilled eligibility criteria for inclusion. A summary of the screening process is presented in Figure 1.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall Risk
Al-Ramadhani et al(13)	No	No	No	No	Yes	Yes	Yes	Yes	N/A	Include
Al-Shekhlee et al(14)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Ashangari et al(15)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Include
Ashangari et al(16)	No	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	Include
Barazi et al(17)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Include
Chemali et al(18)	No	No	Yes	No	Yes	Yes	Yes	Yes	N/A	Include
Chelimsky et al(19)	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Deb et al(20)	No	Yes	No	Yes	Unclear	No	Yes	Yes	Unclear	Include
Fayyaz et al(21)	No	Yes	Yes	No	Yes	No	Unclear	Yes	N/A	Include
Graf et al(22)	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Hernandez et al(23)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Kanjwal et al(24)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Kanjwal et al(25)	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Khurana et al (26)	No	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	Include
Kovacic et al(27)	No	No	No	No	No	Yes	Yes	Yes	N/A	Include
Ojha et al(28)	No	Yes	No	Yes	Unclear	Yes	Yes	Yes	Unclear	Include
Ross et al(29)	No	No	Yes	Yes	Unclear	No	No	Yes	Unclear	Include
Sousa et al(30)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Include
Staples et al(31)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Shaw et al(32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low/Moderate
Thieben et al(33)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low/Moderate
VanderPluym et al (34)	No	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	Include
Zhang et al(35)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Include

Table 1 JBI Risk of Bias

Included studies

The studies included in the analysis are summarised in Table 2. Of the included studies, 22 were cross-sectional and one a case control study in design. Twenty-one studies

were single-centre studies, and two were patient surveys. All but three studies were conducted in the USA, precluding a geographic analysis. Only two studies reported that they employed the International Classification of Headache Disorders (ICHD-3) in the study design, and three studies interviewed patients to ascertain a headache diagnosis, with the remainder relying upon the electronic medical record (EMR), or patient self-report via questionnaire. The method by which the diagnosis of POTS was established varied between the clinical studies. In 15 studies, it was determined by clinical and/or laboratory assessment, in four by review of the EMR, in two by self-report, and in two the method of diagnosis was not reported.

Risk of bias

A summary of the JBI critical appraisal of risk of bias is included in Table 3. Due to the small number of studies, no studies were excluded from the review on the basis of the risk analysis.

Analysis

Prevalence of migraine

Of the 23 eligible studies, the prevalence of migraine in POTS was reported in 16 studies (Table 4) and included in the meta-analysis. The overall prevalence of migraine in the random-effects model (Figure 2) was 36.8% (95% CI 2.9-70.7%), with a high degree of heterogeneity (I^2=86.75%).

Prevalence of headache disorder

In 12 studies, the authors either did not differentiate the headache disorder, or reported the combined prevalence of both migraine and other headache disorders (Table 4). The pooled prevalence of any headache disorder in these studies was 66.8% (95% CI 0-100%) (Figure 3). Only one of the included studies determined the

prevalence of headache by interview, and the studies had significant heterogeneity (I^2=96%), limiting detailed analysis.

Prevalence of orthostatic headache

The prevalence of orthostatic headache in patients with POTS was reported in four studies, two of which determined the diagnosis by patient interview (Table 4). The prevalence of orthostatic headache in this population ranged between 2.2% to 58.3%. Due to the small number of studies which provided this information, meta-analysis was not performed for orthostatic headaches.

Sub-group analysis based on migraine diagnosis method

A sub-group analysis was performed to explore the effect of differing methodologies for establishing migraine diagnosis on migraine prevalence. In the two studies that directly interviewed patients in order to establish a migraine diagnosis, the pooled prevalence of migraine was 92.3% (95% CI 24.0-100%) (Figure 2). The remaining studies, which relied on self-reporting via survey or EMR documentation, found a lower prevalence of migraine of 40.3% (95% CI 2.5-78.2%) and 32.1% (95% CI 4.0-60.2%), respectively.

Sensitivity analysis

Due to the small number of identified studies, no studies were excluded on the basis of the risk of bias assessment. Two sensitivity analyses were undertaken to determine the potential effect of this decision. Inclusion of articles only of a low or moderate risk of bias (answering yes to at least seven of nine questions) reported a prevalence of migraine of 36.8% (95% CI 3.0-70.7%) (Figure 4). Inclusion of studies that had undergone peer-review, excluding conference proceedings and posters, revealed a prevalence of migraine of 36.4% (95% CI 4.2-68.7%) (Figure 5).

Finally, a sensitivity analysis was undertaken to determine the effect of adult vs paediatric population on the prevalence of migraine in POTS cohorts. Restriction of the analysis to studies evaluating the paediatric population revealed a prevalence of migraine of 50.1% (95% CI 9.9-90.3%). The prevalence of migraine in adult patients with POTS in this analysis was 31.2% (95% CI 5.4-57.0) (
Figure 6).

Discussion

The prevalence of headache disorders in POTS

This is the first publication evaluating the prevalence of headache in patients with POTS through a systematic literature search. Twenty-three eligible studies were identified for inclusion in this review. A meta-analysis was performed for 16 studies evaluating the prevalence of migraine, and 13 studies for headache type unspecified.

The pooled-prevalence estimate of migraine in studies where patients were interviewed to establish the migraine diagnosis was 92.3%, higher than in studies which relied upon self-report (40.3%) or the EMR (32.1%) for migraine diagnosis. The disparity in these estimates provides an insight into the heterogeneity of the literature, and the importance of methodological control and applying ICHD-3 criteria when assessing migraine in this population. Migraine headaches may either be under-recognised by treating clinicians, leading to underestimation, or even mistakenly reported, given light sensitivity may be reported in POTS without migraine(36).

The association of POTS in patients with migraine

The Dutch population-based study of migraine, the CAMERA study, has previously reported that the rate of POTS is not increased in patients with migraine(37). Considering the question from the other perspective, on the basis of this review, it appears that there is an increased prevalence of migraine in patients with POTS compared to population estimates of 15%(38).

The persistence of orthostatic and non-orthostatic symptoms despite control of the heart rate in POTS is suggestive of an ongoing unidentified central process in patients

with POTS. Impaired processing of viscero-sensory information, conditioning, and behavioural amplification have been suggested to be contributory(39).

Orthostatic stress results in reflex sympatho-excitation from the rostral ventro-lateral medulla by reducing baro-receptor input to the nucleus of the solitary tract and activating the vestibulo-sympathetic reflex via the medial vestibular nucleus(40–44). Altered processing of interoceptive information relayed via the nucleus of the solitary tract and the parabrachial nucleus via the ventromedial portion of the thalamus could activate central circuits involved in visceral sensation, stress response and pain processing(39).

This central circuit, including the anterior cingulate cortex, insular cortex, amygdala, hypothalamus, and periaqueductal gray region have significant use-dependent synaptic plasticity which may lead to maladaptive responses to chronic stress or pain, and exhibit reciprocal interconnectivity. They may also have a role in controlling sympathetic cardiovascular output via the medulla(39,40,44–48).

Whilst untested, this theory of orthostatic stress activating the rostral ventrolateral medulla, and nociceptive activation of the thalamus and subsequent activation of

central structures involved in pain modulation, stress response, behavioural arousal, and emotional response may provide a framework for understanding the presence and persistence of orthostatic and non-orthostatic symptoms of POTS and warrants further investigation.

The association of migraine in patients with orthostatic intolerance and POTS

Orthostatic intolerance is a commonly reported symptom amongst patients with migraine. The largest study assessing the prevalence of orthostatic intolerance was the CAMERA study, which found that compared to the general population, people living with migraine had significantly higher rates of orthostatic intolerance (32 vs 12%), and frequent syncopal episodes (13 vs 5%) (37). The study did not find a correlation between severity or sub-type of migraine with autonomic symptoms, and curiously did not find an association between POTS and migraine(37).

In light of the reported orthostatic intolerance associated with migraine, attempts have been made to assess the autonomic system in migraine, with varying results, prohibiting any useful conclusions. In non-invasive assessment of the autonomic system, a majority of studies have found evidence of sympathetic hypofunction(49–

55), while other studies have found evidence of sympathetic hyperfunction(56), parasympathetic hypofunction(49,50), and parasympathetic hyperfunction(56).

Anatomically, there is a plausible connection between migraine and the autonomic nervous system (Figure 7). The nucleus tractus solitarius, locus coeruleus and periaqueductal gray are all involved in migraine as well as cardiovascular control. In particular, the periaqueductal gray region, which receives nociceptive inputs from the spinal and trigeminal dorsal horn, initiates sympathetic activation(57). Functional imaging studies would provide greater insight into the connection of these structures and their activation in patients with orthostatic intolerance.

Treatment of concomitant migraine and POTS

Recognition of the association of migraine and POTS has significance for patient management. Migraine preventative treatment may be chosen to treat both conditions, such as with beta-blockade, and lifestyle advice may need to be tailored in consideration of the co-morbidity(58,59). Further prospective study is required however to determine the optimal treatment of these comorbid conditions.

The association of orthostatic headache in patients with POTS

Orthostatic headaches are so termed due to the nature of the headache worsening with change in posture. Orthostatic headaches occurring in the setting of spontaneous intracranial hypotension is postulated to occur due to the increased gravitational pull when upright leading to an increase in brain sag at the level of the cerebrum and/or CSF hypotension(60). Pain is believed to be caused by traction of pain-sensitive structures caused by brain sag, or dilation of cerebral veins and sinuses(60). The mechanism of orthostatic headache in POTS has not been elucidated.

In the International Classification of Headache Disorders (ICHD-3), orthostatic headache is described as a key clinical feature in most cases of spontaneous intracranial hypotension (SIH)(61). SIH is caused by a spontaneous CSF leak, often due to an underlying structural weakness in the spinal meninges(62). In a prospective study, SIH has been associated with a spectrum of connective tissue abnormalities and genetic disorders(63), however this association has not been found by others(64). Conversely, orthostatic headache has also been proposed as a predictive symptom in POTS. In one study of adolescent patients referred for tilt-table testing, orthostatic headache was observed in 89.2% (33/37) who had POTS and 21.2% (7/33) patients without POTS, which in this population translated to a pre-test sensitivity of 89.2% and specificity of 78.8%(65). Orthostatic headache therefore may be a presenting symptom

of either SIH or POTS, and therefore presents a management challenge for treating clinicians. This diagnostic challenge has been highlighted by Graf, who found that in a study of patients with SIH, all patients otherwise met the criteria for POTS on autonomic testing(66).

The majority of studies included in this analysis did not phenotype orthostatic headaches, and so meta-analysis of the prevalence of orthostatic headache was not possible. Similarly, prospective studies exploring the association of orthostatic headache and POTS are lacking, and as such the cause of the association can only be speculated upon. Prospective study is required in order to characterise orthostatic headache in POTS, formulate diagnostic criteria and gain insight into the underlying aetiology. The high reported prevalence of hereditary connective tissue disorders, and alterations in cerebral blood flow described in patients with POTS are two possibly significant observations that require further enquiry(67–69).

Limitations

The major limitation of this systematic review is the heterogeneity of the literature. The majority of the reviewed articles did not differentiate between headache disorders, employ the ICHD-3 criteria, or interview patients to establish headache

subtype diagnosis, as discussed this could lead to either an under-, or over-reporting of the prevalence of migraine in POTS. Owing to the overall paucity of data, no articles were excluded on the basis of their risk of bias score, and furthermore the authors erred on the side of inclusiveness in their risk assessment, and did not require a 'gold-standard' of prospective collection of data according to ICHD-3 criteria, when considering if the condition was collected in a reliable manner (Q6/7, JBI risk of bias tool). A sensitivity analysis was performed to try and address this issue, which did not identify significant differences between included studies, however given the overall heterogeneity and the overall lack of utilisation of the ICHD-3 criteria in these studies, it remains a significant limitation. Finally, this review provides an estimate of the prevalence of migraine primarily in clinic populations, which may not be representative of the general POTS population. Given the significant disability associated with migraine(6), this review highlights the need for further prospective studies in this area to delineate the true prevalence of headache disorders in POTS.

Conclusion

Migraine and orthostatic headache are commonly reported comorbidities in patients with POTS, however on the basis of the current literature and analysis, the true prevalence cannot be reliably determined. Further studies are required to identify,

address this significant comorbidity, and investigate the underlying mechanisms and most effective treatment strategies.

Clinical Implications

- Migraine and headache disorders are common co-morbidities in patients with POTS
- Further robust prospective trials are required to assess the prevalence and impact of migraine in this population

Author contributions

JR designed the study protocol with the assistance of XP and EH. JR designed the search strategy, reviewed by XP. JR and XP independently reviewed studies for screening and data extraction, with EF as third author for resolving discrepancies. JR, MSM, SC, and EH performed data analysis/interpretation. JR was responsible for the preparation of the manuscript which was revised and edited by all authors.

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Table 2 Summary of studies included in analysis. CS; Cross-sectional, CC; Case-control, JHS; joint hypermobility syndrome, R; retrospective, P; Prospective, NIH; National Institute of Health, CIHR; Canadian Institutes of Health Research, CANet; Cardiac arrhythmia network of Canada, POTS-A; Adults with POTS, POTS-P; Paediatrics with POTS, POTS-B; Both adults and paediatrics with POTS, POTS; population group not defined; EMR, electronic medical record*

Table 3 JBI Risk of Bias

Table 4 Summary of reported prevalence of headache disorders in included studies. ICHD-3; International Classification of Headache Disorders third edition.

Figure 1 PRSIMA flowchart of studies screened for inclusion

Figure 2 Forest plot of the prevalence of migraine in patients with POTS, sub-grouped by method of data collection. CI; confidence interval, wes; weighted effect size, EMR; Electronic medical record

Figure 3 Forest plot of the prevalence of a headache disorder in patients with POTS. CI; confidence interval, wes; weighted effect size

Figure 4 Migraine prevalence sensitivity analysis – risk of bias. CI; confidence interval, wes; weighted effect size, ROB; risk of bias

Figure 5 Migraine prevalence sensitivity analysis – peer reviewed status. CI; confidence interval, wes; weighted effect size

Figure 6 Migraine prevalence sensitivity analysis – Age of population

Figure 7 Shared Migraine and autonomic pathways. Thal: Thalamus, Hyp: Hypothalamus, CVO: Circumventricular organs, PVN: Paraventricular nucleus, SON: Supraoptic nucleus, PAG: Periaqueductal Gray, LC: Locus coeruleus, NTS: Nucleus tractus solitarius, MNX: Motor Nucleus Cranial Nerve X, TCC: Trigeminocervical Complex, CVM: Caudal ventrolateral medulla, RVM: Rostral ventrolateral medulla, TNC: Caudal trigeminal nucleus, SSN: Superior Salivatory Nucleus, Hipp: hippocampus, Amy: Amygdala, ADH: Anti-diuretic Hormone

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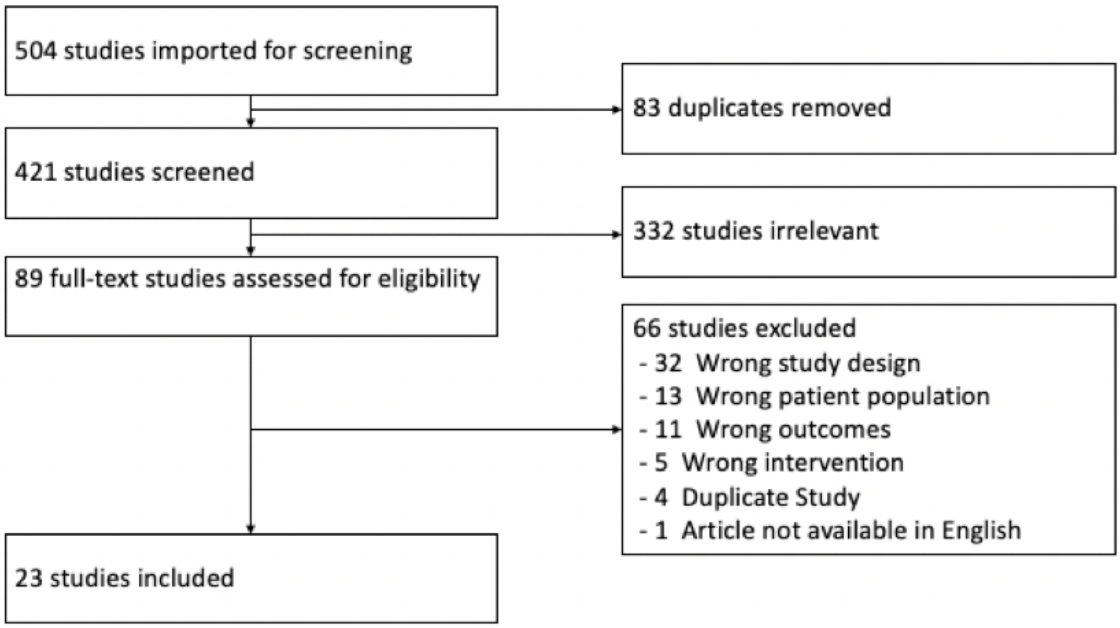
Figures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- 11 Wrong outcomes
- 5 Wrong intervention
- 4 Duplicate Study
- 1 Article not available in English
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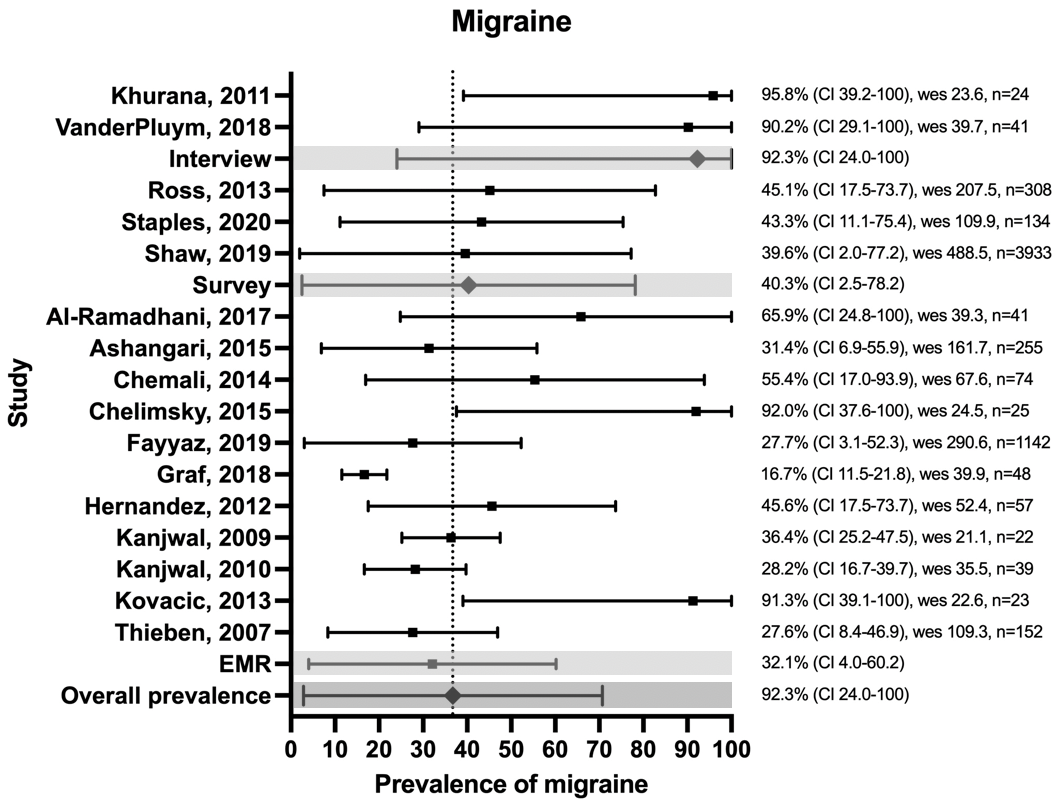
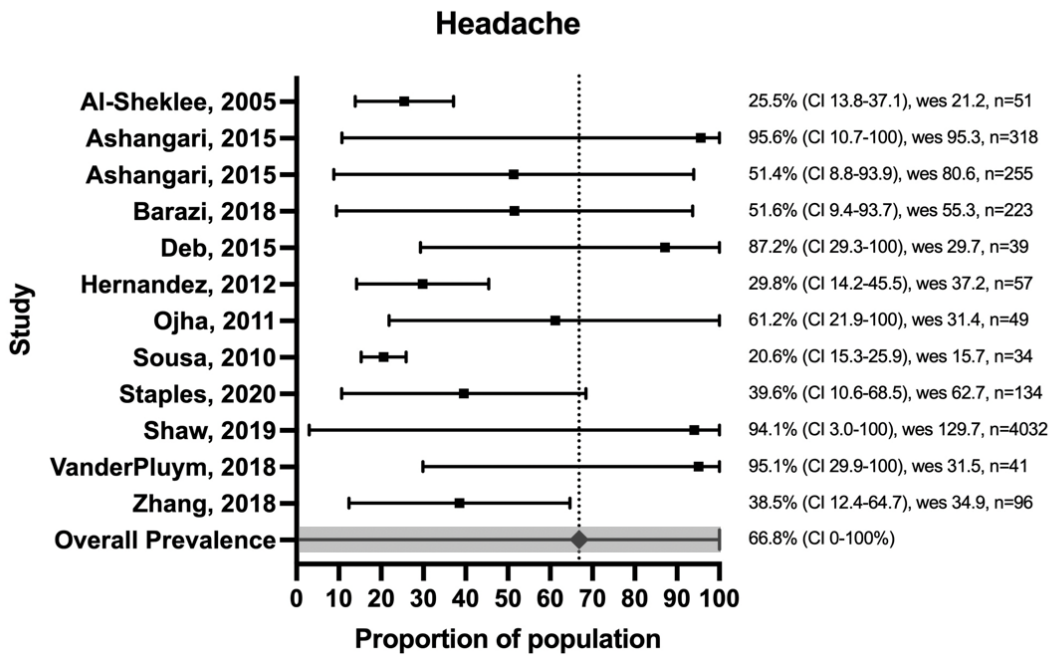
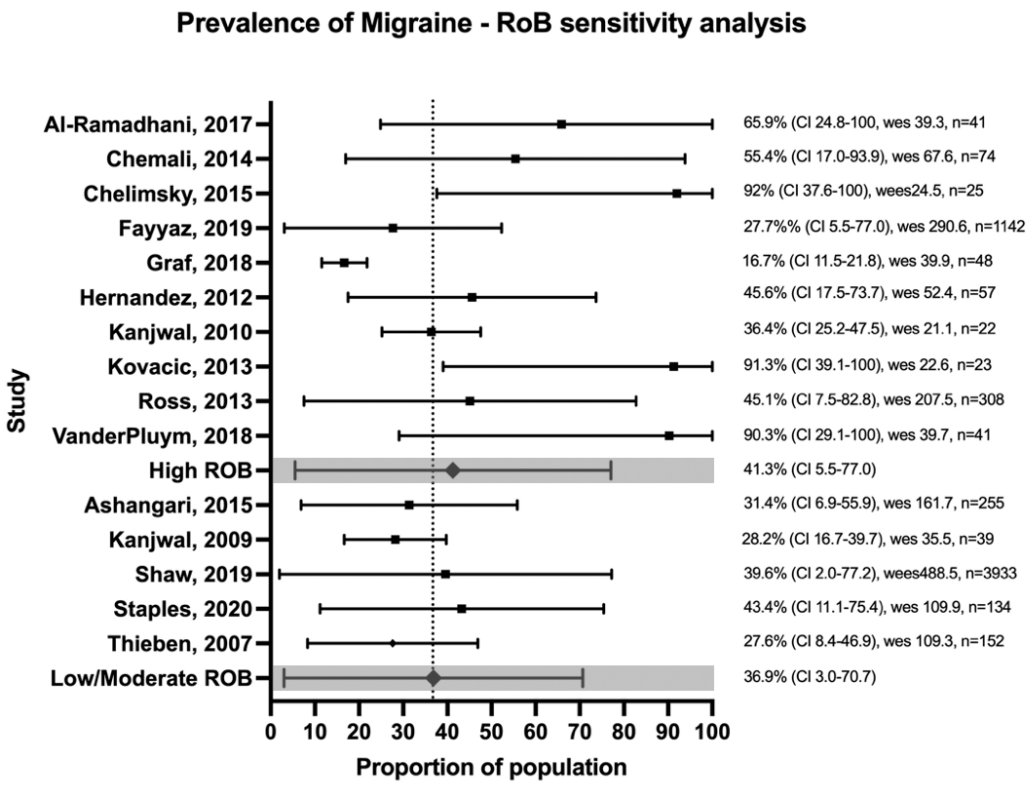
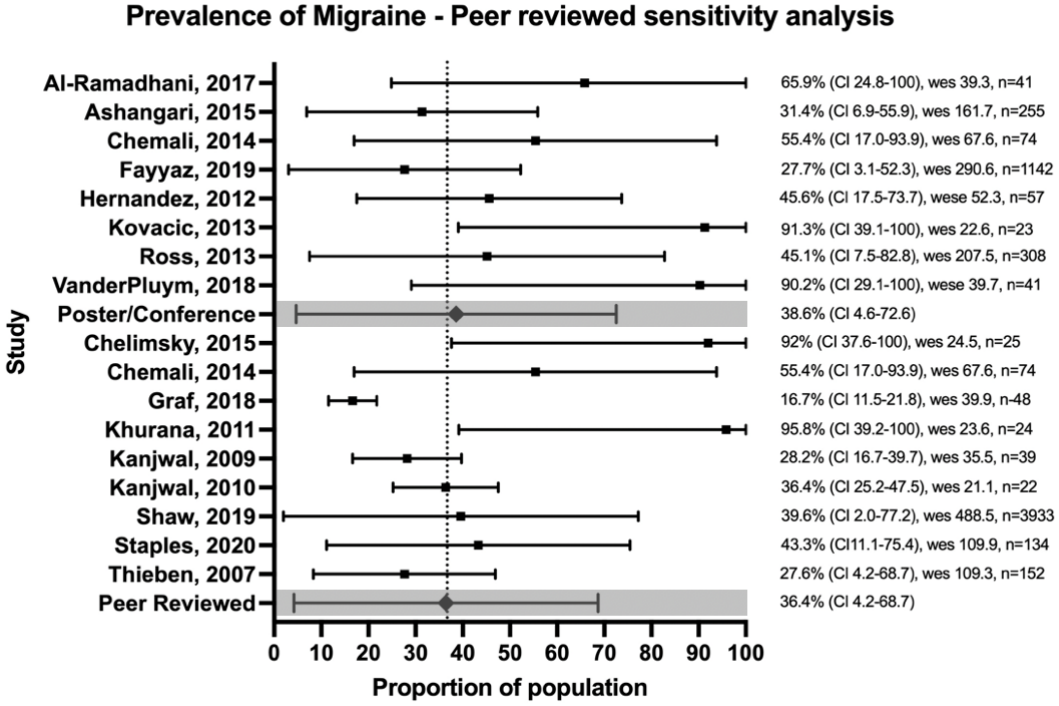

Migraine
Study
Khurana, 2011
VanderPluym, 2018
Interview
Ross, 2013
Staples, 2020
Shaw, 2019
Survey
Al-Ramadhani, 2017
Ashangari, 2015
Chemali, 2014
Chelimsky, 2015
Fayyaz, 2019
Graf, 2018
Hernandez, 2012
Kanjwal, 2009
Kanjwal, 2010
Kovacic, 2013
Thieben, 2007
EMR
Overall prevalence
95.8% (CI 39.2-100), wes 23.6, n=24
90.2% (CI 29.1-100), wes 39.7, n=41
92.3% (CI 24.0-100)
45.1% (CI 17.5-73.7), wes 207.5, n=308
43.3% (CI 11.1-75.4), wes 109.9, n=134
39.6% (CI 2.0-77.2), wes 488.5, n=3933
40.3% (CI 2.5-78.2)
65.9% (CI 24.8-100), wes 39.3, n=41
31.4% (CI 6.9-55.9), wes 161.7, n=255
55.4% (CI 17.0-93.9), wes 67.6, n=74
92.0% (CI 37.6-100), wes 24.5, n=25
27.7% (CI 3.1-52.3), wes 290.6, n=1142
16.7% (CI 11.5-21.8), wes 39.9, n=48
45.6% (CI 17.5-73.7), wes 52.4, n=57
36.4% (CI 25.2-47.5), wes 21.1, n=22
28.2% (CI 16.7-39.7), wes 35.5, n=39
91.3% (CI 39.1-100), wes 22.6, n=23
27.6% (CI 8.4-46.9), wes 109.3, n=152
32.1% (CI 4.0-60.2)
92.3% (CI 24.0-100)
0
10
20
30
40
50
60
70
80
90
100
Prevalence of migraine


Headache
Study
Al-Sheklee, 2005
Ashangari, 2015
Ashangari, 2015
Barazi, 2018
Deb, 2015
Hernandez, 2012
Ojha, 2011
Sousa, 2010
Staples, 2020
Shaw, 2019
VanderPluym, 2018
Zhang, 2018
Overall Prevalence
25.5% (CI 13.8-37.1), wes 21.2, n=51
95.6% (CI 10.7-100), wes 95.3, n=318
51.4% (CI 8.8-93.9), wes 80.6, n=255
51.6% (CI 9.4-93.7), wes 55.3, n=223
87.2% (CI 29.3-100), wes 29.7, n=39
29.8% (CI 14.2-45.5), wes 37.2, n=57
61.2% (CI 21.9-100), wes 31.4, n=49
20.6% (CI 15.3-25.9), wes 15.7, n=34
39.6% (CI 10.6-68.5), wes 62.7, n=134
94.1% (CI 3.0-100), wes 129.7, n=4032
95.1% (CI 29.9-100), wes 31.5, n=41
38.5% (CI 12.4-64.7), wes 34.9, n=96
66.8% (CI 0-100%)
0 10 20 30 40 50 60 70 80 90 100
Proportion of population


Prevalence of Migraine - RoB sensitivity analysis
Study
Al-Ramadhani, 2017
Chemali, 2014
Chelimsky, 2015
Fayyaz, 2019
Graf, 2018
Hernandez, 2012
Kanjwal, 2010
Kovacic, 2013
Ross, 2013
VanderPluym, 2018
High ROB
Ashangari, 2015
Kanjwal, 2009
Shaw, 2019
Staples, 2020
Thieben, 2007
Low/Moderate ROB
65.9% (CI 24.8-100, wes 39.3, n=41
55.4% (CI 17.0-93.9), wes 67.6, n=74
92% (CI 37.6-100), wees24.5, n=25
27.7%% (CI 5.5-77.0), wes 290.6, n=1142
16.7% (CI 11.5-21.8), wes 39.9, n=48
45.6% (CI 17.5-73.7), wes 52.4, n=57
36.4% (CI 25.2-47.5), wes 21.1, n=22
91.3% (CI 39.1-100), wes 22.6, n=23
45.1% (CI 7.5-82.8), wes 207.5, n=308
90.3% (CI 29.1-100), wes 39.7, n=41
41.3% (CI 5.5-77.0)
31.4% (CI 6.9-55.9), wes 161.7, n=255
28.2% (CI 16.7-39.7), wes 35.5, n=39
39.6% (CI 2.0-77.2), wees488.5, n=3933
43.4% (CI 11.1-75.4), wes 109.9, n=134
27.6% (CI 8.4-46.9), wes 109.3, n=152
36.9% (CI 3.0-70.7)
0 10 20 30 40 50 60 70 80 90 100
Proportion of population


Prevalence of Migraine - Peer reviewed sensitivity analysis
Study
Al-Ramadhani, 2017
Ashangari, 2015
Chemali, 2014
Fayyaz, 2019
Hernandez, 2012
Kovacic, 2013
Ross, 2013
VanderPluym, 2018
Poster/Conference
Chelimsky, 2015
Chemali, 2014
Graf, 2018
Khurana, 2011
Kanjwal, 2009
Kanjwal, 2010
Shaw, 2019
Staples, 2020
Thieben, 2007
Peer Reviewed
65.9% (CI 24.8-100), wes 39.3, n=41
31.4% (CI 6.9-55.9), wes 161.7, n=255
55.4% (CI 17.0-93.9), wes 67.6, n=74
27.7% (CI 3.1-52.3), wes 290.6, n=1142
45.6% (CI 17.5-73.7), wese 52.3, n=57
91.3% (CI 39.1-100), wes 22.6, n=23
45.1% (CI 7.5-82.8), wes 207.5, n=308
90.2% (CI 29.1-100), wese 39.7, n=41
38.6% (CI 4.6-72.6)
92% (CI 37.6-100), wes 24.5, n=25
55.4% (CI 17.0-93.9), wes 67.6, n=74
16.7% (CI 11.5-21.8), wes 39.9, n-48
95.8% (CI 39.2-100), wes 23.6, n=24
28.2% (CI 16.7-39.7), wes 35.5, n=39
36.4% (CI 25.2-47.5), wes 21.1, n=22
39.6% (CI 2.0-77.2), wes 488.5, n=3933
43.3% (CI11.1-75.4), wes 109.9, n=134
27.6% (CI 4.2-68.7), wes 109.3, n=152
36.4% (CI 4.2-68.7)
0
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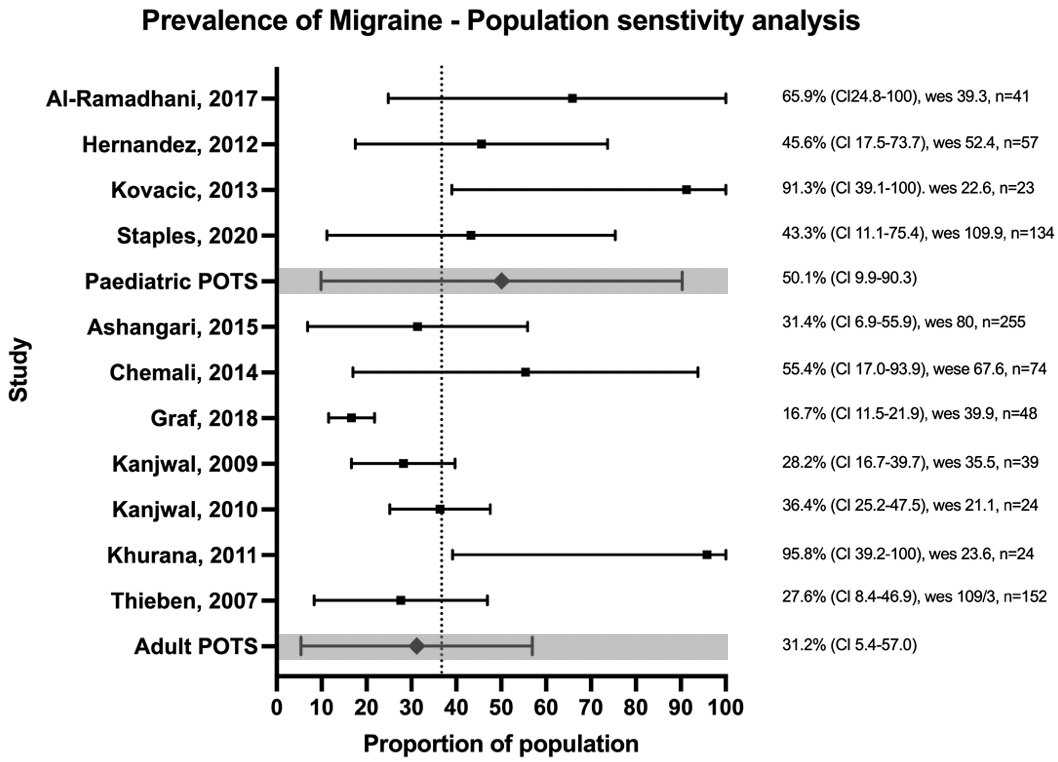
100
Proportion of population


Prevalence of Migraine - Population senstivity analysis
Study
Al-Ramadhani, 2017
Hernandez, 2012
Kovacic, 2013
Staples, 2020
Paediatric POTS
Ashangari, 2015
Chemali, 2014
Graf, 2018
Kanjwal, 2009
Kanjwal, 2010
Khurana, 2011
Thieben, 2007
Adult POTS
65.9% (CI24.8-100), wes 39.3, n=41
45.6% (CI 17.5-73.7), wes 52.4, n=57
91.3% (CI 39.1-100). wes 22.6, n=23
43.3% (CI 11.1-75.4), wes 109.9, n=134
50.1% (CI 9.9-90.3)
31.4% (CI 6.9-55.9), wes 80, n=255
55.4% (CI 17.0-93.9), wese 67.6, n=74
16.7% (CI 11.5-21.9), wes 39.9, n=48
28.2% (CI 16.7-39.7), wes 35.5, n=39
36.4% (CI 25.2-47.5), wes 21.1, n=24
95.8% (CI 39.2-100), wes 23.6, n=24
27.6% (CI 8.4-46.9), wes 109/3, n=152
31.2% (CI 5.4-57.0)
0 10 20 30 40 50 60 70 80 90 100
Proportion of population

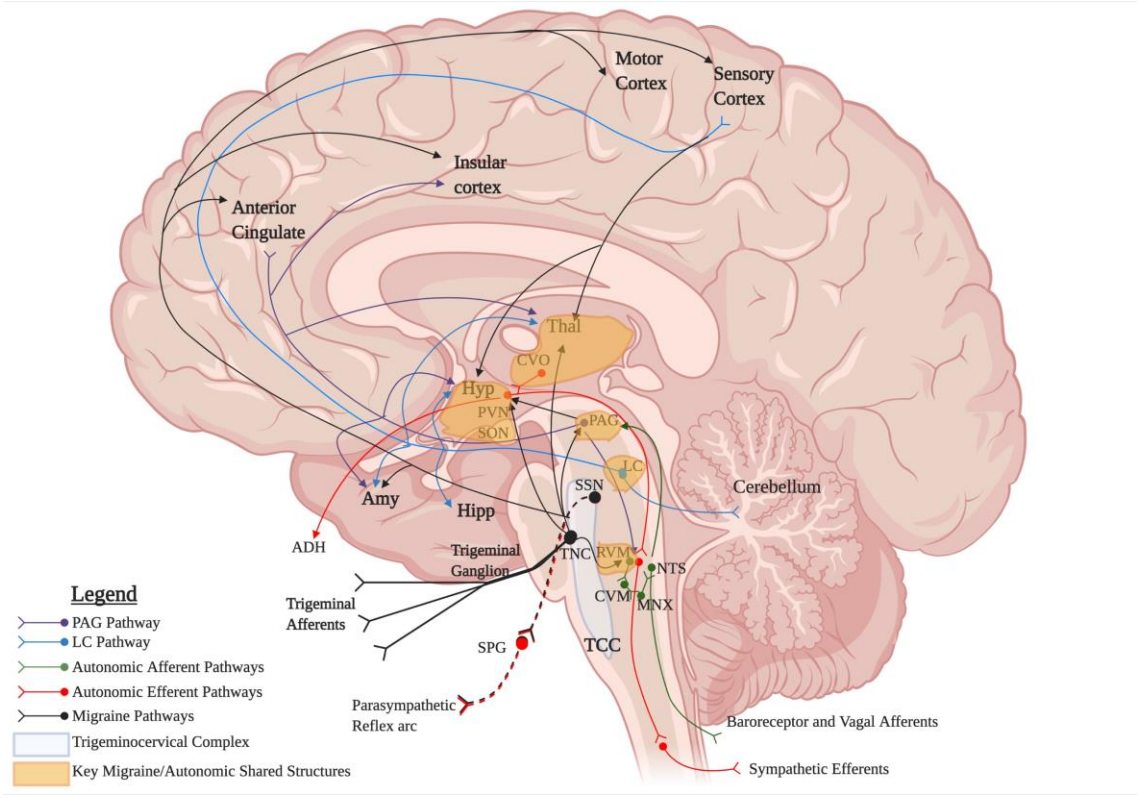

Motor Cortex
Sensory Cortex
Insular cortex
Anterior Cingulate
Thal
CVO
Hyp
PVN
SON
PAG
LC
SSN
Cerebellum
Amy
Hipp
ADH
Trigeminal Ganglion
TNC
RVM
NTS
CVM
MNX
Trigeminal Afferents
SPG
TCC
Parasympathetic Reflex arc
Baroreceptor and Vagal Afferents
Sympathetic Efferents
Legend
PAG Pathway
LC Pathway
Autonomic Afferent Pathways
Autonomic Efferent Pathways
Migraine Pathways
Trigeminocervical Complex
Key Migraine/Autonomic Shared Structures

Table 1

Study	Design	Sample size	Mean sample age (years±SD)*	Median sample age (years, IQR)	Study Location	Group	POTS diagnosis	Headache diagnosis	Evaluated for migraine
Al-Ramadhani et al[13]	CS, R	41	-	-	USA	POTS-P	Lab/clinic	EMR	Yes
Al-Shekhlee et al[14]	CS, R	87	27.7±14	-	USA	POTS-A	Lab/clinic	EMR	No
Ashangari et al[15]	CS, R	255	29.2±10.3	-	USA	POTS-A	EMR	EMR	Yes
Ashangari et al[16]	CS	318	F: 32.8±12.1 M: 31.6±14.8	-	USA	POTS-A	-	Questionnaire	No
Barazi et al[17]	CS, R	223	14.96±1.84	-	USA	POTS-P	Lab/clinic	EMR	No
Chemali et al[18]	CS, R	74	-	-	USA	POTS*	EMR	EMR	Yes
Chelimsky et al[19]	CS, R	25	-	16 (12-24)	USA	POTS-B	Lab/clinic	EMR	Yes
Deb et al[20]	CS	39	35±12	-	USA	POTS-A	Lab/clinic	Questionnaire	No
Fayyaz et al[21]	CS, R	1142	-	-	USA	POTS*	EMR	EMR	Yes
Graf et al[22]	CS, R	48	-	-	Switzerland	POTS-A	Clinical	EMR	Yes
Hernandez et al[23]	CS, R	57	15±2.2	-	USA	POTS-P	Lab/clinic	EMR	Yes
Kanjwal et al[24]	CC, R	65	30±13 (with JHS) 40±1 (without)	-	USA	POTS-A	Lab/clinic	EMR	Yes
Kanjwal et al[25]	CS, R	22	30±7	-	USA	POTS-A	EMR	EMR	Yes
Khurana et al[26]	CS, P	24	33.4±2.08	-	USA	POTS-A	Lab/clinic	Interview	Yes
Kovacic et al[27]	CS, R	23	-	-	USA	POTS-P	Lab/clinic	EMR	Yes
Ojha et al[28]	CS, R	53	P: 15±2, A: 34.8±11.2	-	USA	POTS-B	Lab/clinic	Questionnaire	No
Ross et al[29]	CS,	308	-	-	USA	POTS-B	Self-reported	Questionnaire	Yes
Sousa et al[30]	CS, R	34	-	24 (20-33)	Portugal	POTS-B	Lab/clinic	Questionnaire	No
Staples et al[31]	CS, R	134	-	15 (7-18)	USA	POTS-P	Lab/clinic	EMR	Yes
Shaw et al[32]	CS	4835	-	-	USA	POTS-B	Self-reported	Questionnaire	Yes
Thieben et al[33]	CS, R	152	30.2±10.3	-	USA	POTS-A	Lab/clinic	EMR	Yes
VanderPluym et al [34]	CS, P	41	25	-	USA	POTS*	-	Interview	Yes
Zhang et al[35]	CS, R	96	11±2	-	China	POTS-P	Lab/clinic	Interview	No

Table 1 Summary of studies included in analysis. CS; Cross-sectional, CC; Case-control, JHS; joint hypermobility syndrome, R; retrospective, P; Prospective, NIH; National Institute of Health, CIHR; Canadian Institutes of Health Research, CANet; Cardiac arrhythmia network of Canada, POTS-A; Adults with POTS, POTS-P; Paediatrics with POTS, POTS-B; Both adults and paediatrics with POTS, POTS; population group not defined; EMR, electronic medical record*

Table 2

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall Risk
Al-Ramadhani et al[13]	No	No	No	No	Yes	Yes	Yes	Yes	N/A	High
Al-Shekhlee et al[14]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Ashangari et al[15]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Ashangari et al[16]	No	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	High
Barazi et al[17]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Chemali et al[18]	No	No	Yes	No	Yes	Yes	Yes	Yes	N/A	High
Chelimsky et al[19]	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	High
Deb et al[20]	No	Yes	No	Yes	Unclear	No	Yes	Yes	Unclear	High
Fayyaz et al[21]	No	Yes	Yes	No	Yes	No	Unclear	Yes	N/A	High
Graf et al[22]	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	High
Hernandez et al[23]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	High
Kanjwal et al[24]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	High
Kanjwal et al[25]	No	No	No	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Khurana et al [26]	No	No	No	Yes	Yes	Yes	Yes	Yes	Unclear	High
Kovacic et al[27]	No	No	No	No	No	Yes	Yes	Yes	N/A	High
Ojha et al[28]	No	Yes	No	Yes	Unclear	Yes	Yes	Yes	Unclear	High
Ross et al[29]	No	No	Yes	Yes	Unclear	No	No	Yes	Unclear	High
Sousa et al[30]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	N/A	High
Staples et al[31]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate
Shaw et al[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low/Moderate
Thieben et al[33]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low/Moderate
VanderPluym et al [34]	No	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	High
Zhang et al[35]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Low/Moderate

Table 1 JBI Risk of Bias

Table 3

Study	Headache diagnosis	ICHD-3 reported	Mean sample age (years±SD)	Median sample age (years, IQR)	Female (%)	Migraine n (%)	Any headache n (%)	Orthostatic headache n (%)
Al-Ramadhani et al[13]	EMR	No	-	-	78	27/41 (65.8)	-	-
Al-Shekhlee et al[14]	EMR	No	27.7±14	-	72	-	13/51 (25.5)	-
Ashangari et al[15]	EMR	No	29.2±10.3	-	91	80/255 (31.4)	211/255 (82.7)	-
Ashangari et al[16]	Questionnaire	No	F: 32.8±12.1 M: 31.6±14.8	-	96	-	304/318 (95.6)	-
Barazi et al[17]	EMR	No	14.96±1.84	-	74	-	115/223 (51.6)	-
Chemali et al[18]	EMR	No	-	-	-	41/74 (55.4)	-	-
Chelimsky et al[19]	EMR	No	-	16 (12-24)	69	23/25 (92)	-	-
Deb et al[20]	Questionnaire	No	35±12	-	89	-	34/39 (87.2)	-
Fayyaz et al[21]	EMR	No	-	-	-	316/1142 (27.7)	-	-
Graf et al[22]	EMR	No	-	-	68.8	8/48 (16.7)	-	13/48 (27.1)
Hernandez et al[23]	EMR	No	15±2.2	-	84	26/57 (45.6)	43/57 (75.4)	-
Kanjwal et al[24]	EMR	No	30±13 (with JHS) 40±1 (without)	-	100 90	19/26 (73) 11/39 (28.6)	-	-
Kanjwal et al[25]	EMR	No	30±7	-	100	8/22 (33.3)	-	-
Khurana et al[26]	Interview	Yes	33.4±2.08	-	79.1	23/24 (95.8)	-	14/24 (58.3)
Kovacic et al[27]	EMR	No	-	-	-	21/23 (91.3)	-	-
Ojha et al[28]	Questionnaire	No	15±2, 34.8±11.2	-	75.5 88.7	-	20/44 (45.5) 30/49 (61.2)	-
Ross et al[29]	Questionnaire	No	-	-	89.9	139/308 (45.1)	-	-
Sousa et al[30]	Questionnaire	No	-	24 (20-33)	88	-	7/34 (20.6)	-
Staples et al[31]	EMR	No	-	15 (7-18)	79	58/134 (43.3)	111/134 (82.8)	3/134 (2.2)
Shaw et al[32]	Questionnaire	No	-	-	94	1557/3933 (39.6)	3794/4032 (94.1)	-
Thieben et al[33]	EMR	No	30.2±10.3	-	86.8	42/152 (27.6)	-	-
VanderPluym et al [34]	Interview	Yes	25	-	87.8	37/41 (90.2)	39/41 (95.1)	1/41 (2.4)
Zhang et al[35]	Interview	No	11±2	-	60.4	-	37/96 (38.5)	-

Table 1 Summary of reported prevalence of headache disorders in included studies. ICHD-3; International Classification of Headache Disorders third edition.