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Review

Effectiveness of Exercise and Manual Therapy as Treatment for Patients with Migraine, Tension-Type Headache or Cervicogenic Headache: An Umbrella and Mapping Review with Meta-Meta-Analysis

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Abstract: The aim of the study was to perform a mapping and umbrella review with meta-meta-analysis (MMA) to synthesise and critically evaluate the effectiveness of manual therapy (MT) and aerobic exercise (AE) in relation to pain intensity, frequency, disability and quality of life in patients with migraines, tension-type headaches (TTH) and cervicogenic headaches (CGH). A systematic search was conducted in PubMed, PEDro, Scielo and Google Scholar up to December 2020. A total of 18 articles met the inclusion criteria, and only 8 were included in the quantitative analysis. The MMA showed results in favour of the interventions in terms of pain intensity and quality of life in migraine, TTH and CCH. Data were also in favour of the intervention in terms of pain frequency in migraine and in terms of disability in TTH. However, there were no significant effects on pain frequency in TTH and CGH. The results showed moderate evidence to suggest that AE reduces pain intensity in patients with migraine. In addition, the evidence in favour of MT or a mixed intervention (including therapeutic exercise) was also moderate in terms of reducing pain intensity in patients with TTH.

Keywords: headache; migraine; tension-type headache; cervicogenic headache; aerobic exercise; therapeutic exercise; manual therapy

1. Introduction

Headaches are categorised worldwide into 2 groups: primary and secondary [1]. Among the primary headaches, migraine and tension-type headaches (TTH) are the most prevalent [2]. Secondary headaches include cervicogenic headaches (CGHs), among others [1].

Headaches lead to important deteriorations in patients' quality of life and involve significant economic repercussions, medical expenses, work incapacity and social and familiar impact. Headache disorders were the third-leading cause of disability in 2016 [2].

Regarding the therapeutic approach for headaches, there are both pharmacological and nonpharmacological interventions. Pharmacological treatment appears to be efficient for some acute cases and for prophylaxis [3]. However, this treatment is not effective in all cases, and they can become chronic disorders. Chronic headaches generate an increase in the number of medical consultations at the cost of the health system and can even generate medication-overuse headache [4–6].

The nonpharmacological approach provides therapeutic options to be assessed for the treatment of headaches, such as therapeutic exercise and manual therapy. Some

proposed exercise modalities are aerobic exercise (AE) and exercise focused on retraining the cervical and shoulder muscles, with moderate evidence of reduced pain intensity, symptom frequency and disability and improved quality of life in patients in the short- to medium-term. It should also be noted that these exercise modalities do not generate adverse effects in these patients [7,8].

Manual cervical therapy has shown improvements in the symptomatology of headaches [9]. The most well-founded theory to justify these effects is that manual therapy produces neurophysiological effects on the central and peripheral nervous system, leading to changes in the symptomatology of these patients [10]. There is also evidence of the benefits of therapeutic exercise and manual therapy for individuals with headaches.

Therefore, the aim of the study was to perform a mapping and umbrella review with meta-meta-analysis (MMA) to synthesise and critically evaluate the current evidence on the effectiveness of manual therapy and exercise in relation to pain intensity, frequency, disability and quality of life in patients with migraines, TTHs and CGHs.

2. Materials and Methods

This umbrella and mapping review was performed according to the Preferred Reporting Items for Overviews of Systematic Reviews including the harms checklist (PRIO-harms). The PRIO-harms tool is composed of 27 items and 56 sub-items [11]. The protocol of this systematic review and meta-analysis was registered in an international register prior to starting the review (PROSPERO, CRD42020222573).

2.1. Review Inclusion Criteria

The inclusion criteria for this review were based on methodological and clinical factors, including population, intervention, control, outcomes and study type [12].

2.1.1. Population

The individuals selected for the articles were patients older than 18 years, diagnosed with migraine, TTH and CGH.

2.1.2. Intervention and Control

The interventions were any type of therapeutic exercise and/or manual therapy performed by a physical therapist or health professional. Studies in which the intervention was performed by chiropractors or osteopaths were excluded. The intervention could be provided as an independent treatment or combined with other types of intervention. The control group could include any type of intervention, when it was possible to isolate and evaluate the effectiveness of manual therapy and/or therapeutic exercise.

2.1.3. Outcomes

The measures employed to assess the results and effects were pain intensity, frequency of symptoms, disability and/or quality of life.

2.1.4. Study Design

We included systematic reviews (with or without meta-analysis) of randomised controlled trials (RCTs) or controlled clinical trials (CCTs). No language restrictions were applied, as recommended by international criteria [13].

2.2. Search Strategy

We conducted a search for articles on PubMed, PEDro, Scielo and Google Scholar. The last search was run on December 2020.

The following PubMed search strategy was employed and was adapted to the rest of the databases: (headache [MeSH Terms]) OR ("migraine disorders" [MeSH Terms]) OR (migraine) OR ("tension-type headache" [MeSH Terms]) OR ("tensional headache") OR ("cervicogenic headache") AND (pain [MeSH Terms]) OR (ache [MeSH Terms]) OR (fre-

quency) OR (disability) OR ("quality of life" [MeSH Terms])) OR ("pain intensity") AND (exercise [MeSH Terms]) OR ("exercise therapy" [MeSH Terms]) OR ("physical exercise" [Title/Abstract]) OR ("physical therapy" [Title/Abstract]) OR ("musculoskeletal manipulations" [MeSH Terms]) OR ("manual therapy" [MeSH Terms]) OR ("manual therapy") OR ("manipulation spinal"). We also used the following search filters: "systematic review" and "meta-analysis".

Two independent reviewers conducted the search using the same methodology, and differences during this phase were resolved by consensus. The reference sections of the original studies were screened manually, and the authors were contacted for further information if necessary.

2.3. Selection Criteria and Data Extraction

Initially, analyses were performed by two independent reviewers who assessed the relevance of the systematic reviews (with and without a meta-analysis) regarding the study questions and objectives. The first analysis was performed based on each study's title information, abstract and keywords. If there was no consensus or the abstract did not contain enough information, the full text was reviewed.

In the second phase of the analysis, the full text was assessed if the studies met all of the inclusion criteria. Differences between the reviewers were resolved by a process of discussion, and consensus was moderated by a third reviewer [14]. Data described in the Results section were extracted by means of a structured protocol that ensured that the most relevant information was obtained from each study [15].

2.4. Methodology Quality Assessment

The two independent reviewers assessed the methodological quality of the selected systematic reviews based on the Modified Quality Assessment Scale for Systematic Reviews (AMSTAR) developed by Barton et al. This scale presents 13 items, each worth 2 points (with "yes" scoring 2; "in part" scoring 1; "no" scoring 0), and the maximum possible score is 26. A high-quality cutoff of 20 or more points was provided by the developers of the scale [16].

The two independent reviewers assessed the quality of the studies employing the same methods, and disagreements on the final quality assessment score were resolved by consensus with a third independent reviewer. The inter-rater reliability was estimated using the kappa coefficient (κ): $\kappa > 0.7$ indicated a high level of agreement between the reviewers; κ of 0.5–0.7 indicated a moderate level of agreement, and $\kappa < 0.5$ indicated a low level of agreement [17].

2.5. Risk of Bias Assessment

We assessed the risk of bias using the Risk of Bias in Systematic Reviews tool (ROBIS), which evaluates the quality across 3 phases: (1) relevance assessment; (2) identification of concerns with the review process through 4 domains related to study eligibility, study identification and selection, data collection and study appraisal, and synthesis and findings; and (3) judgment on the risk of bias. The ROBIS tool includes signalling questions to evaluate specific domains by answering "yes", "probably yes", "probably no", "no" or "no information". The risk of bias is therefore judged as "low", "high" or "unclear" [18].

The two independent reviewers evaluated the risk of bias in the selected studies using the same methodology; disagreements were resolved through consensus and mediation by a third reviewer. The interrater reliability was estimated using the same κ cutoffs described in the section Methodology quality assessment.

2.6. Evidence Map

We presented the scientific evidence of each systematic review with meta-analysis through a visual map. We created 2 different maps, one descriptive and the other using

effect size data, and the information from each review was provided using the following criteria:

1. Number of studies (figure size): The size of each figure is directly proportional to the number of original studies included in each of the meta-analyses.
2. Study Population (bubble colour) and type of intervention (symbol): The type of population evaluated in each study is represented by a colour (green: migraine; blue: TTH; yellow: CGH). The type of therapeutic intervention determined each symbol inside the bubble (x: manual therapy; −: therapeutic exercise; +: mixed intervention). In addition, in the second mapping, the plot of the figure represents the study variable.
3. *x*-Axis: In the descriptive mapping, each of the study variables is represented on the *x*-axis. In the second mapping, each of the reviews was classified according to the size effect as described by Hopkins (Hopkins et al., 2009). The categorisation of the effect size is described in the section Data synthesis and analysis.
4. *y*-Axis: The descriptive mapping represents the quality of each of the reviews on the *y*-axis according to the AMSTAR scale. In the second mapping, the reviews were sorted into the following 4 categories according to the Physical Activity Guidelines Advisory Committee (PAGAC): strong, moderate, limited or not assignable.

2.7. Qualitative Analysis

As described earlier, we relied on the assessments of each systematic review with meta-analysis for the methodological quality of the primary studies, using AMSTAR for the included reviews and PAGAC for assessing the evidence across reviews.

For the PAGAC analysis, the findings were evaluated according to 5 criteria: (1) the applicability of the study sample, exposures and outcomes to the research question, (2) generalisability to the population of interest, (3) the risk of bias or study limitations, (4) the quantity and consistency of findings across studies and (5) the magnitude and precision of the effect. The strength of the evidence was classified as strong, moderate, limited or not assignable [19].

2.8. Data Synthesis and Analysis

The statistical analysis was performed using meta-analyses with MetaXL software [20,21].

The same inclusion criteria for the systematic review were employed, but 2 criteria were added: (1) The Results section contained detailed information on the comparative statistical data (mean, standard deviation and/or 95% confidence interval [CI]) of the main variables and (2) data for the analysed variables were represented in at least 2 studies. The summary statistics are presented in the form of forest plots [22], which consist of a weighted compilation of all standardised mean differences (SMDs) and corresponding 95% CIs reported by each study. They provide an indication of heterogeneity among the studies. The statistical significance of the pooled SMDs were examined using Hedges' g to account for a possible overestimation of the true population effect size in small studies [23]. We interpreted the statistical significance of the pooled SMDs as described by Hopkins [24]; that is, we considered an SMD of 4.0 an extremely large clinical effect, 2.0–4.0 a very large effect, 1.2–2.0 a large effect, 0.6–1.2 a moderate effect, 0.2–0.6 a small effect and 0.0–0.2 a trivial effect. When the statistical significance of the pooled data was presented as mean difference, the meta-analysis was replicated using Meta-Essentials (ERIM, Erasmus University Rotterdam, Netherlands) with Microsoft Excel to obtain the SMD values [25]. The degree of heterogeneity among the studies was estimated by employing Cochran's Q statistic test ($p < 0.1$ was considered significant) and the inconsistency index (I^2) [26]. An $I^2 > 25\%$ is considered to represent low heterogeneity, while an $I^2 > 50\%$ is considered medium and an $I^2 > 75\%$ is considered to represent large heterogeneity [27]. The I^2 index is complementary to the Q test, although it has a similar problem with power as does the Q test with a small number of studies [27]. A study was therefore considered heterogeneous when it fulfilled one or both of the following conditions: (1) the Q-test was significant ($p < 0.1$) and (2) the result of I^2 was >75%. To obtain a pooled estimate of the effect in the meta-analysis of the heterogeneous studies, we performed a random-effects model,

as described by DerSimonian and Laird (1986) [28]. Publication bias through the funnel plot and the sensitivity exclusion analysis was not evaluated due to the impossibility of performing it when the MMA includes fewer than 2 studies.

3. Results

The study screening strategy is shown in the flow chart (Figure 1). Eighteen articles met the inclusion criteria and were selected, 9 of which were systematic reviews [7,29–36], while the remaining 9 were systematic reviews with a meta-analysis [8,37–44]. The characteristics of the included studies (study design, original studies included, demographic characteristics, interventions, main outcomes and conclusions) are presented in Tables 1 and 2.

Eight of the studies were included in eight independent MMAs. The MMAs assessed pain intensity and the frequency of symptoms in patients with migraine, TTH and CGH independently, as well as disability in patients with TTH.

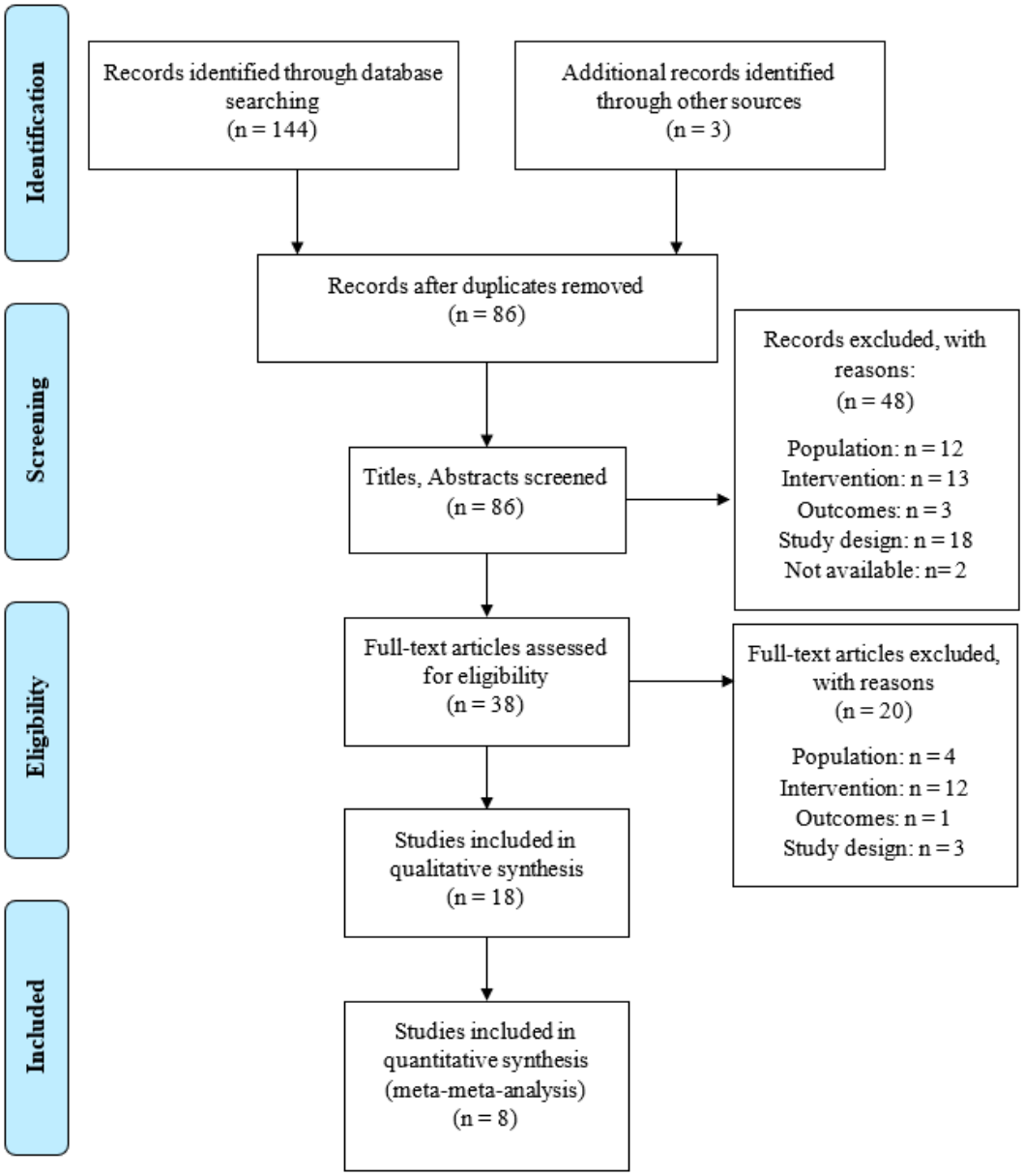

Figure 1. Flow chart according to PRISMA.

Table 1. Characteristics of the included studies.

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
La Touche et al., 2020	7 RCTs (n = 408) 3 CCTs (n = 76)	Evaluate the effects of AE on patients with MH regarding pain intensity, frequency of MH and quality of life	Population: patients older than 18 y diagnosed with MH with or without aura by the ICHD-I, II or III criteria Age (y): 19 to 50 Gender (F/M): 92.35%/7.65% Mean headache duration (y): NA	Intervention group: AE with other forms of exercise therapy and/or minimal usual care Comparison group: Maintenance of daily activity, relaxation or no treatment	Pain intensity		
					5 (n = 166)	VAS	The meta-analysis showed statistically significant differences in the reduction of pain intensity by AE in patients with MH in the short-term (SMD = 1.25; 95% CI 0.47 to 2.04).
					Frequency of symptoms		
					7 (n = 214)	Self-report headache diaries	AE intervention showed statistically significant differences in decreasing the frequency of symptoms in the short-term compared to control group (SMD = 0.76; 95% CI 0.32 to 1.20).
					Quality of life		
					4 (n = 150)	Profil der Lebensqualitat chronisch Kranker, Well-BeingIndex, HIT-6	The meta-analysis showed statistically significant differences in the increase in quality of life in the short-term for the Intervention group compared to the control group (SMD = 2.70; 95% CI 1.17 to 4.24).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Machado-Oliveira et al., 2020	14 RCTs (*n* = 1988) 1 CCT (*n* = 16) 1 noncontrolled clinical trial (*n* = 52)	Investigate the effects of different exercise intensities on headache parameters	*Population*: adults older than 18 y diagnosed with MH or TTH by a neurologist and/or ICHD-I, II or III criteria *Age (years)*: 18 to 55 *Gender (F/M)*: 62%/38% *Mean headache duration (y)*: 18.13	*Intervention group*: AE or resistance exercise *Comparison group*: Usual care, medication, ergonomic and posture correction, health information or no treatment	Pain intensity		
					-	VAS, NPRS	AE or resistance exercise were effective interventions in reducing pain intensity in patients with MH, TTH or CGH.
					Frequency of symptoms		
					-	Self-report headache diaries	Interventions through AE or resistance exercise showed positive results on reduction of the frequency of headache.
Falsiroli-Maistrello et al., 2019	10 RCTs (*n* = 728)	Evaluate the effectiveness of manual therapy on health-related quality of life in patients with TTH, MH or CGH	*Population*: patients older than 18 y diagnosed with MH with or without aura, TTH or CGH by the ICHD-III criteria *Age (y)*: 18 to 65 *Gender (F/M)*: 80%/20% *Mean headache duration (y)*: 12.68	*Intervention group*: Manual therapy *Comparison group*: Usual care, placebo or no treatment	Disability		
					7 (*n* = 495)	HDI	The analysis showed a significant difference in favour of the Intervention group at the post-treatment (MD = −4.01; 95% CI −5.82 to −2.20) and at the follow-up (MD = −5.62; 95% CI −10.69 to −0.54).
					Quality of life		
					9 (*n* = 721)	HIT-6	The combined results between the subgroup of TTH and MH showed a significance difference in favour of the treatment at the post-treatment (MD = −3.67; 95% CI −5.71 to −1.63) and follow-up (MD = −2.47; 95% CI −3.27 to −1.68).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
					Pain intensity		
Jiang et al., 2019	6 RCTs (n = 505)	Evaluate the effectiveness of physical therapy on the suboccipital area of patients with TTH	*Population*: patients older than 18 years with TTH diagnosed by the ICHD-II criteria *Age (y)*: 18 to 65 *Gender (F/M)*: 81.18%/18.82% *Mean headache duration (y)*: 16.10	*Intervention group*: Any direct manual treatment on the suboccipital area *Comparison group*: No treatment	SIT vs. Control 3 (n = 122) OAA vs. Control 3 (n = 126) SIT + OAA vs. Control 3 (n = 122)	VAS	The meta-analysis did not show significant difference at 4 weeks post-treatment but did at 8 weeks for the SIT group (MD = 1.02; 95% CI 1.77 to 0.27). For the OAA group, the meta-analysis showed a significant difference at 4 weeks post-treatment (MD = 0.98; 95% CI 1.83 to 0.12) but no effect at 8 weeks. Finally, the SIT + OAA group showed a decrease in VAS score at 4 weeks (MD = 1.38; 95% CI 2.21 to 0.56) and 8 weeks (MD = 1.29; 95% CI 2.46 to 0.13).
					Disability		
					2 (n = 182)	HDI	The meta-analysis showed that patients treated with SIT + OAA had positive results (MD = −2.66; 95% CI −4.58 to −0.75).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Lemmens et al., 2019	5 RCTs (n = 324) 1 CCT (n = 16)	Investigate the effect of AE on frequency and pain intensity in patients with MH	*Population*: patients with MH with or without aura classified by the ICHD-II criteria *Age (y)*: 18 to 65 *Gender (F/M)*: 88%/12% *Mean headache duration (y)*: 19.10	*Intervention group*: AE *Comparison group*: Usual care, maintenance of daily physical activity, medication, health information or no treatment	Pain intensity		
					-	VAS	Studies reported a low quality of evidence for the reduction of pain intensity by an intervention based on AE in patients with MH.
					Frequency of symptoms		
					4 (n = 176)	Self-report headache diaries	The meta-analysis showed a mean reduction in the number of MH days per month, favouring the AE group (MD = −0.61; 95% CI −1.14 to −0.09).
Falsiroli-Maistrello et al., 2018	7 RCTs (n = 390)	Establish the effectiveness of manual trigger point treatment compared to minimal active or no active interventions in terms of frequency and intensity in patients with primary headache	*Population*: adults older than 18 y with MH or TTH diagnosed by ICHD-III criteria *Age (y)*: 12 to 60 *Gender (F/M)*: 76.15%/23.85% *Mean headache duration (y)*: 9.20	*Intervention group*: Any direct or indirect manual treatment targeting trigger point *Comparison group*: Sham treatment, medication or no treatment	Pain intensity		
					TTH and MH: 5 (n = 208) MH: 2 (n = 88) TTH: 4 (n = 168)	VAS, Numeric Pain Index	Combined MH and TTH results showed statistically significant difference in favouring the Intervention group (MD = −12.93; 95% CI −18.70 to −7.16). Sub-analyses presented a significant reduction of pain intensity in the Intervention group in patients with MH (MD = −13.60; 95% CI −19.54 to −7.66) and TTH (MD = −12.83; 95% CI −19.49 to −6.17).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Falsiroli-Maistrello et al., 2018	7 RCTs (n = 390)	Establish the effectiveness of manual trigger point treatment compared to minimal active or no active interventions in terms of frequency and intensity in patients with primary headache	*Population*: adults older than 18 y with MH or TTH diagnosed by ICHD-III criteria *Age (y)*: 12 to 60 *Gender (F/M)*: 76.15%/23.85% *Mean headache duration (y)*: 9.20	*Intervention group*: Any direct or indirect manual treatment targeting trigger point *Comparison group*: Sham treatment, medication or no treatment	Frequency of symptoms		
					MH and TTH: 6 (n = 277) MH: 2 (n = 88) TTH: 4 (n = 189)	Self-report headache diaries	The analysis of the combined results indicated a statistically significant reduction after treatment, favouring the Intervention group (MD = −3.05; 95% CI −4.11 to −2.00). Sub-analyses showed a significant difference favouring the Intervention group for both MH (MD = −1.92; 95% CI −3.03 to −0.80) and TTH patients (MD = −3.50; 95% CI −4.91 to −2.09).
					Disability		
					-	HDI, HIT-6	The results were controversial, showing significant differences in terms of reduction of disability in the Intervention group or in both groups in different studies.
					Quality of life		
					-	SF-36, McGill Pain Questionnaire	The results reported no significant differences between the intervention and Comparison group.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Luedtke et al., 2016	26 RCTs (n = 3891)	Evaluate the effectiveness of manual therapy or exercise therapy on the intensity and frequency of MH, TTH and CGH	*Population*: adults with MH, TTH, CGH or mixed headache diagnosed by ICHD-I, II or III criteria *Age (y)*: 18 to 70 *Gender (F/M)*: 84.44%/15.56% *Mean headache duration (y)*: 10.97	*Intervention group*: AE, manual therapy or strength and endurance training *Comparison group*: Placebo, usual care, no treatment or any other active treatment	Pain intensity		
					MH: 5 (n = 254) TTH: 3 (n = 176) CGH: 6 (n = 388)	VAS, NPRS	The meta-analysis showed differences but not significant ones, in favour of the Intervention group in patients with MH (MD = −0.62; 95% CI −2.89 to 1.65). The differences were significant in the case of patients with TTH (MD = −1.11; 95% CI −1.64 to −0.57) or GCH (MD = −2.52; 95% CI −3.86 to −1.19).
					Frequency of symptoms		
					MH: 5 (n = 254) TTH: 2 (n = 94) CGH: 4 (n = 296)	Self-report headache diaries	The meta-analysis showed no significative differences in favour of the Intervention group in patients with MH (MD = −2.99; 95% CI −7.85 to 1.87) and TTH (MD = −7.58; 95% CI −18.13 to 2.97). There were significant differences in the case of CGH (MD = −1.34; 95% CI −1.40 to −1.28).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Mesa-Jiménez et al., 2015	5 RCTs (n = 206)	Compare the efficacy of multimodal manual therapy versus pharmacological care in patients with TTH	*Population*: patients with TTH and chronic headache diagnosed by ICHD-II criteria *Age (y)*: 18 to 83 *Gender (F/M)*: 79.12%/20.88% *Mean headache duration (y)*: 12.77	*Intervention group*: Manual therapy in isolation or combined with exercises *Comparison group*: Medication	Pain intensity		
					5 (n = 206)	VAS	The meta-analysis showed significant differences favouring manual therapy compared to medication after the intervention (WMD = −0.59; 95% CI −0.88 to −0.30). There were no significant differences in the long-term (WMD = −0.34; 95% CI −1.10 to 0.40).
					Frequency of symptoms		
					4 (n = 178)	Self-report headache diaries	The meta-analysis showed that manual therapy was more effective than pharmacological medical care (WMD = −0.80; 95% CI –1.66 to −0.44) immediately after the intervention.
Chaibi and Russell, 2014	6 RCTs (n = 288)	Assess the efficacy of manual therapy for chronic TTH	*Population*: patients older than 18 years with headache diagnosed by a neurologist or a physician employing ICHD-I, II or III criteria *Age (y)*: 19 to 68 *Gender (F/M)*: 78.82%/21.18% *Mean headache duration (y)*: 13.26	*Intervention group*: Manual therapy, ultrasound, TENS or exercises *Comparison group*: Usual care, detuned ultrasound, biofeedback treatment, spinal connective tissue manipulation or no treatment	Pain intensity		
					-	VAS, NPRS	The Intervention group had significantly more reduction in their headache intensity than the Comparison group after manual therapy intervention.
					Frequency of symptoms		
					-	Self-report headache diaries	There was a reduction of more than half in the frequency of symptoms post-treatment, and the results were maintained for more than six months..

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Racicki et al., 2013	6 RCTs (n = 457)	Asses the effectiveness of conservative physical therapy management of CGH	Population: patients diagnosed with CGH by the ICHD-II criteria *Age (y)*: 7 to 60 *Gender (F/M)*: 67.20%/32.80% *Mean headache duration (y)*: 6.03	*Intervention group*: Manual therapy, therapeutic exercise or a combination of both *Comparison group*: Conservative treatment, placebo or no treatment	Pain intensity		
					-	VAS, MVK pain scale	The exercise intervention displayed statistically significant improvements at 7 weeks. The combination of exercise and manipulative therapy displayed statistically significant improvements. Those improvements persisted at the 12-month-follow up period.
					Frequency of symptoms		
					-	Self-report headache diaries	The exercise intervention displayed statistically significant improvements at 7 weeks. The combination of exercise and manipulative therapy displayed statistically significant improvements. Those improvements persisted at the 12-month-follow up period.
					Disability		
					-	MVK disability scale	With the exception of one study, all reported reduction in disability but there was conflicting evidence regarding the effects of manipulative therapy.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Fernández-de-las-Peñas et al., 2006	5 RCTs (n = 321) 1 CCT (n = 20)	Establish whether manual therapies have specific efficacy in reducing pain from TTH	*Population*: patients with a diagnosis of episodic and chronic TTH employing ICDH-I or II criteria *Age (y)*: 18 to 70 *Gender (F/M)*: 47.50%/52.50% *Mean headache duration (y)*: 11.71	*Intervention group*: Different type of manual therapies *Comparison group*: Intervention plus other therapy, medication, placebo or no treatment	Pain intensity		
					-	VAS, NPRS, McGill Pain Questionnaire	The results were not generally consistent, as one trial reported positive results, another one reported neutral results, and the last one reported neutral results at the end of treatment and positive results at follow-up.
					Frequency of symptoms		
					-	Self-report headache diaries	The results found were controversial. While some studies found moderate effect in the reduction of this outcome, others revealed similar effects comparing the intervention and Comparison group.
					Disability		
					-	NDI, Headache index value	Only one study evaluated this outcome, showing positive results for the Intervention group with a moderate within-group effect size.
					Quality of life		
					-	SF-36	There were no significant differences between groups at the end of the treatment. However, at 4 weeks follow up, SMT showed greater improvement than medication.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Bronfort et al., 2001	9 RCTs (n = 683)	Assess the clinical efficacy of SMT for chronic headache (MH, TTH and CGH)	*Population*: patients diagnosed with MH, TTH or CGH by the ICHD-I criteria *Age (y)*: 15 to 70 *Gender (F/M)*: NA *Mean headache duration (y)*: NA	*Intervention group*: SMT with or without other therapies *Comparison group*: Medication, other forms of manual therapy, placebo or no treatment	Pain intensity		
					-	VAS	In patients with TTH, it appears to be an advantage for SMT at 4 weeks post-treatment, but 6 weeks later, medication was better. In patients with MH, SMT group showed an advantage after 8 weeks of treatment. The combination of amitriptyline and SMT did not provide any advantage. Patients with CGH, who received SMT, reported approximately twice the reduction in headache intensity per episode than the massage group.
					Frequency of symptoms		
					-	Self-report headache diaries	In patients with CGH, the SMT group showed a decrease of 69% compared with a 47% decrease in the Comparison group at 8 weeks of treatment.
					Disability		
					-	HDI	There appears to be an advantage for chiropractic SMT after 8 weeks.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Coelho et al., 2019	9 RCTs (n = 793)	Evaluate the effectiveness of mobilization and manipulation compared to other conservative treatments in patients with CGH and TTH	*Population*: adults older than 18 y diagnosed with CGH or TTH by the ICHD criteria *Age (y)*: 18 to 70 *Gender (F/M)*: 68.22%/31.78% *Mean headache duration (y)*: NA	*Intervention group*: Different manual therapy techniques *Comparison group*: Conservative treatment	Pain intensity		
					TTH: 2 (n = 146) CGH: 3 (n = 291)	VAS, NPRS	There was significant differences favouring mobilization and manipulation over conservative care at 1–4 weeks in patients with TTH (SMD = 0.49; 95% CI 0.04 to 0.93). In the case of CGH patients, the difference was not significative at 1–3 months (SMD = 0.19; 95% CI −0.24 to 0.62).
					Frequency of symptoms		
					TTH: 2 (n = 146) CGH: 2 (n = 236)	Self-report headache diaries	There was no statistical difference between groups at 1–4 weeks in patients with TTH (SMD = 0.29; 95% CI −0.15 to 0.73) and at 1–3 months in patients with CGH (SMD = 0.22; 95% CI −0.62 to 1.05).
					Disability		
					TTH: 2 (n = 124)	NDI, SF-36, SF-12, HDI	There was a significant difference favouring the Intervention group in patients with TTH (SMD = 0.47; 95% CI 0.10 to 0.84).

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Cumplido-Trasmonte et al., 2018	10 RCTs (n = 731)	Determine the effectiveness of manual and non-invasive techniques in the treatment of patients with TTH	*Population*: patients older than 18 y diagnosed with TTH by the ICHD-II criteria *Age (y)*: 18 to 70 *Gender (F/M)*: 80.79%/19.21% *Mean headache duration (y)*: NA	*Intervention group*: Manual therapy techniques *Comparison group*: Conservative treatment, usual care or sham massage or no treatment	Pain intensity		
					-	VAS, McGill Pain Questionnaire	After the intervention, all articles showed significant improvements over the Comparison group, and better improvements were found when the intervention combined different types of manual therapy.
					Frequency of symptoms		
					-	Self-report headache diaries	The results showed significant improvements for the Intervention group following the intervention. Regarding this group, better outcomes were found when different types of manual therapy were combined.
					Disability		
					-	HDI	All treatment groups showed significant improvements in the overall HDI count, revealing better improvements for the combination of cervical manipulation and suboccipital inhibition.
					Quality of life		
					-	SF-12, HIT-6, SF-36	The studies that evaluated quality of life outcome showed inconclusive results.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Gil-Martínez et al., 2013	10 RCTs (n = 2495)	Investigate the effectiveness of therapeutic exercise on MH and TTH	*Population*: patients older than 18 y diagnosed with MH or TTH by the ICHD-II criteria *Age (y)*: 18 to 65 *Gender (F/M)*: 83.57%/16.43% *Mean headache duration (y)*: 19.87	*Intervention group*: Therapeutic exercise in isolation or combined with other physical therapy treatments *Comparison group*: Conventional medical or physical therapy treatment, education or no treatment	Pain intensity		
					-	VAS, NPRS	There was evidence that therapeutic exercise on the craneocervical and shoulder region significantly improved, in the medium term, the intensity of pain.
					Frequency of symptoms		
					-	Self-report headache diaries	The results showed that therapeutic exercise on the craneocervical and shoulder region significantly improved the frequency of symptoms in the medium term, with a strong level of evidence.
					Disability		
					-	HDI	There was improvement in the disability outcome at medium term regarding therapeutic exercise on the craniocervical and shoulder region, with a strong level of evidence.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Bronfort et al., 2009	22 RCTs (n = 2628)	Evaluate the effect of specific non-invasive physical treatments for chronic/recurrent headaches	*Population*: patients with chronic/recurrent headaches, including episodic and chronic TTH, CGH and MH, classified according to the ICHD-I criteria *Age (y)*: 12 to 78 *Gender (F/M)*: 72.77%/27.23% *Mean headache duration (y)*: 8.75	*Intervention group*: One or more types of non-invasive physical treatment *Comparison group*: Placebo, no treatment and any other type of active intervention	Pain intensity		
					-	VAS	The results showed greater reduction for the Intervention group in the short- and mid-term.
					Frequency of symptoms		
					-	Self-report headache diaries	The Intervention group performed significantly better in terms of headache frequency at 4 and 8 weeks. In addition, the results showed significantly more reduction in headache frequency at 12 months.
					Disability		
					-	HDI, NDI	Significantly fewer patients in the Intervention group experienced a 50% reduction in headache index score after 4 weeks. In addition, there was a significant difference in favor of the Intervention group after 3 weeks.
Fernández-de-las-Peñas et al., 2005	2 RCTs (n = 253)	To assess the effectiveness of SMT in CGH	*Population*: patients older than 18 y, diagnosed with CGH based on ICHD-II criteria *Age (y)*: 18 to 60 *Gender (F/M)*: 67.19%/32.81% *Mean headache duration (y)*: 6.07	*Intervention group*: Exercise or manipulative therapy *Comparison group*: Massage and laser therapy or no treatment	Pain intensity		
					-	VAS	Manipulative therapy reported positive results on headache intensity compared to the control group.
					Frequency of symptoms		
					-	Self-report headache diaries	Only one study evaluated the frequency of symptoms, obtaining positive results for the Intervention group.

Table 1. *Cont.*

Study	No. and Type of Included Studies (Subjects)	Objectives	Population	Intervention	No. of Studies Included in Meta-Analysis (Subjects)	Outcome Measures	Results
Fernandez et al., 2020	6 RCTs (n = 549)	Review the evidence on SMT and manual therapy in the treatment of CGH	*Population*: Patients older than 18 y with CGH diagnosis based on ICHD-III criteria *Age (y)*: 18 to 70 *Gender (F/M)*: 58.83%/41.17% *Mean headache duration (y)*: 7.3	*Intervention group*: SMT *Comparison group*: Sham massage, exercise placebo or no treatment	Pain intensity		
					Short term: 6 (n = 364) Mid term: 3 (n = 157) Long term: 2 (n = 120)	VAS	Analysis revealed a significant small effect favouring SMT over other manual therapies for pain intensity in the short term (MD = −10.88; 95% CI −17.94 to −3.82). However, there was a non-significant difference between groups in the mid- and long-term (MD = −9.77; 95% CI −24.21 to 4.68 and MD = −0.76; 95% CI −5.89 to 4.37, respectively).
					Frequency of symptoms		
					Short term: 3 (n = 163) Mid term: 3 (n = 157) Long term: 2 (n = 120)	Self-report headache diaries	There was a significant small effect favouring SMT for frequency of symptoms in short- and mid-term (SMD = −0.35, 95% CI −0.66 to −0.04 and SMD = −0.32; 95% CI −0.63 to −0.00, respectively) but not in long term follow up (SMD = −0.378; 95% CI −0.84 to 0.10).
					Disability		
					Short term: 2 (n = 142)	MVK, NDI	There was a significant small effect favouring SMT for disability in the short term (MD = −13.31; 95% CI −18.07 to −8.56). It was not possible to assess disability in the mid- and long-term.

AE, Aerobic exercise; CCT, Controlled Clinical Trial; CGH, Cervicogenic headache; CI, confidence interval; F, Female; HDI, Headache Disability Index; HIT-6, Headache Impact Test; ICHD, The International Classification of Headache Disorders criteria; ICHD-II, The International Classification of Headache Disorders criteria, second edition; M, Male; MD, Mean difference; MH, Migraine; MVK, Modified Von Korff scale; NA, not appear; NDI, Neck Disability Index; NPRS, Numeric Pain Rating Scale; OAA, Occiput-atlas-axis global manipulation; RCT, Randomized Controlled Trial; SF-12, Short Form Health Survey-12; SF-36, Short Form Health Survey-36; SIT, Suboccipital soft-tissue inhibition technique; SMD, Standardized mean difference; SMT, Spinal manipulative therapy; TTH, Tension-type headache; VAS, Visual Analogue Scale; WHO-5, Well-Being Index; WMD, Weighted mean difference; Y, Years.

Table 2. Interventions included in each of the studies.

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
La Touche et al., 2020	Intervention group	- AE (fast-walk, jogging, cycling, walking on a treadmill, rowing), - Strength training, - Endurance training, - Stretching, - Progressive muscle relaxation or - HIIT and MCT - Warm-up: 5 to 15 min - Cool-down: 5 to 20 min	2 to 5 times/week 6 to 12 weeks	40 to 60 min HIIT: Intervals of 4 min followed by an active rest period of 3 min	70 to 95% of HRmax RPE (14–16) 45–60% VO_2max
	Comparison group	- Maintain daily living activity, - Relaxation or - No treatment			
Machado-Oliveira et al., 2020	Intervention group	*AE training*: - HIIT, - MCT or - AE exercise (running, biking, step, walking, interval jogging, dancing and home-based exercises)	2 to 5 times/week 6 to 20 weeks	40 to 60 min HIIT: NA	70 to 95% of HRmax RPE (13–16) 60 to 75% of VO_2max
		Resistance training: - Free weights for shoulders and neck, - Training with elastic resistance bands	1 to 5 times/week 10 to 52 weeks	2 to 30 min	10 to 80% of maximal repetition load
	Comparison group	- Usual care, - Medication (topiramate), - Waiting list, - Ergonomic and posture correction, - Health information or - No treatment			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Falsiroli-Maistrello et al., 2019	Intervention group	- Articular mobilizations of the cervico-thoracic region, - Treatment of myofascial trigger points, - Sub-occipital inhibitory pressures and manipulations of upper cervical levels (C0–C1, C1–C2), - Soft tissue techniques (trigger point manual treatment, myofascial release, post-isometric relaxation), - Neural mobilization techniques or - Exercise and postural correction	4 to 14 times/week 4 weeks to 6 months Follow-up: 2 weeks to 9 months	15 to 50 min	NR
	Comparison group	- Usual care, - Sham treatment, - Placebo or - No treatment			
Jiang et al., 2019	Intervention group	- Suboccipital soft-tissue inhibition technique or - Occiput-atlas, axis global manipulation	1 time/week 4 weeks Follow up: 8 weeks	20 min	NR
	Comparison group	- No treatment			
Lemmens et al., 2019	Intervention group	- AE (brisk walking, jogging, cycling, cross training, running, HIIT or MCT)	2 to 5 times/week 10 to 16 weeks	28 to 50 min	RPE (14–16) 70 to 95% of HRmax 60–75% VO_2max
	Comparison group	- Maintain daily physical activity, - Medication (amitriptyline), - Health information, - Relaxation, - Self-management or - No treatment			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Falsiroli-Maistrello et al., 2018	Intervention group	- Ischemic compression, - Myofascial release at craniocervical muscles, - Neural mobilization techniques or - Positional release therapy and routine medications	2 to 5 times/week 2 to 12 weeks Follow up: 2 weeks to 4 months	15 to 100 min	NR
	Comparison group	- Sham massage, - Medication (NSAIDs, nortriptyline, propranolol and depakine), - Waiting list supported with routine medication or - No treatment			
Luedtke et al., 2016	Intervention group	- AE, - Physical training and resistance training with Theraband, - Trigger point treatment, - Mobilization, - Mixed physiotherapy approaches (massage, posture correction, craniocervical exercises, TENS, tape, soft tissue massage) or - Psychological interventions (relaxation and behavioral therapy)	1 to 12 times/week 1 week to 8 months	2 to 50 min	NR
	Comparison group	- Usual care, - Sham treatment, - Waiting list, - Health information or - No treatment			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Mesa-Jiménez et al., 2015	Intervention group	- Mobilization or manipulation of the cervical and thoracic spine, - Low-load stabilization exercises, - Soft-tissue pressure release or - Postural correction exercises	1 to 12 times/week 2 to 8 weeks	10 to 60 min	NR
	Comparison group	- Medication (NSAIDs)			
Chaibi and Russell, 2014	Intervention group	- Head and neck massage, - Superficial heat, - Ultrasound with home exercises and TENS, - Stretching, - Low-load endurance training of cervicoscapular and craniocervical region with daily home exercise combined with postural correction exercises or - Mobilization	2 to 12.8 times/week 8 days to 9 months	30 to 40 min	NR
	Comparison group	- Usual care, - Detuned ultrasound, - Biofeedback treatment, - Spinal connective tissue manipulation or - Observation period			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Racicki et al., 2013	Intervention group	- SMT at the cervical (HVLA lateral directed manipulation without rotation or extension), or upper thoracic region, - Moist heat and light massage, - C1-C2 SNAG using a cervical self-SNAG trap, - Cervical SMT consisting of both low-velocity cervical joint mobilizations and high-velocity cervical manipulations, - Low-load endurance cervico-scapular muscle exercise, - Low-level laser treatment in the upper cervical region and deep friction massage	1 to 12 times/week 6 to 12 weeks Follow up: 4 weeks to 12 months	10 to 30 min	NR
	Comparison group	- Conservative treatment, - Placebo (Light touch to same spinal segments without thrust, moist heat and light massage or C1–C2 SNAG using a cervical self-SNAG strap with force applied to the C1 level via horizontal pressure from the cervical strap with no head movement towards restricted side) or - No treatment			
Fernández-de-las-Peñas et al., 2006	Intervention group	- Spinal manipulation and soft tissue therapy, - Spinal manipulation and cervical manual traction, - Connective tissue manipulation, - Protraction-retraction neck exercises or - CV-4 craniosacral technique	2 to 5 times/week 4 to 6 weeks Follow-up: 4 weeks to 6 months	10 to 30 min	NR
	Comparison group	- Intervention and other therapy, - Medication (Amitriptyline), - Placebo or - No treatment			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Bronfort et al., 2001	Intervention group	- SMT or - SMT combined with massage, azapropazone and deep friction massage	1 to 12 times/week 1 to 8 weeks	15 to 20 min	NR
	Comparison group	- Medication (amitriptyline, azapropazone), - Deep friction with placebo laser, - Mobilization, - Palpation and rest, - Cold packs, - Waiting list or - No treatment			
Coelho et al., 2019	Intervention group	- HVLA cervical and upper thoracic spinal manipulation, - Low velocity passive upper cervical mobilization techniques combined with exercise, - Light massage, - Suboccipital soft tissue inhibition or - Occiput-atlas, axis global manipulation joint manipulation	2 to 4 times/week 4 to 6 weeks Follow-up: Immediately post-treatment to 12 months	5 to 20 min	NR
	Comparison group	- Effleurage and petrissage of neck and upper shoulder muscles, - No intervention, - Soft tissue massage with light laser therapy in upper cervical region or - Medication (amitriptyline)			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Cumplido-Trasmonte et al., 2018	Intervention group	- CV-4 craniosacral technique, - Superficial heat and connective tissue manipulation, - Spinal cyriax mobilization, - Conventional physiotherapy and craniocervical exercises, - Mobilization and exercise combined with postural correction, - Suboccipital soft-tissue inhibition technique, - Occiput-atlas, axis global manipulation or - Neural mobilization and soft tissue techniques	1 to 5 times/week 4 to 6 weeks	10 to 30 min	NR
	Comparison group	- Conventional physiotherapy, - Medication (NSAIDs), - Placebo (sham massage) or - No treatment			
Gil-Martinez et al., 2013	Intervention group	- Acupuncture, - Physical training, - Relaxation, - Craneocervical and upper limb exercises, - Yoga, - Spinal mobilization therapy or - Medication (Topiramate)	1 to 12 times/week 6 to 12 weeks Follow up: Immediately post-treatment to 26 weeks	15–60 min	RPE (14–16)
	Comparison group	- Conservative treatment of physiotherapy and postural correction, - Education and home exercises, - Conventional medical treatment or - No treatment			

Table 2. *Cont.*

Study	Group	Type of Intervention	Frequency and Intervention Time, Follow-Up	Session Duration	Intensity
Bronfort et al., 2009	Intervention group	- SMT, - Mobilization, - Massage, - Therapeutic touch, - Therapeutic exercise, - Cold packs, - Electrical modalities (including pulsating electromagnetic fields [PEMF], cranial electrotherapy, interferential therapy, TENS and ultrasound) or - Different combinations of physical treatments	2 to 5 times/week 1 to 12 weeks Follow up: Immediately post-treatment to 36 months	5 min to 1 h	NR
	Comparison group	- Medication (amitriptyline and NSAIDs) - Placebo, - Waiting list or - No-treatment			
Fernández-de-las-Peñas et al., 2005	Intervention group	- Exercise therapy and/or - SMT	2 times/week 3 to 6 weeks Follow up: 1 week to 12 months	30 min	NR
	Comparison group	- Deep friction massage, - Laser therapy or - No treatment			
Fernandez et al., 2020	Intervention group	- SMT	1 to 3 times/week 3 to 12 weeks Follow up: 1 week to 12 months	10 min	NR
	Comparison group	- Placebo, - Sham massage, - Mobilization with or without exercise or - No treatment			

AE, Aerobic exercise; CV-4, Compression of the Fourth Ventricle; HIIT, High interval intensity training; HRmax, maximum heart rate; HVLA, High velocity low amplitude; MCT, Moderate continuous aerobic training; NA, not reported; NSAID, Nonsteroidal anti-inflammatory drugs; RPE, Rate of Perceived Exertion scale; SMT, Spinal manipulative therapy; SNAG, Sustained natural apophyseal glide; TENS, Transcutaneous electrical nerve stimulation; VO_2max, Maximum oxygen volume consumption.

3.1. Characteristics of the Included Systematic Reviews

Our study included 18 systematic reviews (with or without a meta-analysis), comprising 95 original studies, 90 RCTs, 4 CCTs and 1 non-controlled clinical trial (included by [29]), with a total of 9188 participants. Several original studies appeared in different systematic reviews, but none of the reviews included the same studies (Table S1).

In terms of the populations in the systematic reviews, 9 studies (n = 3693) included patients diagnosed with migraine [7,8,29,33,35,37,39–41], 13 systematic reviews (n = 4435) included patients diagnosed with TTH [7,29,30,32–35,37,38,40–43] and 8 studies included patients diagnosed with CGH (n = 1592) [31,33,35–37,41,43,44]. One of the RCTs included patients with post-traumatic headache (n = 23) (included by Bronfort et al., 2001 [33]), and four of them (n = 173) did not specify which type of headache was studied (included by Chaibi and Russell 2014; Mesa-Jiménez et al., 2015; Luedtke et al., 2016 [30,41,42]).

In three of the systematic reviews, the Intervention group used AE with other forms of exercise therapy in patients with migraine [8,39] or TTH [29]. Ten systematic reviews had an Intervention group that used various types of manual therapy in patients with TTH [30,32,34,38], CGH [44] or populations with various types of headaches included in this study [33,35,37,40,43]. In the remaining five studies, the intervention used a combination of both treatments in patients with TTH [42], CGH [31,36] or several types of headache [7,41].

3.2. Results of the Methodology Quality Analysis

The scores ranged from 7 to 24 out of a possible 26 points, with a mean score of 17.28 ± 4.75 points. Only 6 (33.33%) of the 18 studies were considered high quality, with a score above 20 points [8,37,40–42,44] (Table 3).

Table 3. Quality assessment scores.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Score
La Touche et al., 2020	2	2	1	2	2	2	1	2	2	2	2	2	2	**24**
Machado-Oliveira et al., 2020	2	2	1	1	0	1	2	2	1	0	0	0	0	**12**
Falsiroli-Maistrello et al., 2019	2	0	1	2	1	2	2	2	2	2	2	2	2	**22**
Jiang et al., 2019	2	2	1	1	1	2	0	2	1	2	2	2	0	**18**
Lemmens et al., 2019	2	1	1	1	1	1	2	2	1	2	0	0	2	**16**
Falsiroli-Maistrello et al., 2018	2	1	2	2	1	2	2	2	2	1	2	2	2	**23**
Luedtke et al., 2016	2	2	1	2	1	2	2	2	2	1	2	2	2	**23**
Mesa-Jiménez et al., 2015	1	2	1	1	2	2	2	2	2	2	2	2	0	**21**
Chaibi and Russell, 2014	1	2	1	1	0	1	2	0	2	0	0	0	0	**10**
Racicki et al., 2013	2	2	1	1	0	1	2	2	2	2	1	1	0	**17**
Fernández-de-las-Peñas et al., 2006	1	2	1	1	0	1	2	2	2	2	0	0	1	**15**
Bronfort et al., 2001	1	1	2	1	1	1	1	2	1	2	1	1	1	**16**
Coelho et al., 2019	2	1	2	2	0	1	2	2	2	1	2	2	0	**19**
Cumplido-Trasmonte et al., 2018	1	2	2	1	1	2	2	1	1	0	0	0	1	**14**
Gil-Martínez et al., 2013	0	2	0	2	1	2	0	2	2	2	0	0	1	**14**
Bronfort et al., 2009	1	2	2	0	2	2	2	2	2	2	0	0	2	**19**
Fernández-de-las-Peñas et al., 2005	0	2	0	0	2	0	0	0	1	0	0	1	1	**7**
Fernandez et al., 2020	2	1	2	1	0	2	2	2	1	2	2	2	2	**21**

1. Explicitly described to allow replication; 2. Adequate number and range of databases; 3. Alternative searches; 4. Adequate range of key words; 5. Non-English-language papers included in the search; 6. Inclusion criteria explicitly described to allow replication; 7. Excludes reviews which do not adequately address inclusion and exclusion criteria; 8. Two independent reviewers assessing selection bias; 9. Quality assessment explicitly described to allow replication; 10. Meta-analysis conducted on only homogeneous data or limitations to homogeneity discussed; 11. Confidence intervals/effect sizes reported where possible; 12. Conclusions supported by the meta-analysis or other data analysis findings 13. Conclusions address levels of evidence for each intervention/comparison.

The items with the highest scores were those related to the assessment of selection bias and the adequate description of the quality assessment. The items with the lowest scores were those related to language restrictions and the reporting of confidence intervals

and effect sizes. The inter-rater reliability of the methodological quality assessment was high (κ = 0.790).

3.3. Results of the Risk of Bias Analysis

Of the 18 studies, 6 (33.33%) had a low risk of bias [8,35,37,40,41,44]. The remaining 12 (66.66%) had a high risk of bias [7,29–34,36,38,39,42,43] (Table 4 and Figure 2).

Table 4. Risk of bias assessment in systematic reviews through the ROBIS scale.

Study	Phase 2				Phase 3
	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
La Touche et al., 2020	L	L	L	L	L
Machado-Oliveira et al., 2020	H	L	H	H	H
Falsiroli-Maistrello et al., 2019	L	L	L	L	L
Jiang et al., 2019	H	L	H	L	H
Lemmens et al., 2019	H	H	L	H	H
Falsiroli-Maistrello et al., 2018	L	L	L	L	L
Luedtke et al., 2016	L	L	L	L	L
Mesa-Jiménez et al., 2015	L	L	H	H	H
Chaibi and Russell, 2014	H	H	H	H	H
Racicki et al., 2013	H	H	H	H	H
Fernández-de-las-Peñas et al., 2006	H	H	L	H	H
Bronfort et al., 2001	H	H	H	H	H
Coelho et al., 2019	H	H	L	L	H
Cumplido-Trasmonte et al., 2018	L	H	H	H	H
Gil-Martínez et al., 2013	L	H	H	H	H
Bronfort et al., 2009	L	L	L	L	L
Fernández-de-las-Peñas et al., 2005	H	H	H	H	H
Fernandez et al., 2020	L	L	L	L	L

L, low risk; H, high risk.

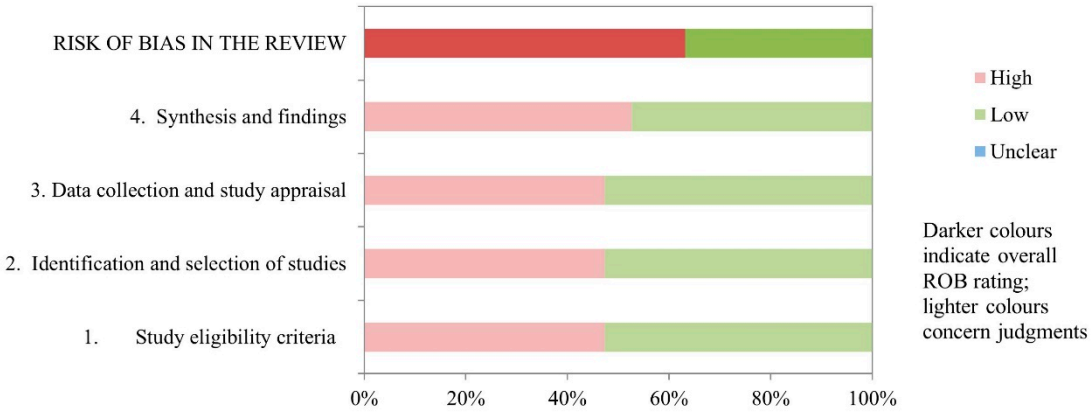

Figure 2. Graphical representation of the ROBIS results.

The domain for "synthesis and findings" had the highest risk of bias, with 10 (55.55%) studies scoring a high risk of bias. In domains for "study eligibility criteria", "identification and selection of studies" and "data collection and study appraisal", 9 (50%) of the 18 studies

had a low risk of bias. The inter-rater reliability for the risk of bias assessment was high ($\kappa = 0.849$).

3.4. Evidence Map

Figures 3 and 4 present the results of the evidence map for the 18 studies. In addition, Table 5 shows the levels of evidence of the meta-analyses included in the study according to the PAGAC.

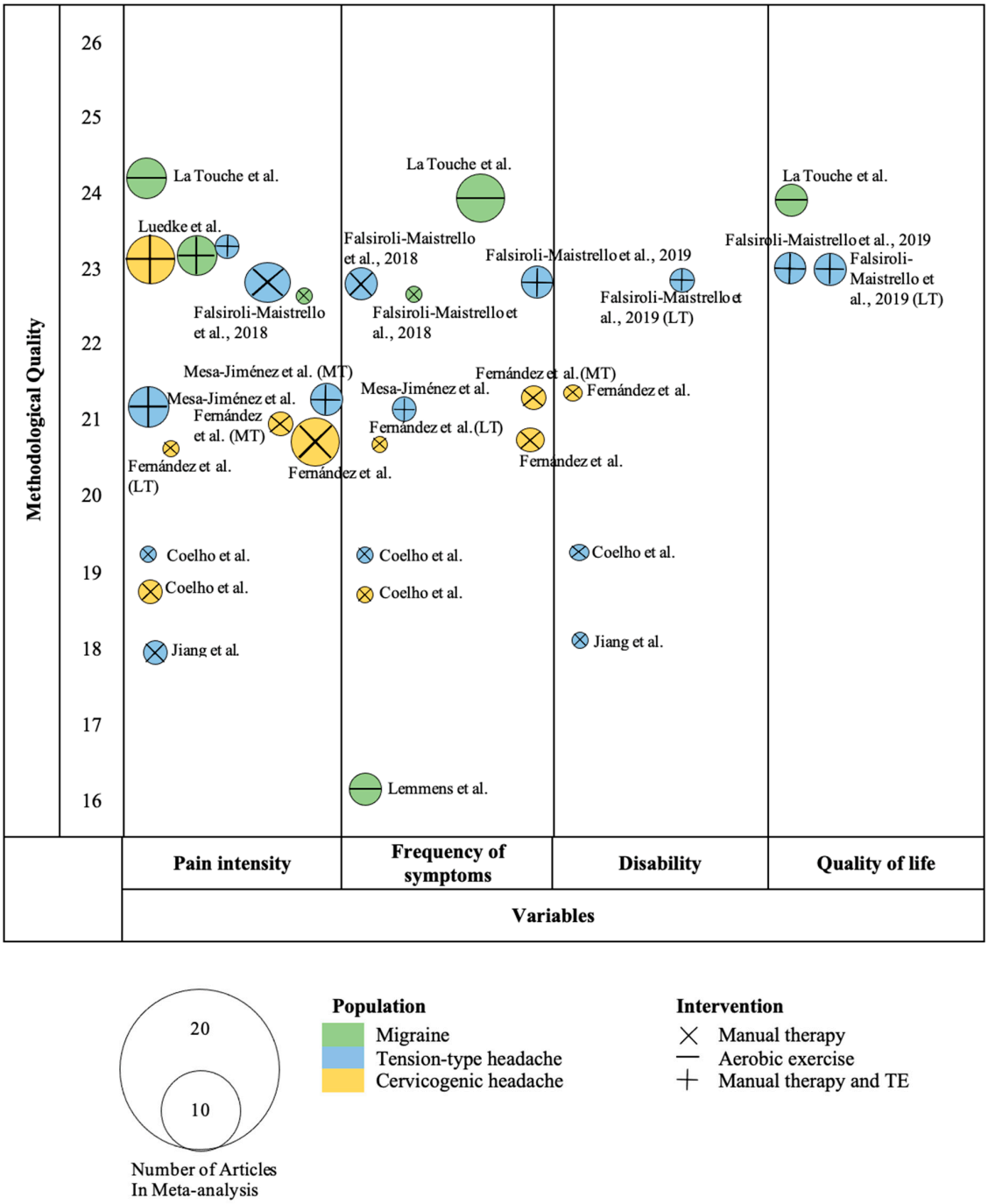

Figure 3. Descriptive evidence map of meta-analyses. TE, therapeutic exercise; MT, mid-term; LT, long-term. On the *x*-axis the studies are classified according to the study variable, while on the *y*-axis they are categorized according to their score on the Modified Quality Assessment Scale for Systematic Reviews (AMSTAR), with a score above 20 being considered high-quality.

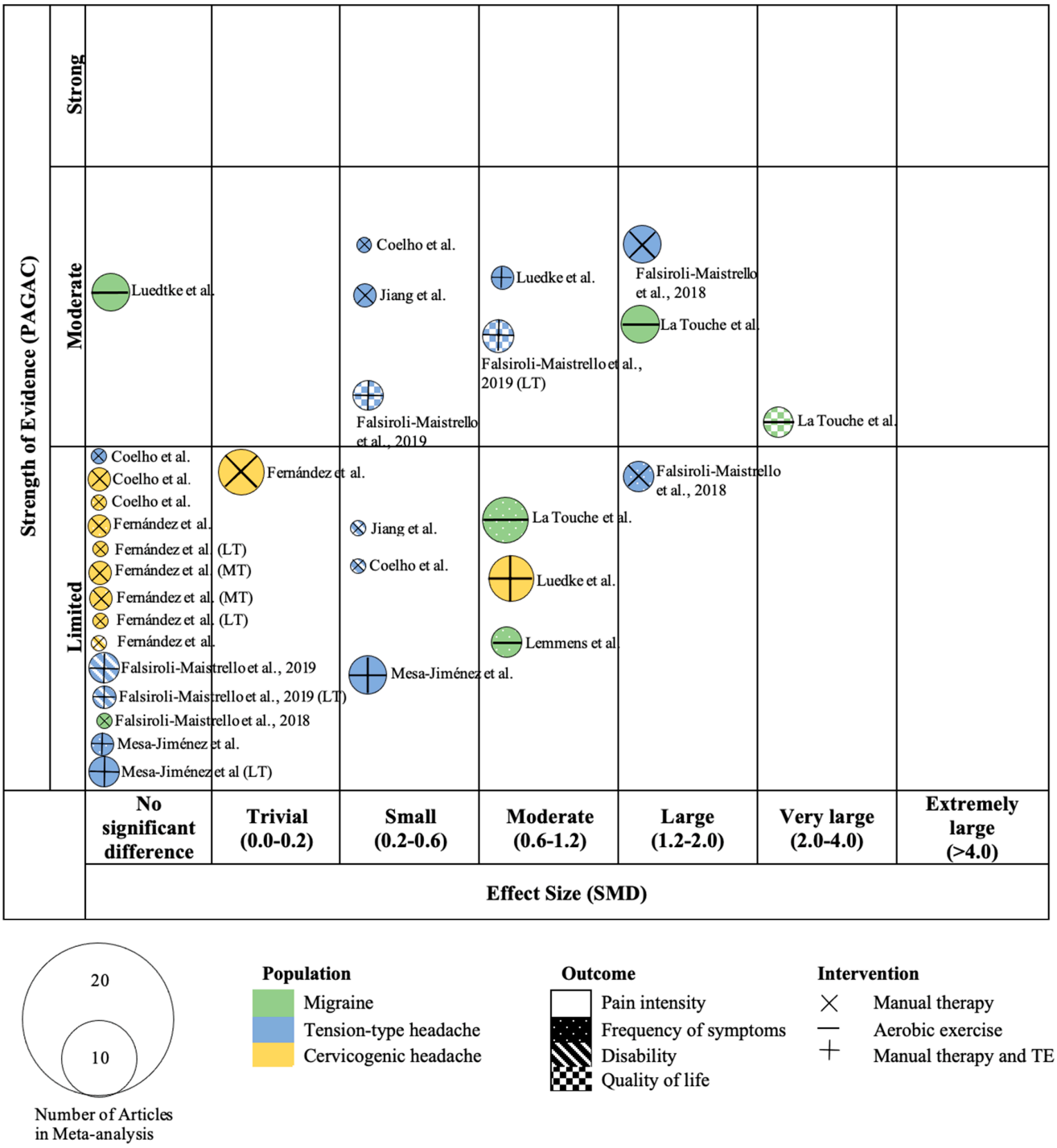

Figure 4. Mapping based on effect size of meta-analyses. TE, therapeutic exercise; MT, mid-term; LT, long-term. On the *x*-axis the studies are classified according to the effect size of the meta-analysis with standard mean difference (SMD). On the *y*-axis they are categorized according to the strength of evidence based on the Physical Activity Guidelines Advisory Committee (PAGAC).

Table 5. Committee assigned grades for the effects of manual therapy or therapeutic exercise on headache-related outcomes.

	Criteria					Effect	Evidence
Outcome Headache and Intervention Type (No. of Meta-Analyses)	**Applicability**	**Generalizability**	**Risk of Bias or Study Limitations**	**Quantity and Consistency**	**Magnitude and Precision of Effect**	**SMD (95% CI)**	
Pain intensity							
- Migraine, AE (2)	Strong	Moderate	Strong	Limited	Moderate	−1.16 (−1.90, −0.41)	**Moderate**
- TTH, MT (3)	Strong	Moderate	Limited	Limited	Moderate	−0.83 (−1.47, −0.19)	**Limited**
- TTH, MIX (2)	Strong	Moderate	Strong	Limited	Limited	−0.59 (−0.85, −0.33)	**Moderate**
- CGH, MIX (3)	Strong	Limited	Moderate	Limited	Limited	−0.49 (−0.86, −0.12)	**Limited**
Frequency of symptoms							
- Migraine, AE (2)	Strong	Moderate	Limited	Limited	Moderate	−0.75 (−1.08, −0.43)	**Limited**
- TTH, MT (2)	Strong	Moderate	Limited	Limited	Moderate	−0.91 (−2.18, 0.36)	**Limited**
- CGH, MIX (2)	Strong	Moderate	Limited	Limited	Limited	−0.30 (−0.84, 0.23)	**Limited**
Disability							
- TTH, MT (2)	Strong	Moderate	Limited	Limited	Limited	−0.27 (−0.47, −0.06)	**Limited**

95% CI, 95% confidence interval; AE, Aerobic exercise; CGH, Cervicogenic headache; MT, Manual therapy intervention; MIX, mixed intervention; SMD, standard mean difference; TTH, tension-type headache.

3.5. Pain Intensity

Seventeen studies assessed pain intensity in patients with headache; 8 of the studies included meta-analyses [8,38–44], and the remaining 9 performed a qualitative synthesis [7,29–36].

Interventions using AE with or without resistance exercise were an effective approach in patients with migraine or TTH in the short term [8,29,39]. Interventions based on manual therapy showed differences in favour of the Intervention group in patients with TTH [30,32,34,38], and in populations that included patients with migraine, TTH and CGH in the short-term [33,35,40,43] and at follow-up [35]. In patients with CGH, manual therapy showed positive results in the short-term [36,44], but not in the medium- or long-term [44]. The combination of manual therapy and therapeutic exercise showed differences favouring the Intervention group in patients with migraine, TTH or CGH in the short-term [41] and medium-term [7,31]. In one study, when comparing manual therapy with or without exercise and medication, they found significant differences in the short-term, but not in the long-term in patients with TTH [42].

With regard to the quantitative analysis, the MMA of pain intensity in patients with migraine revealed significant differences using aerobic exercise in two meta-analyses [8,41] (SMD = −1.16; 95% CI −1.90 to −0.41; $p < 0.05$) without evidence of heterogeneity (Q = 0.61, $p = 0.44$, ($I^2 = 0\%$) (Figure 5).

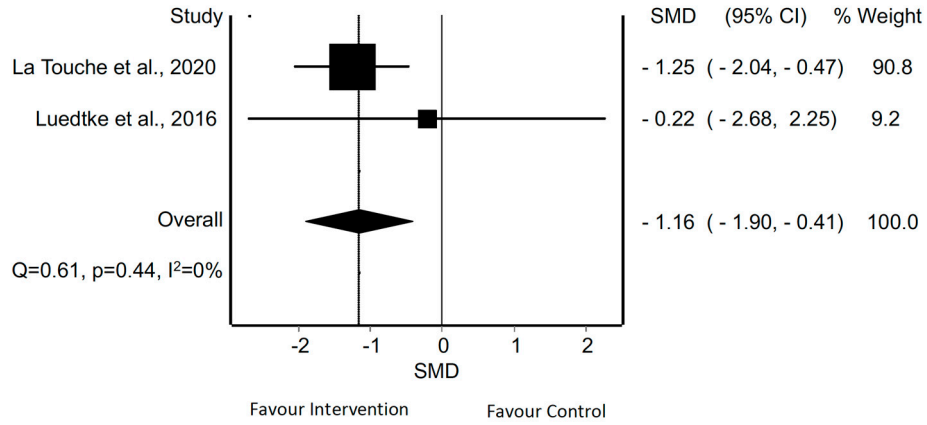

Figure 5. Synthesis forest plot for pain intensity in patients with migraine treated with aerobic exercise. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

The MMA of pain intensity in patients with TTH treated by manual therapy or mixed treatment revealed significant differences in three [38,40,43] and two meta-analyses [41,42], respectively (SMD = −0.83; 95% CI −1.47 to −0.19; $p < 0.05$ and SMD = −0.59; 95% CI −0.85 to −0.33; $p < 0.05$, respectively). There was evidence of heterogeneity in the analysis of manual therapy (Q = 6.39, $p = 0.04$, $I^2 = 69\%$) but not in the case of mixed treatment (Q = 0.01, $p = 0.91$; $I^2 = 0\%$) (Figures 6 and 7).

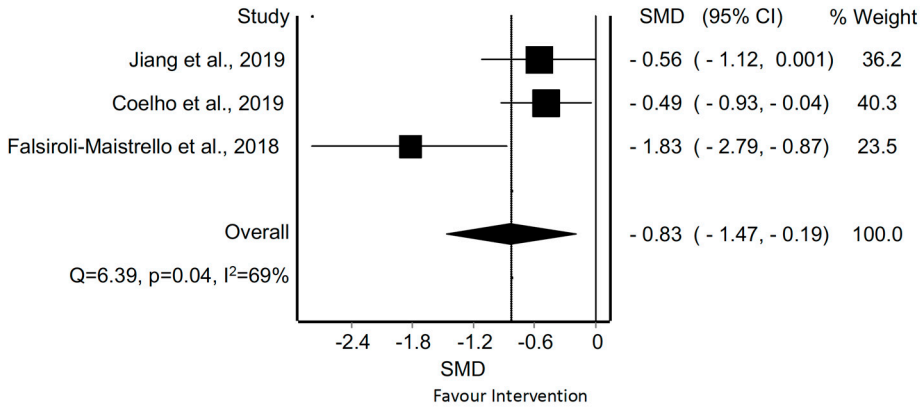

Figure 6. Synthesis forest plot for pain intensity in patients with tension-type headache treated with manual therapy. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

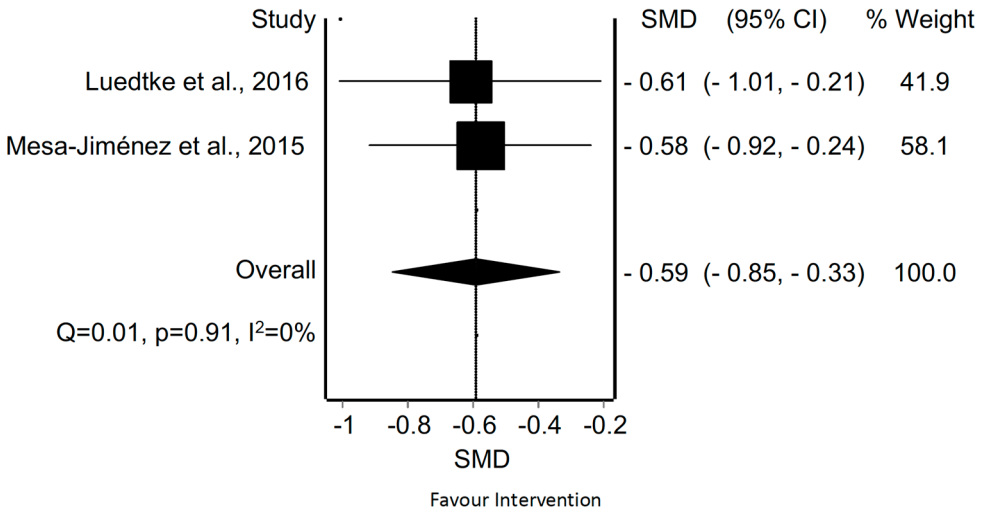

Figure 7. Synthesis forest plot for pain intensity in patients with tension-type headache and mixed intervention (manual therapy and/or therapeutic exercise). The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

In the case of patients with CGH, the MMA of pain intensity also revealed significant differences in three meta-analyses including manual therapy or therapeutic exercise [41,43,44] (SMD = −0.49; 95% CI −0.86 to −0.12.33; $p < 0.05$) without evidence of heterogeneity according to Cochran's Q statistical test (Q = 3.60, $p = 0.16$), but with heterogeneity according to I^2 ($I^2 = 45\%$) (Figure 8).

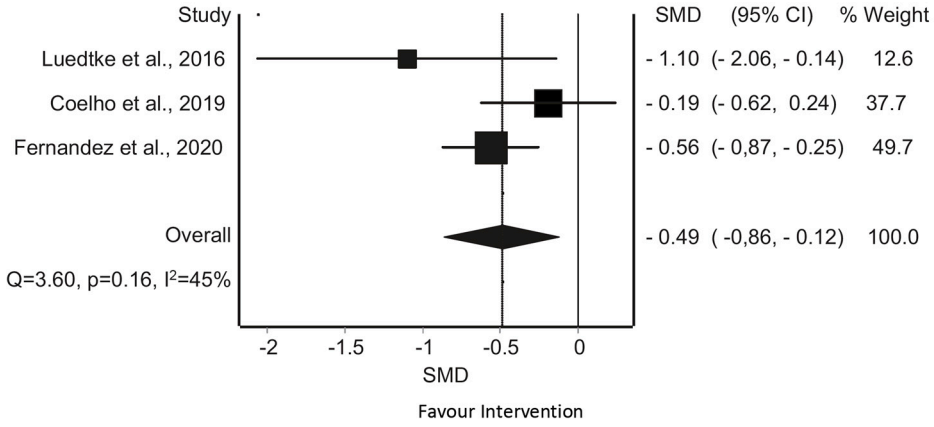

Figure 8. Synthesis forest plot for pain intensity in patients with cervicogenic headache and a mixed intervention. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

3.6. Frequency of Symptoms

Sixteen studies evaluated the frequency of symptoms in patients with headache; 9 performed a qualitative synthesis [7,29–36], while the remaining 7 included a meta-analysis [8,39–44].

Interventions using aerobic exercise have shown significant differences in headache frequency reduction in patients with migraine [8,39] or migraine and TTH [29]. Treatment with manual therapy showed positive results in studies involving patients with TTH in the short-term [30,32,34]. There was also significant differences in patients with CGH in the short-term [36,44] and medium-term [44]. Studies that included populations with migraine, TTH or CGH found positive results favouring the manual therapy group in the short-term [35,40,43] and medium-term [35,43]. Studies using a combination of therapeutic exercise and manual therapy showed a decrease in headache in the days immediately following treatment in patients with migraine, TTH or CGH [33,42] and in both the short- and medium-term [7,31]. Luedtke et al. found significant differences in patients with migraine and TTH but not in the case of CGH [41].

With regard to the quantitative analysis, the MMA of the frequency of symptoms in patients with migraine treated with AE revealed a statistically significant difference in two meta-analyses [8,39] (SMD = −0.75; 95% CI −1.08 to −0.43; $p < 0.05$) and without evidence of significant heterogeneity (Q = 0.00, $p = 0.95$, $I^2 = 0\%$) (Figure 9). In patients with TTH, the MMA of the frequency of symptoms revealed no significant difference in two meta-analyses that employed manual therapy [40,43] (SMD = −0.91; 95% CI −2.18 to 0.36; $p > 0.05$) with evidence of significant heterogeneity (Q = 9.40, $p = 0.00$; $I^2 = 89\%$) (Figure 10). The MMA of patients with CGH revealed no significant difference in 2 meta-analyses in which treatment included manual therapy or exercise in terms of the frequency of symptoms [43,44] (SMD = −0.30; 95% CI −0.84 to 0.23; $p > 0.05$) without evidence of heterogeneity (Q = 0.06, $p = 0.80$, $I^2 = 0\%$) (Figure 11).

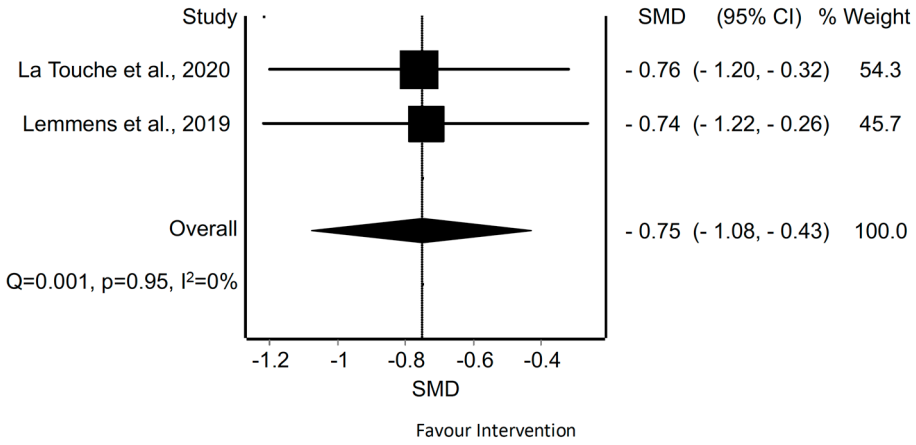

Figure 9. Synthesis forest plot for the frequency of symptoms in patients with migraine treated with aerobic exercise. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs, and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

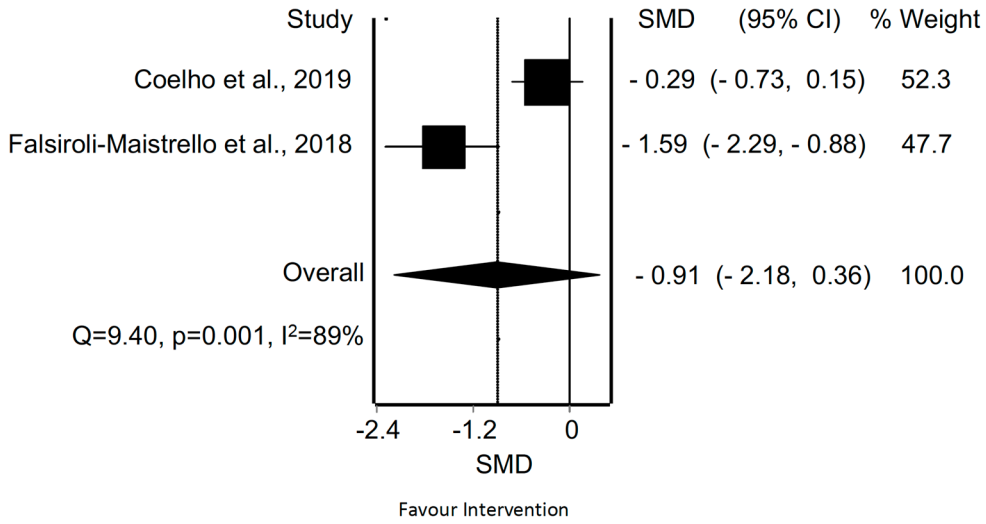

Figure 10. Synthesis forest plot for the frequency of symptoms in patients with tension-type headache treated with manual therapy. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

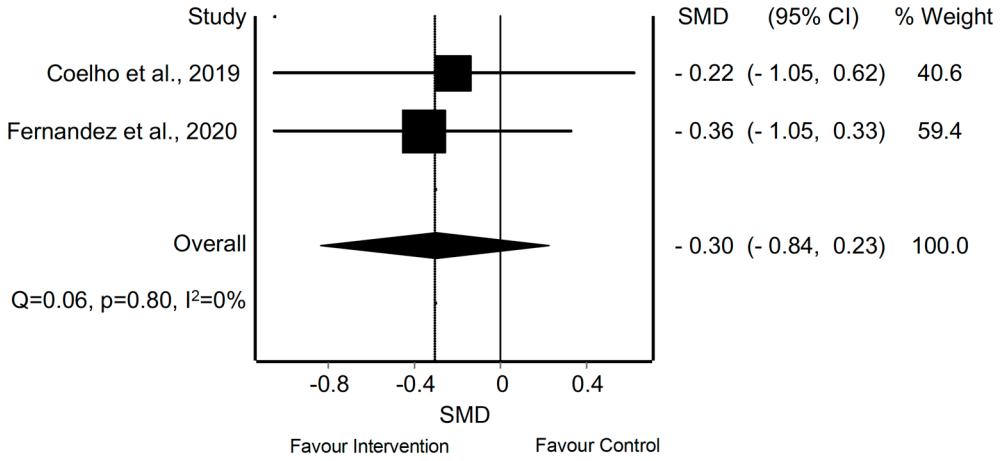

Figure 11. Synthesis forest plot for the frequency of symptoms in patients with cervicogenic headache and mixed intervention. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

3.7. Quality of Life

Quality of life was evaluated in five studies: two included a meta-analysis [8,37], while three performed a qualitative synthesis [32,34,40]. Two studies showed significant differences in the increase in quality of life when using aerobic exercise in patients with migraine [8] or manual therapy in patients with migraine, TTH or CGH [37]. However, the remaining three studies showed no significant differences between groups or showed inconclusive results when the intervention included different manual therapy techniques in patients with TTH [32,34] or migraine and TTH [40].

3.8. Disbility

Ten studies assessed disability in patients with headache; seven were systematic reviews [7,31–35,40], and the remaining three systematic reviews included meta-analysis [37,38,43].

Most studies that evaluated disability associated with headache employed manual therapy, finding positive results in favour of the Intervention group in the short-term in patients with TTH [32,34,38] or GCH [44]. Studies that included patients with migraine, TTH or CGH also showed favourable results after employing manual therapy in the short-term [33,35,37,40,43] and at follow-up [37]. Manual therapy with or without therapeutic exercise produced medium-term improvements in patients with migraine or TTH [7], with conflicting evidence because only one study evaluated disability [31].

With regard to the quantitative analysis, the MMA of disability in patients with TTH revealed a statistically significant difference in two meta-analyses through manual therapy [38,43] (SMD = −0.27; 95% CI −0.47 to −0.06; $p < 0.05$). Based on Cochran's Q statistical test, the heterogeneity among the reviews was not considered significant ($Q = 1.37$, $p = 0.24$). However, we found low evidence of heterogeneity according to the I^2 ($I^2 = 27\%$) (Figure 12).

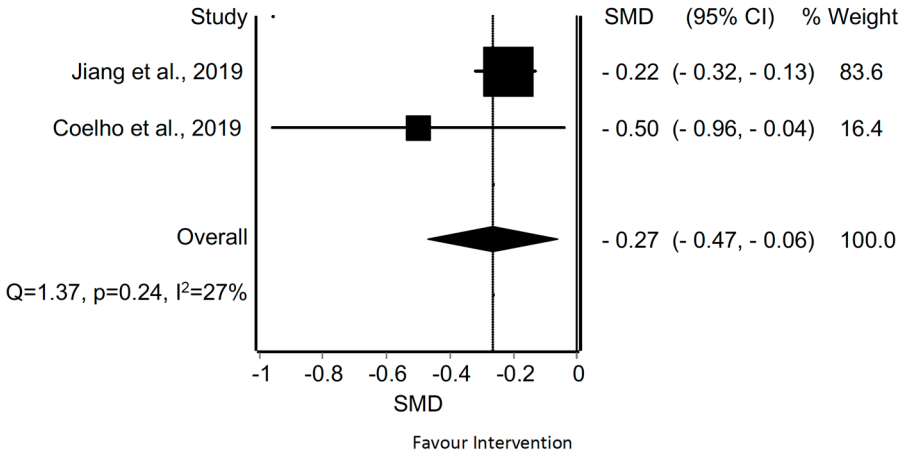

Figure 12. Synthesis forest plot for disability in patients with tension-type headache treated with manual therapy. The forest plot summarizes the results of included studies (review size, standardized mean differences [SMDs] and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

4. Discussion

The present research aimed to synthesise and critically evaluate the evidence on the effectiveness of manual therapy and therapeutic exercise in patients with migraine, TTH or CGH. Results showed, in general, that the interventions with MT and exercise were beneficial for patients with TTH and CCH, and aerobic exercise was beneficial for patients with migraine. Most of the quantitative results favoured the interventions, with statistically significant results supporting the use of MT and exercise to reduce pain intensity in CGH and TTH but not to reduce the frequency of headaches. In addition, the MMA suggested a positive effect of AE for reducing the pain and frequency of migraine. The methodological quality of the eight meta-analyses included in our MMA is low for three of them [38,39,43] and high for the rest; and the risk of bias in general is high, except for three studies that had good methodological quality and also a low risk of bias [8,40,41].

4.1. Migraine

Currently, the management of patients with migraine is complex, given there is no specific treatment that fits all patients, and it sometimes leads to medication overuse and other adverse effects [45]. A lot of effort has been made to find a conservative non-pharmacological approach [46,47]. Therapeutic exercise prescriptions have added some hope for the treatment of this population [48,49]. This non-pharmacological intervention, which lacks adverse effects, helps minimise the need for drugs or other invasive interventions. If the headaches can be improved by reducing the frequency or intensity of the symptoms, medication overuse and adverse effects would be prevented.

Most of the included reviews on migraine have compared AE with other interventions, and the results of moderate, continuous AE appear to be positive. Along these lines, the results of the present MMA showed that AE can reduce pain intensity and frequency of headache in migraine patients, with moderate and limited evidence, respectively, and large effect sizes and low heterogeneity. The sensitivity analyses could not be performed since only two studies were included in each MMA (this also occurred in six out of the eight analyses performed).

In recent decades, the exercise intervention studied for migraine in most of the RCTs comprised moderate, continuous AE performed 2–5 days per week and for 40–60 min at 60–75% VO_2max. The new approaches to therapeutic exercise for migraine use high-intensity exercise or interval exercise (of moderate or high intensity) [50,51]. There is still a lack of evidence regarding the difference between AE intensities and modalities,

because the new approaches have yet to be evaluated in depth. In this regard, contradictory results have been obtained when assessing the effects of continuous moderate versus high-intensity interval training, although in general both interventions might reduce headache frequency and pain [50,51].

It is crucial to determine whether the patient with migraines also presents kinesiophobia, because it could impede successful completion of the exercise program. The first step in implementing exercise treatment for these patients should be to detect any irrational beliefs about movement, so that we can establish adequate management with a biobehavioural approach (therapeutic patient education) [52].

This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

4.2. Tension-Type Headache

Among the treatment options for patients with TTH, the conservative interventions applied by a physical therapist have been given a lot of weight. This type of intervention is justified based on the characteristics of patients with TTH and the involvement of the neck in TTH, which has been described and accepted worldwide [1]. Interventions such as cervical manual therapy and local exercises directed to the neck muscles are the most popular and studied approaches. These interventions are based on findings that suggest the presence of referred pain to the head coming from the cervical structures after manual provocation tests [53–55].

The results of the MMA showed that interventions based on MT might reduce the pain intensity (limited evidence) and disability of patients with TTH (limited evidence). The effect size is large for pain intensity with large heterogeneity. A small effect size and low heterogeneity was found for disability. No effect on frequency was found for manual therapy (limited evidence). The analyses of combined interventions (MT and/or local exercises) favoured the intervention, with moderate evidence; however the effect size was small, although with low heterogeneity.

According to the results of the present review, the physical therapy techniques included in conservative treatment for TTH were articular and soft-tissue techniques (in most cases) combined with therapeutic exercise. The articular approach included cervical and thoracic mobilisations or manipulations, mobilisations of several neck segments and tractions and soft tissue interventions applied to cervical muscle trigger points. In addition to these techniques, neck exercises were employed focused on the strength and endurance of the target muscles. In this regard, manual therapy has been largely studied; however there is a need to study other conservative exercise treatments that could also have positive effects on patients with TTH. This approach might be particularly indicated for those with chronic pain, for whom a generalised exercise intervention based on AE could have positive effects, as has been demonstrated for patients with migraine. It has been reported that patients with chronic TTH have an impairment of pain inhibition in a similar manner as has been observed in other chronic pain conditions [56].

Another interesting point is that patients with migraine as well as TTH typically have low levels of physical activity, and inactivity among pain-free individuals is a risk factor for developing a non-migraine type of headache [57]. These findings justify the implementation of interventions to increase physical activity/exercise among patients with TTH and also CGH. The combination of therapeutic patient education with exercise seems likely to lead to better adherence to exercise [58].

4.3. Cervicogenic Headache

CGH has been included in the International Classification of Headache Disorders as a secondary headache arising from musculoskeletal disorders in the cervical spine, but not necessarily accompanied by neck pain [1,59]. Structures such as the upper cervical synovial joints, upper cervical muscles and C2–C3 intervertebral disc have been raised as possible origins of CGH [60,61]. Some findings suggest the involvement of the neck

structures in CGH; for example a reduction in upper cervical rotation [62] reduced cervical flexion/extension or painful upper cervical joints as assessed by manual palpation [63]. Given the problem of relapses at the neck, conservative treatment has focused on the neck structures. Manual therapy techniques are usually employed for patients with CGH [64,65]. In the present MMA, the data suggest that MT can influence pain intensity, but not pain frequency, both with limited evidence. The effect sizes for both findings were small, with low heterogeneity.

The interventions used in the RCT included in the analysed reviews were MT and/or therapeutic local exercise or MT alone. There is evidence suggesting positive effects for therapeutic exercise on patients with neck pain [66]; thus, it would be interesting to assess the effect of therapeutic exercise alone in CGH, given that there is scarce but favourable evidence for it [67].

4.4. Clinical Implications

The present review attempts to provide clear data and conclusions to be applied in practical terms to patients with headaches. More high-quality research is needed to be able to offer more specific recommendations, but with the results of this MMA, some suggestions can be made. Patients with headache might benefit from manual therapy and exercise. Physical therapists should be able to establish a specific and appropriate treatment for patients with headache according to their type of headache. Based on the data, for example, it would be preferable to employ a general exercise intervention for patients with migraine instead of a specific MT intervention.

From a clinical point of view, even a small intervention of 2 min per day of resistance exercise can reduce headache frequency by up to 50% [68]. This result highlights the importance of frequent therapeutic exercise for patients with headaches.

4.5. Research Implications

In general terms, further research with a combination of interventions, such as exercise, education and various MT techniques, is needed for the several types of headaches. This approach could establish new models of combined treatments for patients with headache. Regarding the exercise interventions, there is a great variety of exercise options to be compared, such as high-intensity general exercise for migraine and TTH or general AE for TTH. Another pending subject to assess is the dosage of the interventions, which needs to be established through further investigation.

It would also be interesting to assess whether a high-intensity interval training intervention would be more effective than a moderate AE intervention. Finally, general strength training should be assessed in patients with migraine.

4.6. Limitations

The present review has some limitations. First, many of the included studies had low methodological quality and a high risk of bias. The results should be analysed with caution. Second, there was considerable variability between the systematic reviews in terms of the interventions used. Third, six of the MMAs performed included only two meta-analyses, and the other two MMAs included three meta-analyses. Fourth, with the small number of studies included in each of the MMAs, the sensitivity was impossible to calculate. Sixth, due to the lack of data, it was not possible to conduct an MMA for quality of life and disability. Finally, there were significant inconsistencies among the RCTs included in the meta-analyses regarding the diagnostic criteria used to classify the patients. Likewise, it could have been interesting to evaluate the effectiveness of exercise and manual therapy according to the existing subdivisions within each of the headache types, for example, in patients with migraine with or without aura; however, that information was not present in the included studies.

5. Conclusions

The present umbrella and mapping review with MMA provide an overview of the effects of physical therapy interventions on pain intensity, pain frequency, disability and quality of life of patients with primary headaches. The MMAs showed results in favour of the interventions in terms of pain intensity and quality of life in patients with migraine, TTH and CCH. The data are also in favour of the intervention in terms of frequency of migraine and disability in TTH. However, there were no significant effects on pain frequency in patients with TTH and CGH.

There is moderate evidence to suggest that AE reduces pain intensity in patients with migraine. In addition, the evidence in favour of MT or a mixed intervention (including therapeutic exercise) is also moderate in terms of reducing pain intensity in patients with TTH.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app11156856/s1, Table S1: Citation matrix for the assessment of study overlap within systematic reviews.

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