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Disturbi temporomandibolari nelle cefalee primarie: epidemiologia ed efficacia del trattamento

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ABSTRACT

Background: Headaches and temporomandibular disorders (TMD) are common problems in the general population that contribute to reduce quality of life. Over the years, literature has tried to understand the link between headaches and TMD. Many studies suggest that one disorder may be the cause of the development of the other and vice versa, but the exact relationship between these two disorders is still unknown.

Objectives: the primary aim of this study is to identify the prevalence of TMD in primary headaches as well as the prevalence of headache in TMD, in order to correctly diagnosing and managing patients with these conditions. The secondary aim is to assess the effectiveness of the physiotherapy treatment in TMD patients to reduce intensity, duration of the attacks or frequency of the pre-existent primary headache.

Materials and methods: A systematic review has been conducted according to the guidelines of the PRISMA statement. For the primary aim of the study the research for scientific articles was performed using PubMed from inception to August 2022, while for the secondary aim, the research was conducted in PubMed and Cochrane databases. The checklist of The Joanna Briggs Institute Critical Appraisal tools was used to investigate the risk of bias of the prevalence studies, while Cochrane risk of bias tool (RoB2) was used to assess risk of bias of the RCTs. Two independent reviewers performed the data analysis, assessing the relevance of the articles regarding the studies' objectives.

Results: Our review shown that the prevalence of TMD in the headache population was in a range between 25,5% to 76,6%, while the prevalence in the healthy population is around 10-15%. This shows an increase in temporomandibular disorders in patients with primary headaches. On the other hand, the prevalence of headache in TMD ranged from 6,8 to 51,5%. In both cases migraine seems to be the most frequent primary headache. Since only one study was evaluated, it was not possible to compare different articles on the effect of TMD treatment to reduce primary headache symptoms.

Conclusion: The results of this systematic review confirm that there is a strong correlation between primary headache and temporomandibular disorders and vice versa. As far as concerned the effectiveness of physical therapy treatment, the study analyzed suggests that a cervical treatment combined with a TMJ-specific one can be effectiveness for reducing pain and the impact of headache on daily life in patients with chronic migraine and TMD.

INTRODUCTION

Both headache and temporomandibular disorders (TMD) are very prevalent conditions in the general population, representing a serious health problem and a major impact on society and on the quality of life of affected individuals. (1)

The International Headache Society (IHS) defines as Primary Headaches Migraine (MH), Tension-Type Headache (TTH), Trigeminal Autonomic Cephalalgias (TACs) and Chronic Daily Headaches (CDH). In 2016, both TTH and MH were among the ten causes of greatest prevalence worldwide, with migraine as the second largest cause of disability in 2016 according to the global burden of disease (GBD). (2)

Migraine is a disabling neurovascular disorder characterized by mostly unilateral throbbing head pain and a range of neurological symptoms including hypersensitivity to light, sound, and smell; nausea; and a variety of autonomic, cognitive, emotional, and motor disorders. (3)

The pathophysiology of migraine is very complex, and studies are still underway to understand the mechanism underlying this pathology.

Most probably, migraine depends both on the activation of the trigeminovascular pathway by pain signals originating from peripheral intracranial nociceptors, and on the dysfunction of the CNS structures involved in the modulation of neuronal excitability and pain. (4)

Tension-type headache is a neurological disorder characterized by a predisposition to attacks of mild to moderate headache with few associated symptoms. The diagnosis is based on the history and examination. The underlying cause of tension-type headache is uncertain. Activation of hyperexcitable peripheral afferent neurons from head and neck muscles is the most likely explanation for episodes of infrequent tension-type headache. (5) Muscle tenderness and psychological tension are associated with and aggravate tension-type headache but are not clearly its cause. Abnormalities in central pain processing and generalized increased pain sensitivity are present in some patients with tension-type headache. (6)

It is known that patients with primary headache may suffer from other comorbidities such as psychological disorders caused by the chronicity of the problem (7) or musculoskeletal problems such as neck pain (reported in 62-90% of MH and TTH patients) (8); or temporomandibular disorders.

Temporomandibular disorders (TMD) are a group of heterogeneous conditions affecting the masticatory muscles, temporomandibular joint (TMJ), and associated structures.1 According to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/ TMD), common categories of TMD include group I Muscle Disorders, group II Disc Displacements, and group III Arthralgia, Arthritis, and Arthrosis. (9)

The pathophysiology of temporomandibular pain appears to be related to peripheral mechanisms, which may be initiated by excessive TMJ loading, causing pain by mechanical stimulation of nociceptors, increased release of neuropeptides and inflammatory mediators, and/or local hypoxia. Nociceptive input sustained by painful TMJ appears to lead to sustained sensitization of central nervous system neurons intercalated in ascending pain pathways. This central sensitization is thought to help lower TMJ pain thresholds and tolerance, as well as provide a neural mechanism that may underlie the development of referred pain and generalized pain sensitivity in patients with TMD. (10)

Some patients with TMD may also have a reduced capacity for endogenous pain modulation that causes an increased propensity to develop chronic pain conditions. Psychosocial stressors can also directly and/or indirectly influence the biological processes involved in craniofacial pain, as many of the molecules that mediate stress responses are the same as those associated with pain modulation. Indeed, stress can both increase parafunctional activities and activate the sympathetic nervous system to alter metabolism and blood flow. (11)

In 2018, the International Classification of Headache Disorders 3rd edition (ICHD-3) defined headaches attributed to TMD (TMDH) as a headache caused by a disorder involving the structures in the temporomandibular region. The diagnostic criteria included evidence of causation as demonstrated by at least 2 of the following criteria: 1. The headache has developed in temporal relationship to the onset of TMD, or led to its discovery; 2. The headache is aggravated by jaw motion, jaw function (e.g., chewing), and/or jaw parafunction (e.g., bruxism); and 3. The headache is provoked on physical examination by temporalis muscle palpation and/or passive movement of the jaw. (3)

However, TMDs can co-occur with primary headaches. This is important to know because often in clinical practice the physiotherapist is faced with headache patients suffering from TMJ disorders and could attribute the cause of the headache to temporomandibular disorder just because the primary headache has not yet been diagnosed by a neurologist.

In the past years, many studies tried to understand the link between headache and TMD, suggesting that TMD could be a risk factor for the development of Headaches and viceversa. However, the exact relationship between these two diseases is still unknown. (12)

The association between migraine and TMD may be due to multiple biopsychosocial factors, such as shared physiology, genetics, psychological traits, and environmental influences.
Among psychological factors, depression and anxiety are consistently reported as risk factors for both migraine and TMD. (13) (14)2 In addition, behavioral factors, such as stress, can also contribute to the pathogenesis of both conditions. (15)

Therefore, the primary aim of this study is to identify the prevalence of TMD in primary headaches as well as the prevalence of headache in TMD, in order to correctly diagnosing and managing patients with these conditions.

The secondary aim is to assess the effectiveness of the physiotherapy treatment in TMD patients to reduce intensity, duration of the attacks or frequency of the pre-existent primary headache.

METHODS

Part 1. Systematic Review of prevalence

Protocol and registration

The Systematic Review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA-P) guidelines. (16)

Eligibility Criteria

The selection criteria employed in this review was based on population and study design, since the reviewers investigated the epidemiology in people who have been diagnosed with concurrent presence of primary headache and Temporomandibular Disorders (TMD).

We included studies assessing male and female participants without any age restriction with a diagnosis of primary headaches such as migraine, tension-type headache (TTH), and any kind of TMD.

The diagnosis of headaches had to take place through a neurological examination by a neurologist specialized in the diagnosis of primary headache according to the second or third edition of the International Classification of Headache Disorders (ICDH-II/ICDH-III). (3,17)

We included any type of study design aiming to investigate prevalence of TMD in primary headaches and viceversa (e.g., cross-sectional, case-control, prospective and retrospective cohort studies).

There were no restrictions on publication dates. The authors excluded articles which were not English or Italian-published.

Descriptive observational designs, such as case report and case series were excluded.

Search Strategy

The search for scientific articles was performed using PubMed and Cochrane from inception to August 2022. The authors used MeSH and non-MeSH terms to run the search strategy and combine them with boolean operators. The MeSH terms are the following: "migraine disorders", “headache”, “headache disorders”, "temporomandibular joint disorders", “temporomandibular joint dysfunction syndrome”, "craniomandibular disorders", “epidemiology”, “prevalence”, “incidence“, “population”. On the other hand, the non-MeSH terms are: "primary headache", “headache”, "head pain", “cephalalgia”, “cephalgia”, “hemicrania”, “migraine”, "migraine disorder", "migraine headache", "hemicrania migraine", “tension-type headache”, "temporomandibular joint disorders", "temporomandibular joint dysfunction syndrome", "TMJ disorders",

"temporomandibular disorders", "temporomandibular joint diseases", "TMJ diseases" and “temporomandibular”. The entire Pubmed search strategies are reported in the appendix. [A]

Study selection

The selection and data collection process were done by two independent reviewers.

The authors used “Rayyan” (https://rayyan.qcri.org), a software used to screen and select studies, to manage records and data throughout the review. (18)

We didn’t extract any useful articles from the search strategy Cochrane because the database provides only systematic reviews and not prevalence studies.

Titles and abstracts obtained from Pubmed only were screened. Then, full texts of the identified studies were obtained for further assessment and analyzed independently according to the eligibility criteria by two reviewers.

Data collection

Two independent reviewers extracted the following information from the included studies: study design; author and year of publication; the number and characteristics of participants/populations; location of study, method of diagnosis of primary headache and TMD; outcomes (prevalence of TMD in association with primary headaches and viceversa).

Risk of bias in individual studies

Two independent reviewers assessed the Risk of Bias (RoB) of the included studies using the Joanna Briggs Institute Critical Appraisal tools (19) according to the specific study design.

The following checklist was used for the prevalence studies:

1) Was the sample frame appropriate to address the target population?
2) Were study participants recruited in an appropriate way?
3) Was the sample size adequate?
4) Were the study subjects and the setting described in detail?
5) Was the data analysis conducted with sufficient coverage of the identified sample?
6) Were valid methods used for the identification of the condition?
7) Was the condition measured in a standard, reliable way for all participants?
8) Was there appropriate statistical analysis?

9) Was the response rate adequate, and if not, was the low response rate managed appropriately?

Data Synthesis and Analysis

We used descriptive statistics to synthesize data in narrative formats and tabulating study characteristics. We reported the data related to the prevalence and incidence from each study.

Part 2: Systematic Review of intervention

Eligibility Criteria

The selection criteria employed in this review was based on methodological and clinical aspects such as the Population, Intervention, Control, Outcomes, and Study design (PICOS).

The Systematic Review (SR) included studies with male and female participants of any age diagnosed with concurrent presence of primary headache and Temporomandibular Disorders (TMD).

We included RCTs only as they are the best study design to assess the effectiveness of health-related interventions.

There were no restrictions on publication dates. Non-English and non-Italian articles were excluded.

We included any type of physical therapy treatment such as manual therapy (e.g., mobilization, manipulation), exercise (e.g., aerobic, strength), stretching, education (e.g., pain neuroscience education) and self-management compared to any control (e.g., no-treatment, usual care or any other conservative intervention). Articles were excluded when acupuncture and stabilization splint were the only intervention.

Search Strategy

The search for scientific articles was performed using PubMed (1963-2022) Cochrane (1985-2022) and PEDro (1988-2021). The search string was carried out in August 2022.

The authors used MeSH and non-MeSH terms to run the search strategy and combine them with boolean operators. The MeSH terms are the following: "migraine disorders", “headache”, “headache disorders”, "temporomandibular joint disorders", “temporomandibular joint dysfunction syndrome”, "craniomandibular disorders", "musculoskeletal manipulations", "physical therapy modalities", “rehabilitation” and "exercise therapy”. On the other hand, the non-MeSH terms are: "primary headache", “headache”, "head pain", “cephalalgia”, “cephalgia”, “hemicrania”,

“migraine”, "migraine disorder", "migraine headache", "hemicrania migraine", “tension-type headache”, "temporomandibular joint disorders", "temporomandibular joint dysfunction syndrome", "TMJ disorders", "temporomandibular disorders", "temporomandibular joint diseases", "TMJ diseases", “temporomandibular”, "musculoskeletal manipulation", "physical therapy modality", "physical therapy techniques", "manual therapy", "physical therapy", “rehabilitation”, “physiotherapy”, “management”, “treatment”, "aerobic exercise", "physical activity", “education”, “multidisciplinary”, "exercise programs", “exercise” and “multimodal”.
The entire Pubmed, Cochrane and Pedro search strategies are reported in the appendix. [A]

Study selection

The selection and data collection process were done by two independent reviewers.
The authors employed “Rayyan”, a software used to screen and select studies, to manage records and data throughout the review. (18)
Titles and abstracts obtained from PubMed and Cochrane were screened. Then, full texts of the identified studies were obtained for further assessment and analyzed independently according to the eligibility criteria by two reviewers.

Data collection

Two independent reviewers extracted the following data: study, population features, TMD and headache classification, type of interventions and outcomes.

Outcomes and Prioritization

The primary outcome was the reduction of headache pain intensity. The secondary outcomes were the reduction of frequency of attacks and duration. Other symptoms and any adverse event were reported.

Risk of bias in individual studies

Quality assessment of the studies was performed using the Cochrane Risk of Bias tool (RoB 2). Particularly two independent reviewers assessed the following domains:

1) bias arising from the randomization process;
2) Bias due to deviations from intended interventions;
3) Bias due to missing outcome data;

4) Bias in measurement of the outcome;
5) Bias in selection of the reported result. (20)

The response options for the signaling questions were:

1) Yes: it may be indicative of either a low or high risk of bias, depending on the most natural way to ask the question.
2) Probably yes: it has the same implications for risk of bias as the answer "yes"
3) No: it may be indicative of either a low or high risk of bias, depending on the most natural way to ask the question.
4) Probably no: it has the same implications for risk of bias as the answer "no"
5) No information: it should be used only when both insufficient details are reported to permit a response of “Probably yes” or “Probably no”.

The tool includes algorithms that map responses to signaling questions onto a proposed risk-of-bias judgement for each domain. The possible risk-of-bias judgements were:

- Low risk of bias: the study is judged to be at low risk of bias for all domains for this result.
- Some concerns: the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- High risk of bias: the study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result. (20)

Data Synthesis and Analysis

We synthesized data in narrative formats and tabulated the studies' intervention characteristics by descriptive statistics. We summarized the main results in the RCTs and compared each primary and secondary outcome.

RESULTS

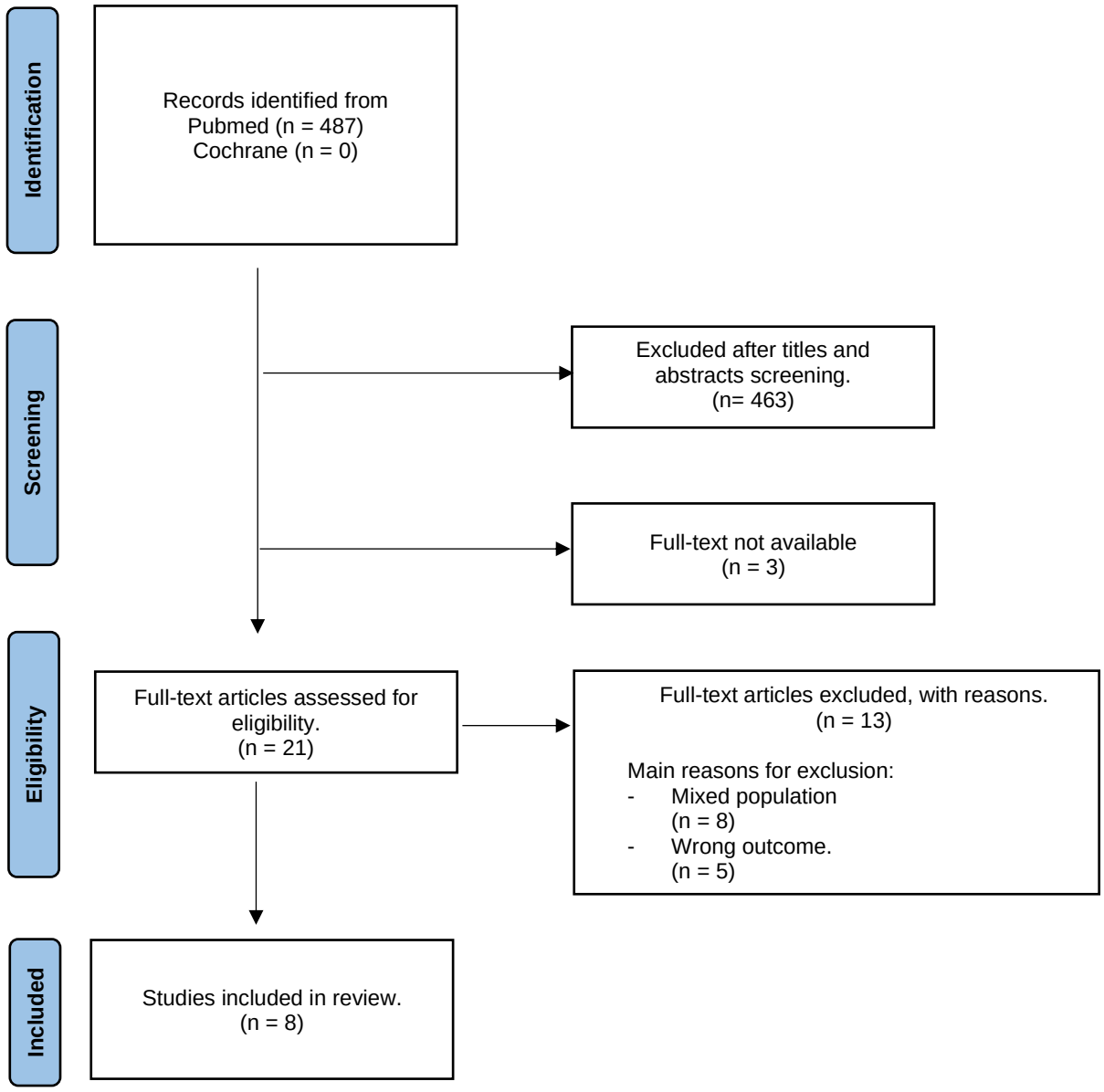
Part 1. Part 2: Systematic Review Prevalence

Study selection

Overall, 487 records were screened and 463 were discarded. No studies were retrieved on Cochrane.

Of 24 articles 3 articles were not found. The full text of the remaining 21 potentially eligible articles was assessed, 13 of which did not meet inclusion criteria because they were on non-specific headaches and didn't involve primary headaches (n=8). On the other hand, most of the studies analyzed different types of outcomes (e.g., the comorbidities TMD-related), but not the relationship between primary headaches and TMD) (n=5). Finally, 8 studies (listed in **Appendix A**) were included in the systematic review.

Figure 1 illustrates the flow diagram of study selection.



General characteristics

Four studies were cross-sectional studies, four cohort, published between 2010 and 2020. Half studies (n=4) reported a healthy control group. Half studies were conducted in Brazil (n=4; 50%). Five studies assessed the epidemiology of **TMD in 2203 headache patients (652 migraine; 1448 TTH; 88 CDH; 15 TACs).** Of these, four assessed the prevalence and one assessed the incidence in one year. Conversely, three studies assessed the prevalence of headache in 6640 TMD patients. In six studies, primary headaches were diagnosed by the diagnosed criteria of ICDH-III, whereas in two studies (21)(22) the diagnostic criteria were unclear (diagnosis on assurance codes and self-reported

headaches). As regards TMD the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) were used in three articles (22–24); the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) in one article (25); questionnaires (26–28) and assurance code (21) in the other four articles.

All details about general characteristics are presented in **Table 1.**

Table 1

Prevalence of TMD in headache								
	Study design	**Author, year**	**Location**	**Simple size**	**Setting**	**Gender**	**% males**	**Mean age (years) +SD**
1	Cross sectional	Fergane et al., 2021	Turkey	316 headaches 32 secondary headaches	Neurology Clinic and Research Hospital	90 Males 258 Females	25.8%	37.3 ± 13.2
2	Cross sectional	Florencio et al., 2017	Brasil	84 samples: episodic migraine (EM)= 31, chronic migraine (CM) = 21, healthy women = 32	University-based hospital	All Women	0%	M= 33 ± 11 CM= 35 ± 10 controls= 31 ± 9
3	Cohort study	Goncalves et al., 2011	Brasil	235 Headaches (ETTH= 43 MH= 104 CDH= 88)	University-based specialty clinic	52 Males 248 Females	17.3%	37.84 ± 13,03

				53 controls				
4	Cohort study	Tchivileva et al., 2017	USA	1571 (TTH= 1310 MH=248 Mixed=13)	Multicenter	967 Males 1443 Females	40.10%	52.5% were in te 18-24 yo
5	Cross sectional	Tomaz-Morais et al., 2015	Brasil	42 Headache patients	Neurology clinic	25 males 17 females	59.5 men	31

Prevalence of headache in TMD								
	Study design	**Author, year**	**Location**	**Simple size**	**Setting**	**Gender**	**% males**	**Mean age (years) +SD**
6	Cohort study	Byun et al., 2020	Korea	3884 TMD patients	General Population	1753 males 2131 females	45.1%	Not provided
				15536 controls		7012 males 8524 females		
7	Cohort study	Di Paolo et al., 2017	Italy	929 TMD patients	TMD Clinic	Not provided	Not provided	25.3% were in the 26–40
8	Cross-sectional	Gonçalves et al., 2010	Brazil	1230 (at least one TMD symptom = 430)	General Population	597 Males 633 Females	48.5%	51% were in the 20-45

Prevalence of TMD in headache

Five studies assessed the epidemiology of TMD in headache (four assessed the prevalence and one assessed the incidence in three years). The prevalence of the four studies ranged from 25.5% to 76,6% (Table 2).

Incidence of TMD in headache

The incidence of TMD in subgroups was 2.6 % (2.1-3.2) in TTH patients and 3.7% (2.6-5.3) in patients with migraine.

Prevalence of headache in TMD

Three studies assessed the prevalence of headache in TMD patients. The prevalence ranged from 6,8 to 51,5%. All details are presented in Table 3.

Risk of bias

In general, the quality of the prevalence studies was quite good. Di Paolo et al. did not distinguish between primary and secondary headaches but indicated the prevalence data on general headaches, which was quite high. Furthermore, the article reported only the percentage of some subgroups of primary headaches in association with TMD disorders, without reporting the total. This could be considered a coverage bias. In addition, the study subjects and setting were not described in detail. In Tchivileva's et al. study, on the other hand, patients were not properly recruited, but they were screened by telephone interviews. In almost all studies, valid methods were used to identify conditions, except in Tchivileva and Byun's et al studies. The most appropriately conducted studies are those of Goncalves 2010, 2011 et al.

All details about Risk ok Bias are presented in **Table 4**.

Table 2

Prevalence of TMD in headache					
	Author, year	**TMD diagnosis**	**Headache diagnosis**	**Prevalence**	**Subgroups**
1	Fergane et al., 2021	RDC/TMD	ICHD-III	25,5% of participants with primary headache reported TMD.	Prevalence of TMD in subgroups of headache: TTH: 17,6% MH: 30%
2	Florencio et al., 2017	The Fonseca's questionnaire	ICHD-III	Headache group: 76,6% reported TMD pain. Control group: 54% reported TMD pain.	Prevalence of TMD in subgroups of headache: EM: 78% CM: 100%
3	Gonçalves et al., 2011	RDC/TMD	ICHD-II	Headache group: 31,5% reported TMD pain. Control group: 55,4% reported TMD pain.	Prevalence of TMD in subgroups of headache: ETTH 14,98% CDH 35,22% MH 35,22%
4	Tomaz-Morais et al., 2015	The Fonseca's questionnaire	ICHD-II	54,8% of participants with primary headache reported TMD.	Prevalence of TMD in subgroups of headache:

					TTH: 38,1% MH: 71,4%
5	Tchivileva et al., 2017	RDC/TMD	Self-reported headache and ICHD-III		Incidence of TMD in subgroups: TTH 2,6 % (2.1-3.2) MH 3,7% (2.6-5.3)

Table 3

Prevalence of headache in TMD					
	Author, year	**TMD diagnosis**	**Headache diagnosis**	**Prevalence**	**Subgroups**
6	Byun et al., 2020	ICD-10	ICD-10	6,8% of participants with TMD reported primary headache (migraine).	0,3% of participants with TMD reported migraine with aura and 6,5% reported migraine without aura.
7	Di Paolo et al., 2017	DC-TMD	ICHD-III	The prevalence of all primary headache was not proved.	22,28% of participants with TMD reported TTH; 40,6% reported MH.

8	Gonçalves et al., 2010	Questionnaire adapted from AAOP proposal	ICHD-II	TMD group: 51,5% reported primary headache. Control group: 27,7% of participants without TMD reported primary headache.	58,2% of participants with TMD reported MH; 66,7% reported CDH; 41% reported ETTH.

Table 4

PREVALENCE STUDIES		**Fergane**	**Florencio**	**Tomaz-Morais**	**Gonçalves 2010**	**Byun**	**Di Paolo**	**Gonçalves 2011**	**Tchivileva**
1	**Was the sample frame appropriate to address the target population?**	yes	yes	yes	yes	yes	yes	yes	yes
2	**Were study participants recruited in an appropriate way?**	yes	yes	yes	yes	yes	yes	yes	no
3	**Was the sample size adequate?**	unclear	unclear	unclear	yes	unclear	unclear	no	yes
4	**Were the study subjects and the setting described in detail?**	yes	yes	yes	yes	yes	no	yes	yes

5	**Was the data analysis conducted with sufficient coverage of the identified sample?**	yes	no	yes	yes	unclear	no	yes	yes
6	**Were valid methods used for the identification of the condition?**	yes	yes	yes	yes	no	yes	yes	no
7	**Was the condition measured in a standard, reliable way for all participants?**	unclear	unclear	unclear	unclear	unclear	yes	yes	no
8	**Was there appropriate statistical analysis?**	yes	yes	yes	yes	yes	yes	yes	yes
9	**Was the response rate adequate, and if not, was the low response rate managed appropriately?**	yes	yes	yes	yes	yes	yes	yes	yes

Part 2: Systematic Review of intervention

Study selection

Overall, 1050 records were screened and after removing the duplicates we obtained 936 articles. The full text of the remaining 14 potentially eligible articles was assessed, 13 of which did not meet the inclusion criteria, the treatment approach was more often based on a splint or acupuncture or wasn't defined the type of headache. Finally, 1 study (listed in **Appendix B**) was included in the systematic review. **Figure 2** illustrates the flow diagram of study selection.

General characteristics

We included a randomized clinical trial conducted in Spain and published in 2018. The patients in the study were randomized into a Cervical Group (CG) and a Cervical and Orofacial Group (COG). In both groups, patients received cervical physical treatment, but an orofacial treatment was added to the COG. Detailed general characteristics are in **Table 5a** and **Table 5b**.

Risk of bias

The only study evaluated was Miriam Garrigós-Pedrón's et al., which was found to have a low risk of bias in all its domains. (**Figure 3**)

All details about Risk ok Bias are presented in **Table 6.**

Figure 2 illustrates the flow diagram of study selection.

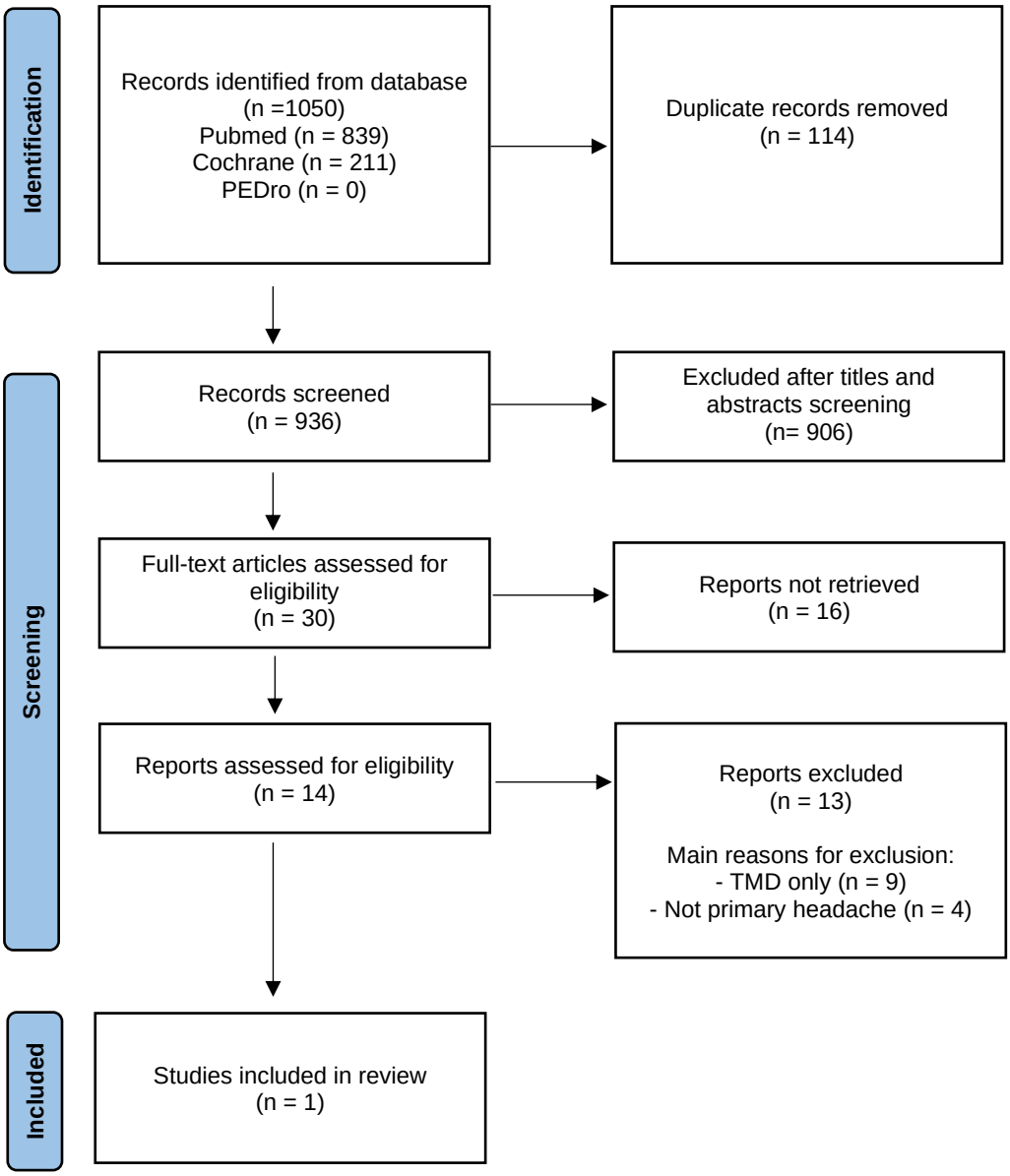


Table 5a

Cervical Group				Cervical Orofacial Group		
Author, year	**Sample size**	**% males**	**Mean age (years) +SD**	**Sample size**	**% males**	**Mean age (years) +SD**
Garrigós-Pedrón, 2018	n=22	13,6	48,2 (11,3)	n=23	13	46,0 (9,1)

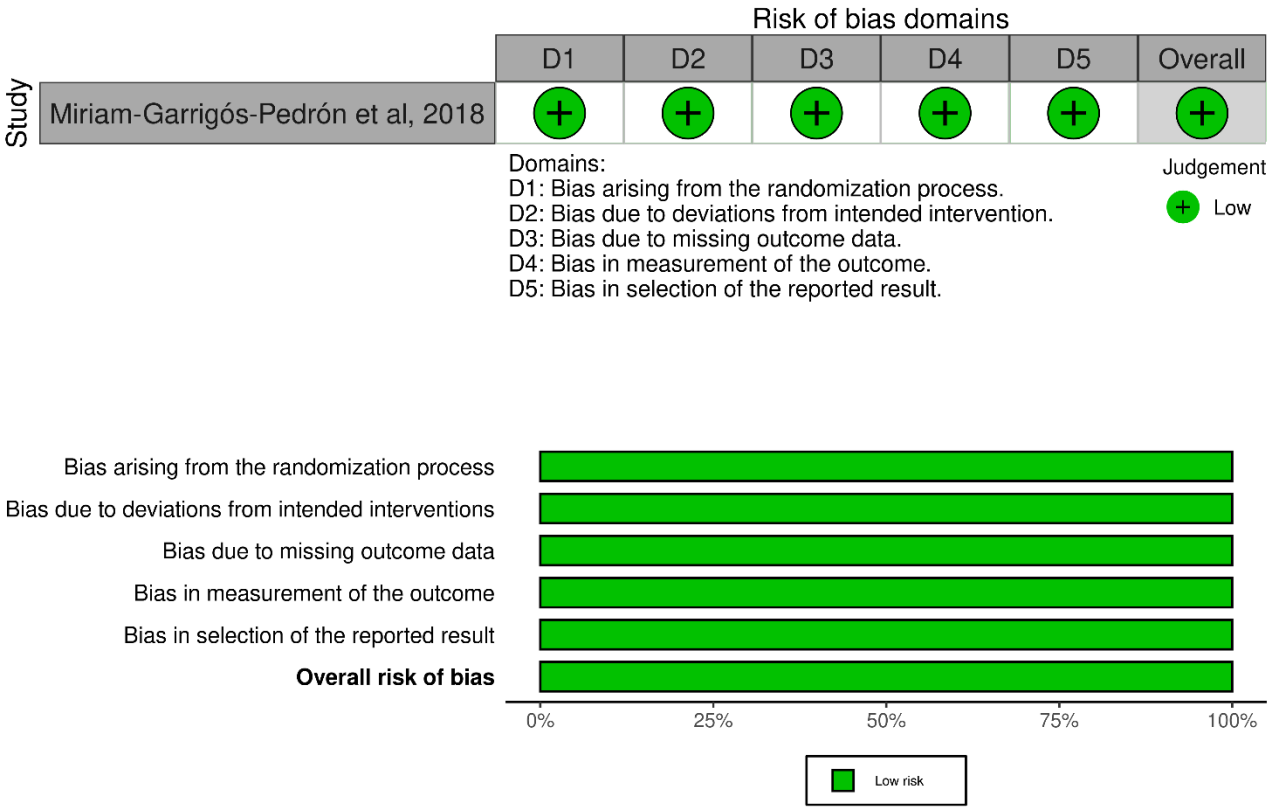
Table 5b

Cervical Group					Cervical Orofacial Group			
			HIT-6				**HIT-6**	
Author, year	**Intervention**	**Freq. intervention**	**Baseline**	**Follow-up**	**Intervention**	**Freq. Intervention**	**Baseline**	**Follow-up**
Garrigós-Pedrón, 2018	Only cervical treatment. Manual therapy and home exercises.	6 sessions of 30 minutes for 3-6 weeks.	66,59 (6,05)	62,23 (6,23)	Cervical treatment + orofacial therapy. Manual therapy and exercises.	6 sessions of 30 minutes for 3-6 weeks.	65,52 (3,69)	60,87 (6,68)

Table 6

1.1 Random Allocation Sequence	**1.2 Allocation Sequence Concealed**	**1.3 Baseline Differences**					**Domain 1 RoB**
Y	**PY**	**N**					**LOW**
2.1 Participant Awareness	**2.2 Delivery Awareness**	**2.3 Deviations Due to Context**	**2.4 Affected Outcome**	**2.5 Deviation Balancing**	**2.6 Appropriate Analysis**	**2.7 Substantial Impact**	**Domain 2a RoB (Part 1)**
Y	**Y**	**N**	NA	NA	**Y**	NA	**LOW**
3.1 Data Randomized	**3.2 No Bias from Missing Data**	**3.3 Missingness Dependency**	**3.4 Missingness Likelihood**				**Domain 3 RoB**
PY	NA	NA	NA				**LOW**
4.1 Inappropriate Method	**4.2 Outcome Difference**	**4.3 Assessor Awareness**	**4.4 Assessment Influence**	**4.5 Influence Likelihood**			**Domain 4 RoB**
PN	**N**	**N**	NA	NA			**LOW**
5.1 Appropriate Analysis	**5.2 Multiple Outcomes**	**5.3 Multiple Analyses**					**Domain 5 RoB**
PY	**N**	**N**					**LOW**

Figure 3


Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Miriam-Garrigós-Pedrón et al, 2018
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
Low
Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
Low risk

DISCUSSION

Despite Primary Headaches and TMD being really common problems in the general population that brings disability and loss of quality of life, we found a lack of literature because most of the studies, also reviews, didn't distinguish the kind of headache which the patient was suffering from, rather, they focus their aim to found only the association of secondary headaches and TMD. (7) For that, the primary aim of this study was to identify the prevalence of primary headaches in TMD and vice versa. In fact, in six studies of our review, primary headaches were diagnosed in a valid and reliable way using the diagnosed criteria of ICDH-III, only in two studies Byun et al. (21) and Tchivileva et al. (22) the diagnostic criteria were unclear because the first one based the diagnosis on assurance codes and the second one on self-reported headaches.

As regards TMD the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) were used in three articles (22–24), Di Paolo et al. (25) used the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), the other four articles used questionnaires (26–28) and assurance code (21) so not a totally valid method to make a diagnosis to TMD.

In this review, 8 studies were analyzed, 3 reported the prevalence of Headaches in TMD, four the prevalence of TMD in Headaches and only one examined the incidence of TMD in patients with headaches.

In the study that takes into consideration the prevalence of headaches in TMD Byun et al. (21)and Gonçalves et al., 2010,(26) took a homogeneous sample size from the general population between males and females while Di Paolo et al.(25) in the study didn't express the sex of the population. This one analyzed an older population, the patients were in the range of age between 40 and 85 years old, whereas 25,3% of the population were between 26-40 years old in Di Paolo et al. and 51% were in 20-45 in Gonçalves et al., 2010.

The only two authors who analyzed the prevalence of total headaches were Byun's et al. (21)and Gonçalves et al. (2010)(26). In the first one 6.8% of patients suffered from both primary headache and TMD whereas in the second article, as many as 56.5 % of patients reported primary headache and at least one symptom of TMD.

The gap between the two studies can be explained because Byun et al. considered only migraine as a primary headache and didn't use a valid method to identify conditions, especially for this reason this article has a high risk of bias.

Both articles had a control group with health patients, in the one by Gonçalves and Bigal 27,7% of participants without TMD reported primary headache. More detailed, when at least 1 TMD symptom was reported, any headache happened in 56.5% vs 31.9% in those with no symptoms with a statistically significant value ($P < .0001$). (26)

In Byun's et al. (21) to assess hazard ratios (HR) and 95% confidence intervals (CIs) for migraine stratified Cox proportional hazard models were used in both groups. The adjusted HR for migraine was 2.10 (95% CI: 1.81–2.44) in the TMD group compared to the control group.

The article of Di Paolo et al. reported only the prevalence of subgroups so 22,28% of participants with TMD reported TTH and 40,6% reported MH, but for the inadequate sample size, the fact that the study subjects and the setting were not described in detail and the insufficient coverage of the identified sample the bias of this study is quite high.

Also, the other two authors make a subgroups analysis of the prevalence, Gonçalves et al., 2010, was the one that evaluated not only the prevalence of MH (58,2%) and of ETTH (41%) but also the CDH (66,7%). Byun et al. differenced migraine with and without aura, the first one was presented in 0,3% of participants with TMD, the second one in 6,5%.

Migraine seems to be in all the studies the most common headache subtype in TMD patients and patients with TMD have a higher risk of migraine, we especially take into consideration Gonçalves et al. (2010) article with a low risk of bias. (21,25,26)

Regarding the articles that estimate the prevalence of TMD in primary headaches, the population analyzed is unbalanced because women are more present, like in the articles of Florencio et al. only women were selected (28)and also, the age of the participants may confound the prevalence result, as the population on which this epidemiological study is based is a young population, with a total average age of 35 years old. Usually, the prevalence of TMD is higher in these two subgroups. (29) For all these reasons and because the sample size is not accurate, the sample coverage is not sufficient and because the condition was not measured validly, they used a questionnaire to diagnose temporomandibular disorders, this article has a high risk of bias.

Florencio and De Oliveira (28) took in their article only MH patients so is impossible to estimate a prevalence of TMD in this kind of headaches, in fact, the criticality of this article is the high risk of bias that we estimated. They made a distinction between patients suffering from Chronic Migraine (CM) and Episodic Migraine (EM) where the whole participant in the CM reported TMD and 78% of the EM had a correlation with TM problems. This article had also a control group with healthy women where 54% reported TMD pain.

Also, Gonçalves et al. (2011) reported a headache-free control group where 55,4% reported TMD pain, less than the headaches group where the TMD prevalence was 91.6%. As we can read in his article: "In patients with myofascial TMD, compared with individuals with no TMD, migraine (RR=4.4; 95% CI, 1.7-11.7), and ETTH (RR=4.4; 95% CI, 1.5-12.6) were significantly more common." In this article, which has a low risk of bias, the authors concluded also that increased severity of TMD pain was found to be associated with an increased risk of any type of headache. (23)

Fergane et al. made a comparison between males and females with TMD in two different headache groups, TTH and MH. In the Tension Type, 48 females and 26 males are reported, 182 women and only 45 men are counted in the Migraine one. (24) These results agree with what was said earlier concerning the association between female sex and the coexistence of temporomandibular disorders and primary headache.(29)

Tomaz-Morais et al., 2015 in his article concluded that "there is a high prevalence of > 6 signs and symptoms among patients with primary headaches. TMD is more frequent among migraine patients. Headache associated or attributed to medication overuse is a potential risk factor for comorbid TMD." The same author points out that temporomandibular disorders occur more often in patients with migraine and TTH ($p < 0.005$; OR=4.1), more frequently especially in migraine without aura with a p-value less than 0.001. (27)

Our review shown that the prevalence of TMD in the headache population was in a range between 25,5% in Fergane et al. (24) study to 76,6% in Florencio et al. one (28) while the prevalence in the healthy population is around 10-15%. This shows an increase in temporomandibular disorders in patients with primary headaches.

Regarding the subgroups of headaches, migraine seems to be the most frequent again, with a value of 30% in Fergane et al.(24), 35.22% in the study by Gonçalves et al. (2011) (23)and 71.4% in the articles of Tomaz-Morais et al.(27)

In our review, only one article evaluated the contribution of headache to the risk of developing TMD and describe patterns of change in headache types in three years assessing the incidence. (22)Where headache prevalence and frequency increased across the observation period among those who developed TMD but not among control groups. In summary, the data in this article support the hypothesis that migraine and frequent headaches contribute to the risk of developing TMD, but the risk of bias of this study is quite high. As we can find in Tchivileva et al.: ”Baseline reports of migraine (hazard ratio [HR] 5 1.67, 95% confidence interval [CI]: 1.06-2.62) or mixed headache types (HR 5 4.11, 95% CI: 1.47-11.46), or headache frequency (HR 5 2.13, 95% CI: 1.31-3.48) predicted increased risk of developing TMD.” We cannot totally trust the results of this article because based on what we have analyzed it has a high risk of bias. (22)

The secondary aim of this study was to systematically evaluate the literature on the effectiveness of physical therapy for TMD to reduce the symptoms of primary headache.

Over the years, many authors have tried to investigate the efficacy of TMD treatment in headache patients, (30) (31) but to date, only Garrigós-Pedrón’s et al. article in 2018 has investigated this aspect in primary headaches. Overall, the quality of this study was good.

The sample of the study consisted of two groups of participants diagnosed with chronic migraine and myofascial TMD. One group received treatment only in cervical region, while the second one received treatment both in cervical and orofacial regions. The results of this study suggest that both treatments were effective for reducing pain and the impact of headache on daily life in patients with chronic migraine and TMD.

Since only one study was evaluated, it was not possible to compare different articles on the effect of TMD treatment to reduce primary headache symptoms.

Comparison with previous studies

Our study showed a strong correlation between temporomandibular disorders and primary headaches, especially for migraine, which seems to be significantly more present.

These results find support in the literature in fact the articles of Mitrirattankul et al. and Cingaglini et al. find a strong association between migraine and orofacial pain and as we can read in Cingaglini and Redaelli 70% of headache patients had also a clinical confirmation of TMD. (32,33)

Other studies support our findings, Franco et al. in his study reported that among individuals with TMD, migraine was the most prevalent primary headache (55.3%). (34) In Bevilaqua-Grossi et al. 72.2% of subjects with episodic migraine met the criteria for TMD. (35) Also Fernandes et al. found an association between painful TMD and chronic and episodic migraine, higher for chronic migraine (odds ratio = 95.9; 95% confidence intervals = 12.51-734.64), followed by episodic migraine (7.0; 3.45-14.22). (36) A high prevalence of TMD was found by Bellegaard et al. in the headache population, compared to previous findings in the general population, particularly in patients with migraine and TTH combined.(37)

Even in Cruz's et al. review in which the authors looked for a genetic correlation between primary headaches and temporomandibular disorders, there is evidence of an association between the two disorders due to the co-presence of the ESR1 gene. This confirms the fact that the two disorders are extremely complex and closely related.(38)

Another review dated December 2021 reported the prevalence or incidence of chronic pain conditions among patients with any type of TMD showed a co-presence of chronic migraine in 40% of patients. (39)

Research Implications

Since the main biases found in the studies analysed were on sample size and the use of appropriate diagnostic criteria to clarify the details of the epidemiological association between TMD and headache, large population-based studies using uniform diagnostic criteria will be necessary.

Clinical Implications

Since there may be an association between the two conditions, it is crucial to evaluate TMJ in patients with headache as well as headache in TMD. When TMD and headache co-exist, the management of both conditions may lead to a better outcome and patient satisfaction, as suggested by the results of Garrigós-Pedrón et al. study, according to which patients suffering from both migraine and TMD should be guaranteed comprehensive treatment for both conditions. Certainly, more studies should be conducted on this population with a combination of TMD and primary headache.

CONCLUSIONS

The results of this systematic review confirm that there is a strong correlation between primary headache and temporomandibular disorders and vice versa.

Migraine seems to be, among the primary headaches, the most frequent in association with TMDs as well as patients suffering from TMDs report a higher percentage of migraine as a headache. It is still not totally clear which subtype of TMD is more frequent in patients with primary headache.

Studies based on larger populations with homogeneous diagnostic criteria would be needed to define in detail the epidemiological association between primary headache and TMD.

However, today's literature shows the importance of the correlation of these two disorders for better prevention and treatment.

Future studies should better investigate the epidemiological association and evaluate the effectiveness of combined physiotherapy treatment for both conditions.

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APPENDIX A

Pubmed search strategy:

("primary headache*" [tiab] OR headache* [tiab] OR "head pain"[tiab] OR Cephalalgia [tiab] OR Cephalgia [tiab] OR Hemicrania [tiab] OR migraine* [tiab] OR "migraine disorders"[MeSH Terms] OR "Migraine Disorder*" [tiab] OR "Migraine Headache" [tiab] OR "Hemicrania Migraine*"[tiab] OR "tension-type headache" [tiab] OR "cervical headache" [tiab] OR "cervicogenic headache" [tiab] OR "headache disorders" [MeSH Terms] OR headache [MeSH Terms])

AND ("Temporomandibular Joint Disorder*" [tiab] OR "Temporomandibular joint dysfunction Syndrome" [tiab] OR "TMJ Disorder*" [tiab] OR "Temporomandibular Disorder*"[tiab] OR "Temporomandibular Joint Disease*" [tiab] OR "TMJ Disease*" [tiab] OR "temporomandibular joint disorders" [MeSH Terms] OR temporomandibular [tiab] OR tmd [tiab] OR "Temporomandibular Joint Dysfunction Syndrome" [MeSH Terms] OR "craniomandibular disorders" [MeSH Terms])

AND (epidemiology [MeSH Terms] OR prevalence [MeSH Terms] OR incidence [MeSH Terms] OR population [MeSH Terms] OR epidemiology [tiab] OR prevalence [tiab] OR incidence* [tiab] OR population* [tiab])

APPENDIX B

Pubmed search strategy:

("primary headache*" [tiab] OR headache* [tiab] OR "head pain"[tiab] OR Cephalalgia [tiab] OR Cephalgia [tiab] OR Hemicrania [tiab] OR migraine* [tiab] OR "migraine disorders"[MeSH Terms] OR "Migraine Disorder*" [tiab] OR "Migraine Headache" [tiab] OR "Hemicrania Migraine*" [tiab] OR "tension-type headache" [tiab] OR "headache disorders" [MeSH Terms] OR headache [MeSH Terms])

AND ("Temporomandibular Joint Disorder*" [tiab] OR "Temporomandibular joint dysfunction Syndrome" [tiab] OR "TMJ Disorder*" [tiab] OR "Temporomandibular Disorder*"[tiab] OR "Temporomandibular Joint Disease*" [tiab] OR "TMJ Disease*" [tiab] OR "temporomandibular joint disorders" [MeSH Terms] OR temporomandibular [tiab] OR tmd [tiab] OR "Temporomandibular Joint Dysfunction Syndrome" [MeSH Terms] OR "craniomandibular disorders" [MeSH Terms])

AND ("Musculoskeletal Manipulations" [MeSH Terms] OR "Musculoskeletal Manipulation*" [tiab] OR "Physical Therapy Modalit*" [tiab] OR "Physical Therapy Modalities" [MeSH Terms] OR "Physical Therapy Technique*" [tiab] OR "Manual Therap*" [tiab] OR "Physical Therap*" [tiab] OR Rehabilitation [tiab] OR rehabilitation [MeSH Terms] OR physiotherapy [tiab] OR management [tiab] OR treatment [tiab] OR "exercise therapy" [MeSH Terms] OR "Aerobic Exercise" [tiab] OR "physical activity" [tiab] OR education [tiab] OR multidisciplinary [tiab] OR "Exercise programs" [tiab] OR exercise [tiab] OR multimodal [tiab] OR "soft tissue" [tiab] OR "soft tissue mobilization" [tiab] OR "manipulation" [tiab] OR MWM [tiab] OR "Cognitive Behavior Therapy" [tiab] OR "trigger point*" [tiab] OR Mulligan [tiab] OR Traction [tiab])

Cochrane search strategy:

ID	Search
#1	(headache):ti,ab,kw
#2	(primary headache):ti,ab,kw
#3	(head pain):ti,ab,kw
#4	("cephalalgia"):ti,ab,kw
#5	(hemicrania):ti,ab,kw
#6	(migraine):ti,ab,kw
#7	MeSH descriptor: [Migraine Disorders] explode all trees
#8	(Migraine Headache):ti,ab,kw
#9	(Hemicrania Migraine):ti,ab,kw
#10	(tension-type headache):ti,ab,kw
#11	(cervical headache):ti,ab,kw
#12	(cervicogenic headache):ti,ab,kw
#13	(headache disorders):ti,ab,kw
#14	MeSH descriptor: [Headache] this term only
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	(Temporomandibular Joint Disorder*):ti,ab,kw
#17	(Temporomandibular joint dysfunction Syndrome):ti,ab,kw
#18	(TMJ Disorder*):ti,ab,kw
#19	(Temporomandibular Joint Disease*):ti,ab,kw
#20	(TMJ Disease*):ti,ab,kw
#21	MeSH descriptor: [Temporomandibular Joint Disorders] explode all trees
#22	(temporomandibular):ti,ab,kw
#23	(TMD):ti,ab,kw
#24	MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees

#25 MeSH descriptor: [Craniomandibular Disorders] explode all trees

#26 (Temporomandibular Disorder*):ti,ab,kw

#27 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26

#28 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees

#29 (Musculoskeletal Manipulation*):ti,ab,kw

#30 (Physical Therapy Modalit*):ti,ab,kw

#31 MeSH descriptor: [Physical Therapy Modalities] explode all trees

#32 (Physical Therapy Technique*):ti,ab,kw

#33 (Manual Therap*):ti,ab,kw

#34 (Physical Therap*):ti,ab,kw

#35 (Rehabilitation):ti,ab,kw

#36 MeSH descriptor: [Rehabilitation] explode all trees

#37 (physiotherapy):ti,ab,kw

#38 (management):ti,ab,kw

#39 (treatment):ti,ab,kw

#40 MeSH descriptor: [Exercise Therapy] explode all trees

#41 (Aerobic Exercise):ti,ab,kw

#42 (physical activity):ti,ab,kw

#43 (education):ti,ab,kw

#44 (multidisciplinary):ti,ab,kw

#45 (Exercise programs):ti,ab,kw

#46 (exercise):ti,ab,kw

#47 (multimodal):ti,ab,kw

#48 (soft tissue) :ti,ab,kw

#49 (manipulation) :ti,ab,kw

#50 (Cognitive Behavior Therapy) :ti,ab,kw

#51 (trigger point*):ti,ab,kw

#52 (Mulligan) :ti,ab,kw

#53 (Traction) :ti,ab,kw

#54 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53

#49 #15 AND #27 AND #54

PEDro Keywords:

Head, Mograine, Temporomandibular, Craniomandibular, Headache, TMJ, TMD.