Pericranial Total Tenderness Score in Patients with Tension-type Headache and Migraine

Castien, Rene; Duineveld, Marc; Maaskant, Jolanda; De Hertogh, Willem; Scholten-Peeters, Gwendolyne

published in
Pain Physician
2021

Systematic Review

Pericranial Total Tenderness Score in Patients with Tension-type Headache and Migraine. A Systematic Review and Meta-analysis

René Castien, PhD[1-3], Marc Duineveld, MSc[4], Jolanda Maaskant, PhD[4], Willem De Hertogh PhD[5], and Gwendolyne Scholten-Peeters PhD[1]

From: [1]Department of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, The Netherlands; [2]Amsterdam Public Health Research Institute, Department of General Practice & Elderly Care Medicine, Vrije Universiteit Amsterdam, The Netherlands; [3]Health care centre, Hoofddorp, The Netherlands; [4]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp, Belgium

Address Correspondence:
René Castien, PhD
Vrije Universiteit Amsterdam
Van der Boechorststraat 9
1081BT Amsterdam
The Netherlands
E-mail:
r.castien@amsterdamumc.nl

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-24-2021
Revised manuscript received: 07-31-2021
Accepted for publication: 08-31-2021

Free full manuscript:
www.painphysicianjournal.com

Background: Increased pericranial tenderness is considered to be a typical characteristic of tension-type headache (TTH). Assessment of pericranial tenderness in TTH using the total tenderness score is recommended by the International Classification of Headache Disorders-3 (ICHD-3). However, to what extent pericranial tenderness differs between patients with TTH or migraine and healthy patients is unknown.

Objective: To assess the presence and differences in total tenderness score between patients with TTH or migraine, and healthy patients.

Study Design: Systematic review and meta-analysis.

Methods: A literature search was performed in Pubmed/MEDLINE, EMBASE, CINAHL, and Google Scholar databases from inception to August 14, 2020 and identified 4,197 hits. Two independent reviewers selected the studies, extracted data, and performed a risk of bias assessment according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Overall evidence was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. From the 185 papers identified, 15 case-control and 2 cross-sectional studies were included.

Results: In total 1,200 (327 men, 873 women) patients with TTH or migraine were included in the systematic review. In the meta-analysis, 15 studies were analyzed and showed that the total tenderness score is higher in people with episodic TTH (standardized mean difference [SMD] 0.91; 95% confidence interval [CI]: 0.63 to 1.19), chronic TTH (SMD 1.57; 95% CI 1.24 to 1.91) and migraine (SMD 1.27; 95% CI: 0.91to 1.63) compared to healthy patients.

Limitations: The description and performance of the total tenderness score differed across the studies. In 7 studies, patients were included with coexisting types of headache.

Conclusion: We found moderate quality evidence for higher tenderness in chronic TTH and migraine, and low quality evidence for higher tenderness in episodic TTH compared to healthy patients. Pericranial tenderness is a common finding in patients with headache and healthy patients. These findings apply for a critical evaluation of the total tenderness score in the current ICHD-3 classification of TTH.

Key words: Tension-type headache, migraine, pericranial muscles, mechanical sensitivity, tenderness, meta-analysis, diagnostic criteria, ICHD-3

The study protocol is preregistered in the Prospective Register of Systematic Reviews under number CRD42019103583.

Pain Physician 2021: 24:E1177-E1189

Tension-type headache (TTH) and migraine cause a high rate of disability and absenteeism at work in Western society (1). According to the Global Burden of Disease Study, TTH and migraine are among the leading neurological disorders that affect more than 10% of the global population (2-4). The total European costs of TTH and migraine are over €24 billion (5).

The diagnostic criteria for primary headache are predominantly based on the patient interview (6). In all 3 editions of the International Classification of Headache Disorders (ICHD-1,-2,-3) the total tenderness score (TTS) is recommended as a physical test for the classification of TTH (6). In the ICHD-3, the total tenderness score aims to differentiate between TTH associated with increased pericranial tenderness (ICHD-3: code 2.1.1, 2.2.1, 2.3.1) or without increased pericranial tenderness (ICHD-3 III: code 2.1.2, 2.2.2, 2.3.2) (6).

Pericranial tenderness is manually assessed by small rotating movements and pressure of the second and third finger, while the other hand supports the head (7). This test includes a 4-point scale: 0 = no visible reaction and denial of tenderness; 1 = no visible reaction but verbal report of discomfort or mild pain; 2 = verbal report of painful tenderness, facial expression of discomfort or no reaction; and 3 = marked grimacing or withdrawal, verbal report of marked painful tenderness and pain. Tenderness is assessed on 10 sites in total: frontalis-, temporal-, lateral and medial pterygoid-, masseter-, trapezius-, and sternocleidomastoid muscles; the neck insertions, the mastoid process, and coronoid process. So, the maximum total score is 60 points (10 X 3 points on each side) (7). Higher scores indicate the presence of increased pericranial muscle tenderness. A palpometer can be used to control the amount of pressure (8,9). The total tenderness score is easy to administer and perform by clinicians such as general practitioners, physiotherapists, and other health care providers to determine pericranial tenderness.

Increased pericranial tenderness has been observed in patients with TTH and is considered as the most apparent clinical finding in TTH (6,7,10,11). This finding seems not to be restricted to TTH, as pericranial tenderness is also found to be present among other types of headache, i.e., migraine and cervicogenic headache (12-16). At this moment, it is unknown to what extent pericranial tenderness, measured by the total tenderness score, is present in patients with TTH, migraine, and healthy patients. To assess potential differences in pericranial tenderness in different types of headache and healthy patients, we performed this systematic review.

This systematic review aims to summarize the score of pericranial tenderness by using the total tenderness score in patients with TTH, migraine, and cervicogenic headache, compared to healthy patients.

Methods

This systematic review was conducted and reported according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (17). The study protocol is registered in the Prospective Register of Systematic Reviews (PROSPERO) under number CRD42019103583.

Inclusion Criteria

Published case-control or cross-sectional studies which assessed the total tenderness score in adults above 18 years old, who suffered from TTH, migraine, or cervicogenic headache as diagnosed by the ICHD-1, -2 or -3 were eligible for inclusion. Studies had to be written in English and published after Langemark & Olesen (7) released their paper in 1987, in which they described the procedure for the total tenderness score.

Exclusion Criteria

Studies were excluded when they a) involved animals, b) involved patients with comorbidities like fibromyalgia or cancer, c) did not have TTH, migraine, or cervicogenic headache, d) contained no comparison with healthy patients, e) used a total tenderness score with less than 4 palpation sites, f) were published as poster presentations, conference, or abstract reports or g) did not involve unique cohorts. Studies were also excluded if they used a spin-off of a large survey by researching a small part of the total study population and reiterating the main results. Only those studies that used the total tenderness score on the entire study population were selected.

Study Selection

The systematic search was conducted by a librarian at the Amsterdam University Medical Centre (UMC) and commissioned by M.D. and R.C. The following primary databases were searched: MEDLINE, EMBASE, and CINAHL up to August 14, 2020. Simultaneously, Google Scholar and Web of Science were searched as secondary resources. The search string is presented in the Appendix. In addition, the reference lists of the included studies were searched for relevant papers. Two review authors (M.D. and R.C.) independently removed duplicates and uploaded the articles

in Mendeley reference management software version 1.18 (Elsevier, Amsterdam, Netherlands). The 2 review authors (M.D. and R.C.) independently screened titles and abstracts, and assessed potential full texts. If there were any disagreements, a third reviewer (G.S.P.) was approached to reach consensus. If there was a reason to assume the researchers used identical study populations within 2 or more studies, we included the study with the lowest risk of bias.

Data Extraction

Data from included studies were extracted by 2 review authors (M.D. and R.C.) and entered into a table. A third review author (G.S.P.) solved any discrepancies between data extractions. If numeric data were not described, authors were contacted by email. The data extraction included the following items: authors, publication date, study design; population: country, number of patients, ratio men/women, age; headache: type of headache, frequency of headache, diagnostic criteria per ICHD, sites of tenderness, use of palpometer, the timing of measurement, confounders; and outcome: scale and results.

Palpation was performed in all studies and a score for pericranial muscle tenderness was calculated.

Assessment of Risk of Bias

Risk of bias was assessed independently by 2 review authors (M.D. and R.C.) using the Dutch EBRO assessment tool III and IV (18). If necessary, we contacted the authors by email to gain more detailed information on methodological issues and extracted data.

For case-control studies, the tool contained the following items: "adequate defined cases," "adequate defined controls," "risk of selection bias," "clear and adequate measure of exposure," "blinding of participants and personnel," and "sufficient and adequate identification of confounders." For cross-sectional studies, the term "adequate defined controls" was replaced for "clearly defined outcome." All criteria were separately scored as "high," "low," or "unclear" risk of bias. Any disagreement was resolved through discussion, with the involvement of G.S.P. as a third researcher when necessary to reach consensus. To quantify the agreement, an unweighted Cohen's Kappa between the 2 reviewers was calculated. The agreement was scored as poor (0.0), slight (0.0-0.2), fair (0.21-0.4), moderate (0.41-0.6), substantial (0.61-0.8), or almost perfect (0.81-1.0) (19).

Assessment of Reporting Biases

Funnel plots were created to explore publication bias.

Assessment of Heterogeneity

Clinical homogeneity and statistical heterogeneity was assessed by M.D. and verified by R.C. Statistical pooling was considered for studies that were clinically homogeneous in terms of patient characteristics, interventions, diagnosis, study design, and outcome measures. Statistical heterogeneity was assessed by visual inspection of the Forest plots and calculation of both the Q-statistic (χ^2) and I^2-index. Meta-analyses were performed if there was clinical homogeneity and $I^2 < 75\%$ (20). The robustness of effects was verified by comparing the differences between a random effect model and the fixed effect model .

Analyses

We (re)calculated means and standard deviations (SD) when necessary from medians and range according to Luo et al (21) and Wan et al (22). If studies presented a stratified outcome by separating gender, left or right sides, or palpatory region (e.g., cervical/cephalic), a weighted mean and the SD was calculated by use of Cohen's d formula for SDpooled (23).

M.D. synthesized the outcome data from the included studies. R.C. and J.M. independently checked this procedure for potential flaws. In the pooled results, the total tenderness score is expressed as a standardized mean difference (SMD), including 95% confidence intervals.

The software used in this review consisted of R-software 3.6.0 (The R Foundation, Vienna, Austria), Microsoft Office Excel 16.16.10 (Microsoft Corp., Redmond, WA), Review Manager (RevMan) 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and GRADEpro GDT (McMaster University, Hamilton, Canada).

Quality of Evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to judge the quality of evidence for the meta-analyses data on the pericranial tenderness score (20). The quality of evidence is ranked from high to very low based on the following factors: 1) risk of bias assessment; 2) inconsistency of results, 3) indirectness of evidence, 4) imprecision of the results, and 5) other factors as publication bias. A high quality of evidence

recommendation was derived when all 5 factors met the criteria. This level was downgraded with one level (moderate) if one domain included substantial or serious risks. When 2 domains had substantial or very serious risk, the level of quality was downgraded to low or to very low when 2 or more items contained serious risks. Concerning study limitations, the evidence was downgraded when > 75% of the patients were in high risk-of-bias studies. Inconsistency was present if the direction of the effect differed (i.e., higher versus lower tenderness scores). Limitations in indirectness were reported if the study population or outcome differed. Limitations regarding imprecision were determined by the width of the 95% confidence interval (CI).

The quality of evidence was upgraded by one level if there was a large effect size (> 0.8) or 2 levels if there was a very large effect size(> 1.0, with a lower limit > 0.80).

Two authors (R.C and M.D) graded the evidence independently using Gradepro with participation of a third (G.S.P.) to reach consensus.

Results

Flow of Studies

The systematic search resulted in 2,837 relevant hits. One hundred and eighty-five hits were potentially eligible for inclusion; subsequently, 168 studies were excluded as they did not meet the inclusion criteria. We excluded one case-control study (24) that had an identical registration number and study population and was conducted by the same authors as another study. Finally, 17 studies were included in this review, all published between from 1992 through 2020: 15 case-control (25-39) and 2 cross-sectional studies (11,40). The process of study selection and reasons for exclusion are presented in Fig. 1.

Patient Characteristics

All included studies involved patients with TTH or migraine. No study on cervicogenic headache met the criteria for inclusion. In total, 1,200 patients (327 men, 873 women) were included in this review. The characteristics of the studies are summarized in Table 1.

Two cross-sectional studies (11,40) included people from a general population, which consisted of people who were randomly drawn from a central civil registration in Norway and Denmark. One cross-sectional study (40) stratified their sample by age and gender. Case-control studies recruited their patients from neurology or headache clinics (26-32,35-38), general population (39), students (25), via telephone interviews (34), or did not describe the recruitment setting (33). We calculated the mean total tenderness score for the patients with headache and healthy patients (Table 2).

Risk of Bias in Included Studies

None of the case-control and cross-sectional studies scored low risk on selection bias. Ten studies (26-29,32,34,36,37,39) had admission rate bias by not describing the origin of the control group. Other studies showed inadequate descriptions of patients with headache or controls (35,39). Six studies (26-28,34,35,40) scored high risk due to the lack of blinded examiners. Although a description of confounders is important for the interpretation of the outcome, 4 studies (11,24,26,27) reported no sufficient or inadequate identification of potential confounders. Six studies (11,27,28,30,36,40) did not mention the timing of measurement during the headache cycle (e.g., measurements in the ictal phase or interictal phase), showing no clear or adequate measure of exposure. The risk of bias of the cross-sectional and case-control studies are summarized in Figs. 2a and 2b. The scores on the risk of bias between the reviewers showed an overall agreement of 81.4% and an unweighted kappa score k = 0.91 (95%CI: 0.81 to 0.99).

Publication bias is expressed for studies describing the results of chronic TTH versus healthy patients (11,25-32,36,38,39) in Fig. 3.

Exploring Sources of Heterogeneity

We explored the methodological and statistical heterogeneity. After screening on study design, type of headache, total tenderness score measurement and outcome, one study was excluded from the meta-analysis because of the absence of dispersion measures (37). Another study was excluded because they used a reference group from another study (40). Finally, we included 15 studies (11,25-36,38,39) for a meta-analysis of total tenderness score in patients with chronic TTH and migraine versus healthy participants. Statistical heterogeneity was assessed by visual inspection of the Forest plots and calculation of both the Q-statistic and I^2-index. The robustness of effects was verified by comparing the differences between a random effect model and fixed effect model.

Episodic tension-type headache versus healthy patients

Two case-control studies (34,36) and one cross-sectional study (11) were included in the analysis and

reported a significant SMD of 0.91 (95%CI: 0.63 to 1.19), I^2 0% between episodic TTH versus healthy patients (Fig. 4). The quality of evidence for increased total tenderness score in patients with episodic TTH was low (downgraded for indirectness, see Table 3).

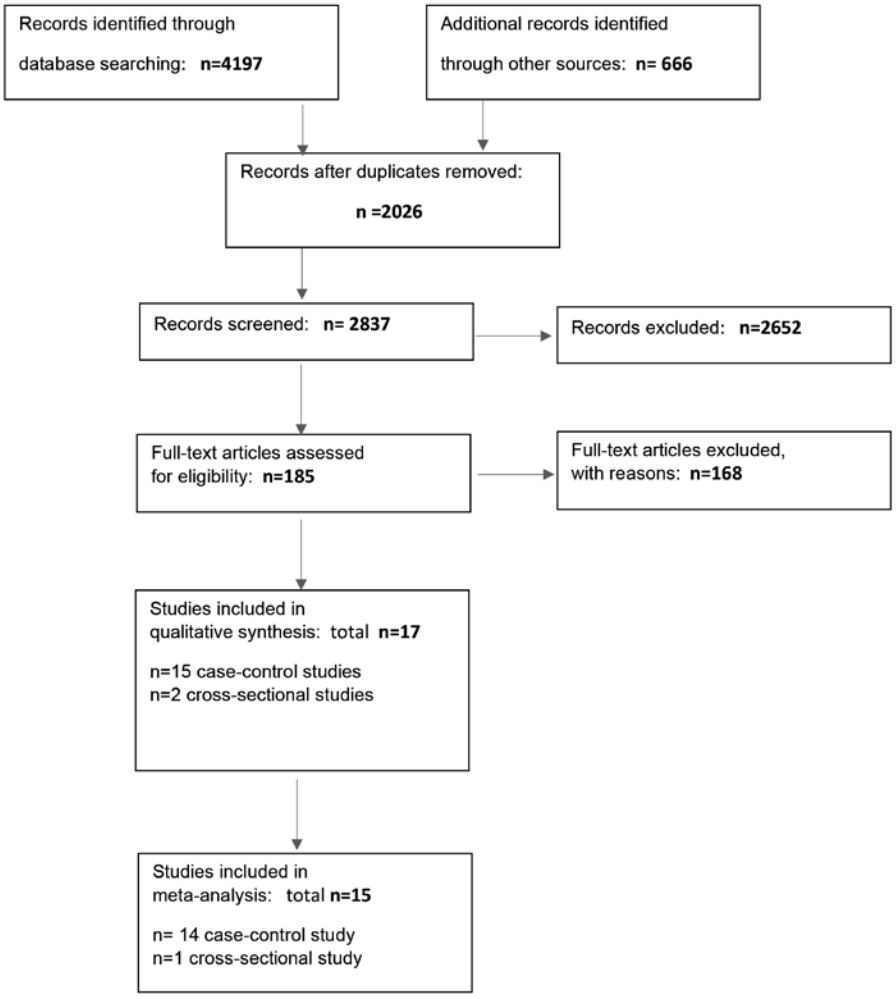

Fig. 1. *Flow diagram.*

Chronic Tension-type Headache vs Healthy Patients

Eleven case-control studies (25-32,36,38,39) and one cross-sectional study (11) were selected for statistical pooling. All studies reported higher tenderness scores in patients with chronic TTH with a pooled SMD of 1.95 (95%CI: 1.48 to 2.43], but showed an I^2 of 83% (Fig. 5). Prerequisite statistical heterogeneity was obtained after removing 2 studies (11,31), whereby I^2 was reduced from 83 to 63% with an SMD of 1.57 (95%CI: 1.24 to 1.91).

Overall, we found moderate quality evidence (downgraded for indirectness and upgraded 2 levels for effect size, see Table 3) for an increased total tenderness score in patients with chronic TTH.

Migraine vs Healthy Patients

Five studies (3 case-control studies (25,33,35) and 2 cross-sectional studies (11,40) reported tenderness scores in migraine compared to healthy patients. From the study of Hvedstrup et al (35) we retrieved 2 comparisons from healthy patients to patients with migraine without or with ictal neck pain. One cross-sectional study was excluded for statistical pooling; this study described a total mean score of the total tenderness score in patients with migraine of 21.4 points but provided no further data, even after contacting the authors (40). Statistical pooling of the results of the 3 case-control studies (25,33,35) and one cross-sectional study (11) showed an SMD of 1.27 [95%CI: 0.91 to 1.63] (Fig. 6). The quality of evidence for the total tenderness score in patients with migraine was moderate (downgraded for indirectness and upgraded 2 levels for effect size, see Table 3)

Differences Between Tension-type Headache and Migraine

In the included studies that compared patients with

Table 1. *Summary of studies.*

Author/ Year of publication	Study design, ICHD version.	Type of headache (Number of participants (men/ women)	Age (years)	TTS sides, (scale) Cervical sites	Cephalic sites	Timeframe of measurement	Blinding (yes/no)	Outcome
Aaseth et al (38)	Cross-sectional	Chronic TTH, n = 275 (64/211)	Range (30-44)	Bilateral, (0-3)		unknown	no	Mean TTS Chronic TTH: 19.7, sd 7.2
	ICHD-2	Controls, n = 31 (26/5)34		M. sternocleido-mastoideus M. trapezius Neck muscle insertion Processus mastoideus	M. masseter M. temporalis M. frontalis M. pterygoideus lateralis			
Ashina et al (24)	Case-control	Chronic TTH, n = 20 (8/12)	Mean 41,5 sd 8,2 range (26-63)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	ictal, interictal	no	Mean TTS chronic TTH 14, sd 15.96
	ICHD-1	Controls, n = 20 (8/12)	Mean 41,2 sd 13,6 range (26-62)					Mean TTS Controls 3.6 sd 5.6
Ashina et al (25)	Case-control	Chronic TTH, n= 20 (14/6)	Mean 46 sd 11 range (26-63)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	unknown	no	Mean TTS Chronic TTH: 18.9 sd 10.7
	ICHD-1	Controls, n= 20 (9/12)	Mean 46 sd 12 range (26-62)					Mean TTS Controls: 3.9 sd 3.3
Ashina et al (26)	Case-control	Chronic TTH, n = 21 (10/11)	Mean 38 range (20-59)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	unknown	no	Mean TTS Chronic TTH: 18 sd 11.6
	ICHD-1	Controls, n = 21 (9/12)	Mean 41 range (25-57)					Mean TTS Controls: 3 sd 3.2
Bendtsen et al (27)	Case-control	Chronic TTH, n = 40 (15/25)	Mean 40 range (18-60)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	unknown	yes	Mean TTS Chronic TTH: 17.7 sd 10.8
	ICHD-1	Controls, n = 40 (15/25)	Mean 39.8 range (18-60)					Mean TTS Controls: 3.4 sd 3.4
de Tommaso et al (28)	Case-control	Chronic TTH n = 18 (8/10)	Mean 39.1 sd 11.5	Unilateral, right side, (0-3)		interictal	yes	Mean TTS Chronic TTH: 5.2 sd 2.8
	ICHD-2	Controls, n = 12 (6/6)	Mean 33.6 sd 12.8	M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Sternocleidomastoid insertions M. pterygoideus			Mean TTS Controls: 0.2 sd 3.5

Table 1 (cont.). *Summary of studies.*

Author/ Year of publication	Study design, ICHD version.	Type of headache (Number of participants (men/ women)	Age (years)	TTS sides, (scale) Cervical sites	Cephalic sites	Timeframe of measurement	Blinding (yes/no)	Outcome
Fernandez-de-Las-Penas et al (29)	Case-control	Chronic TTH n = 25 (13/12)	Mean 41 sd 14 range (21-70)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Suboccipital muscles	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	headache intensity less than VAS 4	yes	Mean TTS-Total Chronic TTH: 25.6 sd 5.8
	ICHD-2	Controls, n = 25 (12/13)	Mean 39 sd 13 range (25-70)					Mean TTS-Total Controls: 9 sd 2.3
								Mean TTS-Cephalic Chronic TTH: 13 sd 3.3
								Mean TTS-Neck Chronic TTH: 12.6 sd 3
								Mean TTS-Cephalic Controls: 3.9 sd 1.8
								Mean TTS-Neck Controls: 5 sd 1.9
Fernandez-de-Las-Penas et al (30)	Case-control	Nummular Headache, n = 10 (4/6)	Mean age 39 sd 14 years	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Suboccipital muscles	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	interictal	yes	Mean TTS Nummular headache 6, sd 2.3
	ICHD-2	Chronic TTH, n = 10 (5/5)	Mean 43 sd 10 years					Mean TTS Chronic TTH: 21.7 sd 5.2
		Controls, n = 10 (5/5)	Mean 39 sd 9 years					Mean TTS Controls: 7 sd 1.9
Fernández-De-Las-Peñas et al (31)	Case-control	Episodic Migraine, N = 25 (8/17)	Mean 32 sd 7 range (20-45)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Suboccipital muscles	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus	interictal	yes	Mean TTS-Symptomatic side episodic migraine: 10.5 sd 3.4; non-symptomatic side: 5.6 sd 0.4
	ICHD-2	Controls, n = 25 (10/15)	Mean 31 sd 9 range (22-44)					Mean TTS-Dominant side Controls: 6.1 sd 2.4; non-dominant side: 5.8 sd 2.7
Hatch et al (32)	Case-control	Episodic TTH, n = 27 (5/22)	Mean 33.2 sd 8.9	Bilateral, (1-4) M. sternocleidomastoid M. trapezius Posterior cervical Suboccipital muscles	M. masseter M. temporalis	interictal	no	Mean TTS Episodic TTH: 2.26 sd 2.7
	ICHD-1	Controls, n = 32 (13/19)	Mean 32.1 sd 9.1					Mean TTS Controls: 0.06 sd 0.4

Table 1 (cont.). *Summary of studies.*

Author/ Year of publication	Study design, ICHD version.	Type of headache (Number of participants (men/ women)	Age (years)	TTS sides, (scale) Cervical sites	Cephalic sites	Timeframe of measurement	Blinding (yes/no)	Outcome
Hvedstrup et al (33)	Case-control	Migraine without ictal neck pain, n = 48 (4/44	Median 42 IQR 32-52	Bilateral, (0-3)		Interictal	no	Mean TTS migraine without ictal neck pain: 10.4 sd 7.5
	ICHD-3	Migraine with ictal neck pain, n = 52 (5/47)	Median 44 IQR 29-53	M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus			Mean TTS migraine with ictal neck pain: 13.4 sd 7.5
		Controls, n= 46 (3/43)	Median 42 IQR 31-52					Mean TTS Controls: 3.3 sd 2.9
Jensen. (35)	Case-control	Chronic TTH, n = 28 (11/17)	Mean 45 range (28-63)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus M. pterygoideus	ictal, interictal	yes	Mean TTS Chronic TTH: not estimated
	ICHD-1	Controls, n = 30 (12/18)	Mean 42 range (23-67)					Mean TTS Controls: not estimated
Jensen et al (34)	Case-control	Chronic TTH, n = 28 (6/22)	Mean 48.75 range (34-64)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus coronoideus Processus mastoideus M. pterygoideus	unknown	yes	Mean TTS Chronic TTHl: 14.1 sd 8.9
	ICHD-1	Frequent episodic TTH, n = 28 (14/14)	Mean 41.2 range (20-59)					Mean TTS Frequent episodic TTH in total: 9.8, sd 8.6
		Controls, n= 30 (12/18)	Mean 42 range (23-67)					Mean TTS Controls: 4.7, sd 7
Jensen et al (11)	Cross-sectional	Chronic TTH, n = 14 (2/12)	Range (25-64)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions M. rectus capitis post M. Splenius	M. masseter, profundus M. masseter, superficialis M. temporalis, anterior M. temporalis, posterior M. frontalis Processus coronoideus Processus mastoideus Hamulus pteryg. M. pterygoideus, lateral	79 patients had headache on the day of examination.	yes	Mean TTS Chronic TTH 32.31, sd 7.8
	ICHD-1	Episodic TTH, n = 144 (60/84)						Mean TTS EpisodicTTH 17.7, sd 5.5
		Migraine, n = 70 (16/54)						Mean TTS Migraine 16.2, sd 13.1
		Controls, n = 31 (26/5)						Mean TTS Controls 5.5, sd 6.3
Kolding et al (36)	Case-control	Chronic TTH n = 17 (7/10)	Mean 33.7 sd 14.3	Bilateral, (0-3) M. sternocleidomastoid M. trapezius Neck muscle insertions	M. masseter M. temporalis M. frontalis Processus mastoideus Processus coronoideus	Without severe headache and migraine	yes	Mean TTS Chronic TTH: 20.9 , sd 9.8
	ICDH-3	Controls, n = 29 (9/20)	Mean 32.6 sd 15.1					Mean TTS Controls: 6.9, sd 5.12

Table 1 (cont.). *Summary of studies.*

Author/ Year of publication	Study design, ICHD version.	Type of headache (Number of participants (men/ women)	Age (years)	TTS sides, (scale) Cervical sites	Cephalic sites	Timeframe of measurement	Blinding (yes/no)	Outcome
Lipchik et al (23)	Case-control	Chronic TTH n = 25 (0/25)	Mean 19 range (18-27)	Bilateral, (0-3) M. sternocleidomastoid M. trapezius (upper) Posterior cervical muscles Suboccipital muscles	M. masseter M. temporalis	interictal	yes	Mean TTS Chronic TTH: 8.1 sd 4.7
	ICHD-1	Migraine without aura n = 20 (0/20)						Mean TTS Migraine without aura: 7.6 sd 4.8
		Controls, n = 23 (0/23)						Mean TTS Controls: 1.4 sd 1.6
Lipchik et al (37)	Case-control	Chronic TTH, n = 245 (52/191)	Mean 37 range (17-65)	Bilateral, (0-3) M. trapezius (middle) Posterior cervical muscles Suboccipital muscles	M. masseter M. temporalis	ictal, interictal	yes	Mean TTS Chronic TTH Women: 7, sd 5.7 Mean TTS Chronic TTH Male: 3.8, sd 5
	ICHD-1	Controls, n = 47 (12/35)	Mean 37					Mean TTS Chronic TTH: 8.1 sd 4.7 Mean TTS Migraine without aura: 7.6 sd 4.8

TTH = Tension Type Headache, C = Controls, IQR = Inter Quartile Range, ICHD = International Classification of Headache Diseases, TTS = Total Tenderness Score, VAS = visual analog score.

Table 2. Mean total tenderness score in participants with chronic TTH, episodic TTH, migraine and healthy patients.

	Chronic TTH n = 786	Episodic TTH n = 199	Migraine n = 215	Healthy Patients n = 441
Mean	34.65	18.35	21.33	7.89
95% CI	(29.6 to -39.65)	8.54 to 28.17	16.19 to 26.48	5. to -10.48
SD	9.73	10.01	4.14	4.86

headache to controls, 3 studies (one case-control study [24], 2 cross-sectional studies [11,40]) also described the differences in tenderness score between chronic TTH and migraine. Two studies (11,24) reported no significant difference between chronic TTH and chronic migraine. One cross-sectional study showed a significant mean difference between women with chronic TTH versus migraine (mean difference 15.00 points [95%CI:8.12 to 21.88]) (40).

Discussion

This is the first systematic review with meta-analysis describing the total tenderness score in patients with headache. Low-quality evidence was found for higher total tenderness scores in patients with episodic TTH, and moderate-quality evidence for patients with chronic TTH and migraine compared to healthy patients. As pericranial and cervical tenderness is also present in patients with migraine, it seems not to be a typical characteristic of TTH.

We performed our literature search in the most relevant databases, and selected papers written in English. Because of this restriction, selection bias could be present meaning that we might have missed relevant studies.

In 10 studies (25,27,28,30-35,39) the inclusion of patients was restricted to one type of headache, i.e., migraine or TTH; the other studies (11,26,29,36,37,38,40) included patients with co-existing types of headache. Therefore, the combination of headaches in patients hampered us from drawing firm conclusions on a total tenderness score in strictly TTH or migraine, and was a reason to downgrade for indirectness. On the other hand, since many patients with headache suffer from more than one type of headache, the included combination of headaches reflects daily practice. This may increase the generalizability of our results (15,41-43).

Spectrum bias may have influenced the total tenderness score since most case-control studies recruited

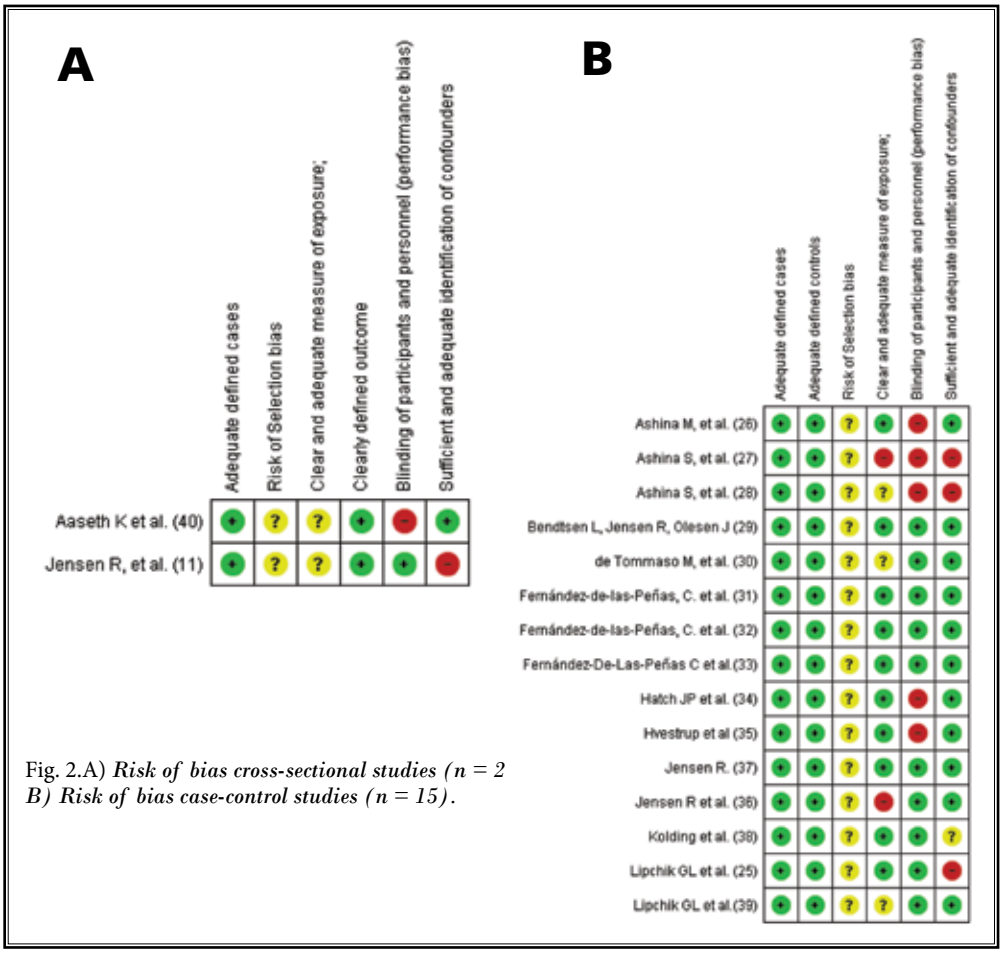

Fig. 2.A) *Risk of bias cross-sectional studies (n = 2 B) Risk of bias case-control studies (n = 15).*

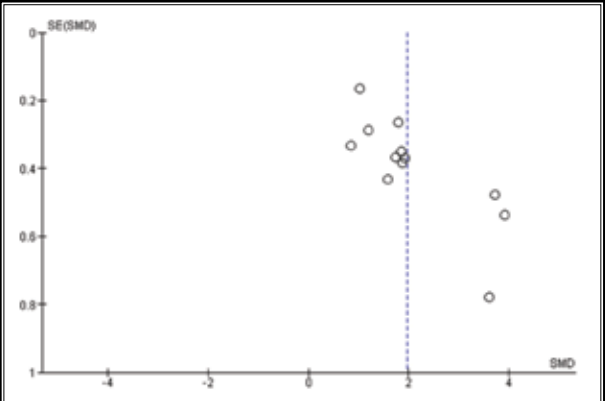

Fig. 3. *Funnel plot: chronic TTH vs healthy controls.*

their patients in headache centers. There was a wide variation in performance of the total tenderness score. None of the descriptions of the score were identical to the first published total tenderness score by Langemark & Olesen (7). Differences were noted in number, description, and scoring of measured sites. Therefore, if the total tenderness score is considered in future research, we recommend standardization of the number and localization of sites and a scoring system according to the total tenderness score described by Langemark & Olesen (7).

Three (30,31,38) out of 17 of the included studies used the ICHD criteria for chronic TTH with pericranial tenderness as an inclusion criterion. The SMDs of the TTS score in these studies are not significantly different from the other studies (Fig. 5). So, we do not believe that the difference in inclusion of TTH with or without pericranial tenderness has affected the results of our review.

In our analysis, we recalculated median scores, ranges and 95%CI intervals into mean scores and standard deviations to determine a pooled estimate. Though legitimized (21,22), this could have affected the outcome. Because the scoring of the total tenderness score differed across the studies, we calculated the standardized mean difference in the meta-analysis.

The Cochrane GRADE handbook recommends determining statistical heterogeneity by visual inspection of the Forest plots and calculation of both the Q-statistic and I^2-index with a cut-off point of 75% (20). To adhere to these recommendations, we had to modify our protocol as registered in PROSPERO in which we previously predefined a cut-off point of 70%. To fulfil the requirement for statistical homogeneity (I^2 < 75%) to pool the total tenderness score in chronic TTH compared to healthy patients, we decided to exclude

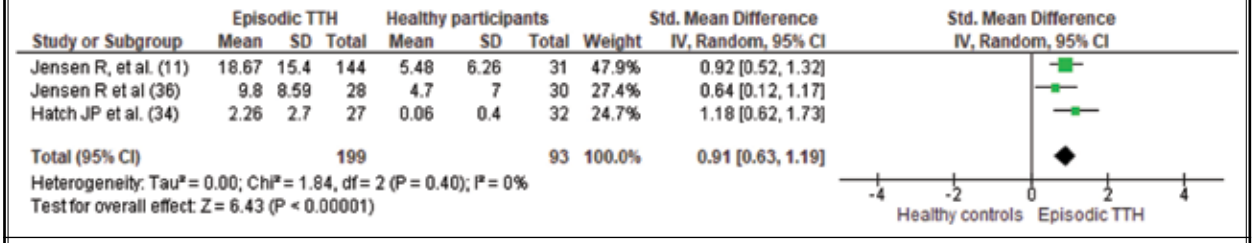

Fig. 4. *Pooled effect of the total tenderness score in episodic TTH versus healthy patients.*

Table 3. *GRADE: Level of evidence.*

	Headache type Number of patients	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Publication bias	SMD (95%CI)	Quality of evidence
	Episodic TTH versus healthy patients							
3 studies	Episodic TTT/ healthy patients: 199/93	No serious risk of bias	No inconsistency	Serious risk	No imprecision	No publication bias	0.91 (0.63 to 1.18)	low
	Chronic TTH versus healthy patients							
10 studies	Chronic TTH/ healthy patients 469/277	No serious risk of bias	No inconsistency	Serious risk	No imprecision	No publication bias	1.57 (1.24 to 1.91)	moderate
	Migraine versus healthy patients							
4 studies	Migraine/ healthy patients 215/171	No serious risk of bias	No inconsistency	Serious risk	No imprecision	No publication bias	1.27 (0.91 to 1.63)	moderate

GRADE: level of evidence SMD: standard mean difference.

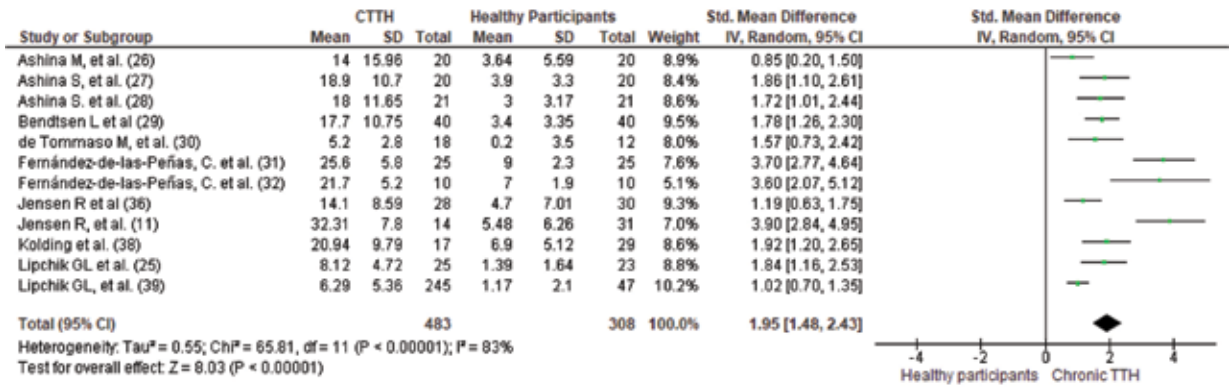

Fig. 5. *Pooled effect of the total tenderness score in chronic TTH versus healthy participants.*

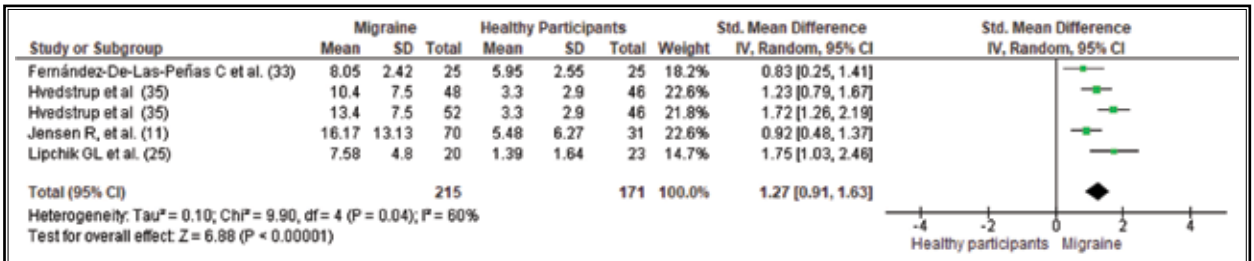

Fig. 6. *Pooled effect of the total tenderness score in migraine versus healthy participants.*

2 (11,31) out of 12 studies from the pooled results. By removing these studies one by one from the analysis in RevMan, these studies, with a total of 39 patients (8% of all patients with chronic TTH in this meta-analysis) appeared to be responsible for 20% of the change in the I^2-index, and were considered as outliers (44). The results of the remaining 10 studies were tested by using a random effect model SMD (1.57 [95%CI:1.24 to 1.91], I^2 = 63%) and a fixed-effect model SMD (1.41 [95%CI:1.23 to 1.60], I^2 = 63%), showing robust scores on SMD and reflecting a very large effects size.

Future Recommendation

The total tenderness score was promoted in the first edition of the ICHD in 1988, as a criterion for the diagnosis of muscle contraction headache (7). At present, the total tenderness score is recommended in the ICHD-3 to distinguish between TTH associated with or without pericranial tenderness. The results of our review demonstrate that pericranial tenderness assessed with the total tenderness score is a common feature, not only in different types of TTH, but also in migraine and, although lower, in healthy patients. These high scores of pericranial tenderness across multiple types of headache raises questions about the clinical utility of distinguishing TTH with (ICHD-3: 2.1.1, 2.2.1, 2.3.1) and without (ICHD-3: 2.1.2, 2.2.2, 2.3.2) the association of pericranial tenderness.

Conclusion

This meta-analysis found moderate quality evidence for patients with chronic TTH and migraine and low quality evidence for patients with episodic TTH reporting higher total tenderness score than healthy patients.

Pericranial tenderness appears not to be a typical feature of TTH, but is also present in migraine. Therefore, future updates of the ICHD should reconsider the assessment of pericranial tenderness in discriminating patients with TTH.

References

1. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. *Lancet Neurol* 2008; 7:354-361.
2. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990-2015: A systematic analysis for the Global Burden of Disease Study. *Lancet Neurol* 2015; 16:877-897.
3. Stovner LJ, Hagen K, Jensen R, et al. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007; 27:193-210.
4. Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: A systematic analysis for the Global Burden of Disease Study. *Lancet* 2016; 388:1545-1602.
5. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012; 19:155-162.
6. International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38:1-211.
7. Langemark M, Olesen J. Pericranial tenderness in tension headache: A blind, controlled study. *Cephalalgia* 1987; 7:249-255.
8. Bendtsen L, Jensen R, Jensen NK, Olesen J. Pressure-controlled palpation: A new technique which increases the reliability of manual palpation. *Cephalalgia* 1995; 15:205-210.
9. Bendtsen L, Jensen R, Jensen NK, Olesen J. Muscle palpation with controlled finger pressure: New equipment for the study of tender myofascial tissues. *Pain* 1994; 59:235-239.
10. Bendtsen L. Central sensitisation in tension-type headache--possible pathophysiological mechanisms. *Cephalalgia* 2000; 20:486-508.
11. Jensen R, Rasmussen BK, Pedersen B, Olesen J. Muscle tenderness and pressure pain thresholds in headache. A population study. *Pain* 1993; 52:193-199.
12. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: A population study. *Cephalalgia* 2015; 35:211-219.
13. Calhoun AH, Ford S, Millen C, Finkel AG, Truong Y, Nie Y. The prevalence of neck pain in migraine. *Headache* 2010; 50:1273-1277.
14. Charles A. The pathophysiology of migraine: Implications for clinical management. *Lancet Neurol* 2017; 17:174-182.
15. Fumal A, Schoenen J. Tension-type headache: Current research and clinical management. *Lancet Neurol* 2008; 7:70-83.
16. Knackstedt H, Bansevicius D, Aaseth K, Grande RB, Lundqvist C, Russell MB. Cervicogenic headache in the general population: The Akershus study of chronic headache. *Cephalalgia* 2010; 30:1468-1476.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009; 18:264-269.
18. Burgers JS, Everdingen JJ. [Evidence-based guideline development in the Netherlands: the EBRO platform] In Dutch. *Ned Tijdschr Geneeskd* 2004; 148:2057-2059
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33:159-174.

20. The Grading of Recommendations Assessment Development, and Evaluation (GRADE) https://gdt.gradepro.org/app/handbook/handbook.html
21. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; 27:1785-1805.
22. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14:1-13.
23. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd edition. L. Erlbaum Associates, Hillsdale, NJ, 1988, pp 20-26.
24. Lipchik GL, Holroyd KA, France CR et al. Central and peripheral mechanisms in chronic tension-type headache. *Pain* 1996; 64:467-475.
25. Lipchik GL, Holroyd KA, Talbot F, Greer M. Pericranial muscle tenderness and exteroceptive suppression of temporalis muscle activity: A blind study of chronic tension-type headache. *Headache* 1997; 37:368-376.
26. Ashina M, Bendtsen L, Jensen R, Sakai F, Olesen J. Muscle hardness in patients with chronic tension-type headache: Relation to actual headache state. *Pain* 1999; 79:201-215.
27. Ashina S, Babenko L, Jensen R, Ashina M, Magerl W, Bendtsen L. Increased muscular and cutaneous pain sensitivity in cephalic region in patients with chronic tension-type headache. *Eur J Neurol* 2005; 12:543-549.
28. Ashina S, Bendtsen L, Ashina M, Magerl W, Jensen R. Generalised hyperalgesia in patients with chronic tension-type headache. *Cephalalgia* 2006; 26:940-948.
29. Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol* 1996; 53:373-376.
30. de Tommaso M, Shevel E, Pecoraro C, et al. Topographic analysis of laser evoked potentials in chronic tension-type headache: Correlations with clinical features. *Int J Psychophysiol* 2006; 62:38-45.
31. Fernández-De-Las-Peñas C, Cuadrado ML, Ge HY, Pareja JA. Increased pericranial tenderness, decreased pressure pain threshold, and headache clinical parameters in chronic tension-type headache patients. *Clin J Pain* 2007; 23:346-352.
32. Fernández-De-Las-Peñas C, Cuadrado ML, Barriga FJ, Pareja JA. Pericranial tenderness is not related to nummular headache. *Cephalalgia* 2007; 27:182-186.
33. Fernández-De-Las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Side-to-side differences in pressure pain thresholds and pericranial muscle tenderness in strictly unilateral migraine. *Eur J Neurol* 2008; 15:162-168.
34. Hatch JP, Moore PJ, Cyr-Provost M, Seleshi E, Borcherding S. The use of electromyography and muscle palpation in the diagnosis of tension-type headache with and without pericranial muscle involvement. *Pain* 1992; 49:175-178.
35. Hvedstrup J, Kolding LT, Younis S, Ashina M, Schytz HW. Ictal neck pain investigated in the interictal state - A search for the origin of pain. *Cephalalgia* 2020; 40:614-624.
36. Jensen R, Bendtsen L, Olesen J. Muscular factors are of importance in tension-type headache. *Headache* 1998; 38:10-17.
37. Jensen R. Mechanisms of spontaneous tension-type headaches: An analysis of tenderness, pain thresholds and EMG. *Pain* 1996; 64:251-256.
38. Kolding LT, Do TP, Ewertsen C, Schytz HW. Muscle stiffness in tension-type headache patients with pericranial tenderness. *Cephalalgia Reports* 2018; 1:1-6.
39. Lipchik GL, Holroyd KA, O'Donnell FJ, et al. Exteroceptive suppression periods and pericranial muscle tenderness in chronic tension-type headache: Effects of psychopathology, chronicity and disability. *Cephalalgia* 2000; 20:638-646.
40. Aaseth K, Grande RB, Lundqvist C, Russell MB. Pericranial tenderness in chronic tension-type headache: The Akershus population-based study of chronic headache. *J Headache Pain* 2014; 15:58.
41. Fishbain DA, Cutler R, Cole B, Rosomoff HL, Rosomoff RS. International Headache Society headache diagnostic patterns in pain facility patients. *Clin J Pain* 2001; 17:78-93.
42. Jensen RH. Tension-type headache - The normal and most prevalent headache. *Headache* 2018; 58:339-345.
43. Lyngberg AC, Rasmussen BK, Jørgensen T, Jensen R. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. *Eur J Epidemiol* 2005; 20:243-249.
44. Rubinstein S, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019; 364:l689.

Search strategy.
PubMed/MEDLINE: 1025 hits

#	Searches
#1	"Headache Disorders"[Mesh:noexp] OR "Headache Disorders, Primary"[Mesh:noexp] OR "Migraine Disorders"[Mesh:noexp] OR "Migraine with Aura"[Mesh] OR "Migraine without Aura"[Mesh] OR "Ophthalmoplegic Migraine"[Mesh] OR "Tension-Type Headache"[Mesh] OR "Post-Traumatic Headache"[Mesh] OR cervicogenic headache*[tiab] OR post traumatic headache*[tiab] OR posttraumatic headache*[tiab] OR cgh[tiab] OR ceh[tiab] OR tth[tiab] OR ctth*[tiab] OR migrain*[tiab] OR tension type headache*[tiab] OR nummular headache*[tiab] OR tension headache*[tiab] OR headache disorder*[tiab] OR headache*[ti]
#2	"Sensory Thresholds"[Mesh] OR "Pain Threshold"[Mesh] OR "Central Nervous System Sensitization"[Mesh] OR pain sensitivity[tiab] OR quantitative sensory[tiab] OR qst[tiab] OR pain threshold*[tiab] OR pericranial sensitization[tiab] OR pericranial sensitisation[tiab] OR tenderness[tiab] OR pressure pain threshold*[tiab] OR ppt[tiab]
#3	#1 AND #2 total hits: 1,025

EMBASE (via Ovid): 1566
Database(s): Embase Classic+Embase 1947 to 2020 August 14
Search Strategy:

#	Searches
1	"headache and facial pain"/ or primary headache/ or exp migraine/ or exp tension headache/ or posttraumatic headache/ or (cervicogenic headache* or post traumatic headache* or posttraumatic headache* or migrain* or tension type headache* or nummular headache* or tension headache* or headache disorder*).ti,ab,kw. or headache*.ti.
2	exp perceptive threshold/ or exp pain threshold/ or (pain sensitivity or quantitative sensory or qst* or pain threshold* or pressure pain threshold* or ppt* or pericranial sensitization or pericranial sensitization or tenderness).ti,ab,kw.
3	1 and 2

CINAHL (via Ebsco): 363 hits

#	Searches
#1	(((MH "Tension Headache") OR (MH "Headache, Primary+") OR (MH "Migraine")) OR (TI (cervicogenic headache* or post traumatic headache* or posttraumatic headache* or cgh* or ceh* or tth* or ctth* or migrain* or tension type headache* or nummular headache* or tension headache* or headache* or headache disorder*) OR AB (cervicogenic headache* or post traumatic headache* or posttraumatic headache* or cgh* or ceh* or tth* or ctth* or migrain* or tension type headache* or tension type headache* or nummular headache* or tension headache* or headache disorder*))) OR TI headache*
#2	(TI (pain sensitivity or quantative sensory test* or qst* or pain threshold* or pericranial sensitization or pericranial sensitization or tenderness) OR AB (pain sensitivity or quantitative sensory or qst* or pain threshold* or pericranial sensitization or pericranial sensitization or tenderness)) OR TI (pressure pain threshold* OR ppt*) OR AB (pressure pain threshold* OR ppt*)
#3	#1 AND #2

Web of Science: 1243 hits
Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI

#	Searches
#1	TOPIC: (cervicogenic headache* or post traumatic headache* or posttraumatic headache* or tension type headache* or nummular headache* or tension headache* or headache disorder* or migrain*) OR TITLE: (headache*)
#2	TOPIC: (pain sensitivity or quantitative sensory or pain threshold* or pericranial sensitization or pericranial sensitization or tenderness or pressure pain threshold*)
#3	TOPIC: (test* or score* or measure* or examination or evaluation or assess*)
#4	#2 AND #3
#5	#1 AND #4

Google Scholar: 665 hits
(tension type headache* or tension headache* or migraine*) AND (pain sensitivity or quantitative sensory or threshold* or sensitization or sensitization or tenderness)