EXERCISE THERAPY IMPROVES PAIN AND MOUTH OPENING IN TEMPOROMANDIBULAR DISORDERS. A SYSTEMATIC REVIEW WITH META-ANALYSIS

Running title: Exercise therapy for temporomandibular disorders

Ana María Idáñez-Robles[1], PT, MSc; Esteban Obrero-Gaitán[2], PT, PhD; Rafael Lomas-Vega[2], PT, PhD; María Catalina Osuna-Pérez[2], PT, PhD; Irene Cortés-Pérez[2,*], PT, PhD; Noelia Zagalaz-Anula[2], PT, PhD.

[1] Servicio de Fisioterapia. Residencia de Mayores "Fuente de la Peña". Dean de la Fuente González, 2, 23002, Jaén, Spain.

[2]Physiotherapy Area. Department of Health Sciences. Faculty of Health Sciences. University of Jaén. Campus Las Lagunillas s/n, 23071, Jaén, Spain.

Corresponding author:

Irene Cortés-Pérez

Dependence B3-017. Faculty of Health Sciences. University of Jaén. Campus Las Lagunillas s/n, 23071, Jaén, Spain.

icortes@ujaen.es

Abstract:

Objective: To analyze the effectiveness of exercise therapy in improving pain and active or passive maximum mouth opening in patients with temporomandibular disorders.

Data sources: PubMed Medline, Web of Science (WOS), Scopus, CINAHL Complete and Physiotherapy Evidence Database, until April 2022, in accordance with PRISMA guidelines.

Review methods: We included randomized controlled trials evaluating the effect of exercise therapy on pain and on active and passive maximum mouth opening in patients with temporomandibular disorders. Effect size was calculated using Cohen's standardized mean difference (SMD) and their 95% confidence interval (95% CI) in a random-effects model.

Results: A total of 16 studies with 812 participants were included. Temporomandibular exercise therapy is effective in reducing pain (SMD -0.58; 95% CI, -1.01 to -0.12) and increasing the pain pressure threshold (SMD 0.45; 95% CI 0.14 to 0.76), active and passive maximum mouth opening (SMD 0.43; 95% CI 0.14 to 0.71 and SMD 0.4; 95% CI 0.06 to 0.75, respectively). Subgroup analyses showed more effect of exercise therapy more splints vs splints on pain (SMD -0.5; 95% CI -0.73 to -0.26), active and passive maximum mouth opening (SMD 1.14; 95% CI 0.22 to 2.07 and SMD 0.56; 95% CI 0.06 to 1.06, respectively). On pain pressure threshold, exercise therapy was better than physiotherapy approach (manual therapy and electrotherapy) (SMD 0.48; 95% CI 0.09 to 0.87).

Conclusions: Therapeutic exercise is an effective therapy to reduce pain and increase pain pressure threshold and active and passive maximum mouth opening in patients with temporomandibular disorders.

Keywords: Temporomandibular disorders; exercise therapy; splints; physiotherapy; pain; mouth opening.

Introduction

Temporomandibular disorders are an “umbrella term” for craniofacial pain dysfunctions that include alterations in masticatory muscles, temporomandibular joint, and other related structures.[1] Temporomandibular disorders are considered the main cause of non-dental pain in orofacial structures and head,[2] affecting up to 31% of the adult population and 11% of the children and young adults, being the disk displacement with reduction the most prevalent temporomandibular disorders.[3] Temporomandibular disorders are more frequent in the female population, probably attributed to hormonal and socio-cultural differences between male and female[4,5] (female-male ratio between 2:1 to 8:1[6]) in child-bearing years (20-40 years), decreasing with age.

Etiology of temporomandibular disorders is multifactorial, including physical predisposing factors,[7–9] psychological conditions[10]; comorbidity with other disorders, such as neck and head cancer;[11] and parafunctional habits like cheek or lip biting or teeth clenching (bruxism).[12] The most frequent symptom in temporomandibular disorders is pain in jaw, oral, facial and peri-auricular areas that cause restrictions in jaw movements, such as active or passive mouth opening[13] and noises.[14] Temporomandibular pain affects approximately 10% of adults[15] and can radiate to different structures in orofacial, head and neck areas, and cause other symptoms, such as tinnitus, earaches,[16] headaches[17] or hyperalgesia in neck and trapezius area.[18]

Currently, conservative approach, such as pharmacotherapy, splints and physiotherapy including exercises, prevails over surgery, since it is less aggressive and generally produces satisfactory clinical results[19]. At first, pharmacotherapy is prescribed to reduce temporomandibular joint inflammation and pain.[20–22] Second, splints are considered a basic, non-invasive, and cheap therapy for temporomandibular disorders seeking to correct, realign, and reposition the temporomandibular joint.[23–26] Finally, physiotherapy programs that includes therapeutic exercise is an active and conservative therapy based in jaw muscle training, coordination, mobility and posture exercises. To date, previous reviews have assessed the effect of exercise therapy in improving pain and mouth opening in patients with temporomandibular disorders.[27–30] We consider the necessity to carry out this meta-analysis for different reasons. At first, the review of Dickerson, S (2017) was performed including a low number of studies and new studies have been published in recent years that can increase the robustness of new findings. In addition, in these reviews,[29,30] authors did not find differences between therapeutic exercise and others in reducing pain. In the review of La Touche, R (2020) we found limitations, so these authors did not carry out meta-analysis and only analyzed patients with temporomandibular joint displacement without reduction. Finally, Zhang, L et al (2021), only compared temporomandibular exercise therapy vs. occlusal splints, using only 6 studies. Therefore, the aim of the present review was collect all available evidence to assess the effectiveness of exercise therapy to improve pain and active and passive mouth opening. Secondary we want to check if effect of exercise therapy is major respect to splints, physiotherapy (such as laser, TENS or manual therapy) or counselling education.

Methods

Our meta-analysis followed the PRISMA 2020 Statement[31] and the 2nd Edition of the *Cochrane Handbook for Systematic Reviews of Interventions*[32]. In addition, the protocol was previously registered in PROSPERO database (CRD42020217952).

Two authors (Ana María Idáñez-Robles and Irene Cortés-Pérez) searching in PubMed Medline, Web of Science (WOS), Scopus, CINAHL Complete, PEDRO (Physiotherapy Evidence Database) and in other sources (the reference lists of previous reviews, in the gray literature and in expert documents) until April 9, 2022. The search strategy was based on the use of the PICOS tool to identify conditions[32], such as: (1) population, subjects with temporomandibular joint dysfunctions or temporomandibular symptoms diagnosed using the Research Diagnostic Criteria for Temporomandibular Disorders assessment, magnetic resonance imaging or clinical experience; (2) intervention, temporomandibular exercise therapy; AND (3) design, randomized controlled trials. The main terms included in our search strategy, indexed in the Medical Subjects Headings, were *"temporomandibular joint disorders"* and *"exercise therapy"* and entry terms. These terms were combined using Boolean operators (AND/OR) according each database (Supplementary Table 1). To perform this search, the authors did not use filters related to the publication date and language. This search was supervised by a third author with experience in bibliographical search (Esteban Obrero-Gaitán).

The study selection process was carried out by two authors (Ana María Idáñez-Robles and Irene Cortés-Pérez), who independently, screened each article by title/abstract reason and disappointments were consulted with a third author (Noelia Zagalaz-Anula). A study was included when it met all the following inclusion criteria: (1) Randomized controlled trials or randomized controlled trials pilot; (2) comprised by patients with temporomandibular disorders; (3) with almost two groups, in which one group received temporomandibular exercise therapy as experimental intervention (alone or combined with other therapy) and the other group did not receive intervention or received a control therapy different temporomandibular exercise therapy (splints, physiotherapy or counselling education); and that provided quantitative data of outcomes of interest to be meta-analyzed. As exclusion criteria, we used (1) Randomized controlled trials comprised by patients with temporomandibular disorders and other pathologies, (2) patients diagnosed with head and neck cancer and temporomandibular repercussions, and (3) studies whose data could not be used in meta-analysis.

Two authors (Ana María Idáñez-Robles and Irene Cortés-Pérez), independently, extracted the data, and a third author (Noelia Zagalaz-Anula) resolved any possible discrepancies related to the extracted data. From each study, we extracted the following data: (1) data related to the general characteristics of study (authorship and publication date, country, funding, study design, total sample size, temporomandibular disorders diagnose and number of groups included); (2) characteristics of each group (number of participants, age and sex); (3) characteristics of the experimental and control intervention (intervention and protocol of application); and (4) information about outcomes (outcome's name, tests, time of follow-up and quantitative data). Data used to perform the meta-analysis were the mean and their standard deviations. When a study did not provide the standard deviation, these data were obtained from other data presented in the study, such as range, interquartile range or standard error, according to standardized statistical procedures.[32]

Outcomes assessed in this review were temporomandibular pain, pain pressure threshold, active and passive maximum mouth opening. Pain was assessed with Visual Analogue Scale, Numeric Pain Rating Score and physical pain dimension of the Oral Health Impact Profile short form. Pain pressure threshold was assessed using algometry in active and passive maximum mouth opening was assessed measuring the distance (mm) between the maxillary and mandibular incisal edges.

Two authors (Rafael Lomas-Vega and María Catalina Osuna-Pérez) assessed the quality evidence of our findings and methodological quality of the studies selected. Doubts were consulted with a third reviewer (Noelia Zagalaz-Anula). First, the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) statement[33] was used to analyze the overall quality evidence in each meta-analysis. Quality evidence was determined taking into the account Meader's items checklist,[34] such as the risk of bias of each study, inconsistency, indirectness, imprecision, and risk of publication bias. The quality evidence may be classified like: (1) high when the findings are robust due to the absence of limitations; (2) moderate if limitations may change the generalization of our results; (3) low if the presence of various limitations decreases the level of confidence in our results; and (4) very low when the estimation of the effect is very uncertain. The quality evidence of each meta-analysis was downgraded one level according to the limitations found and two level when appeared high risk of publication bias (> 10% of variation after Trim-and-fill estimation).

PEDro Scale was used to assess the risk of bias of the included studies. The PEDro Scale comprised 11 items with two answer options ("yes" if the criterion was clearly satisfied and "no" if the criterion was not satisfied).[35] The total score could vary across a range from 0 (high risk of bias) to 10 (low risk of bias). Methodological quality in a RCT is considered as: (1) "excellent" if it has a score of 9–10; (2) "good quality" if it has a score of 6 to 8 points; (3) "moderate quality" if it scores between 4 and 5 points; and (5) "low quality" if it scores less than 3.[35]

The meta-analyses were performed by two authors (Irene Cortés-Pérez and Esteban Obrero Gaitán) using Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA). Meta-analysis only was made when almost had two comparisons per outcome. We used a random-effects model of DerSimonian and Laird to estimate the effect of the intervention[36] using the Cohen's Standardized Mean Difference (SMD) with its 95% confidence interval (95% CI),[37] that can be interpreted as no effect (SMD 0), small (SMD 0.2), moderate (SMD 0.5), and large (SMD >0.8).[38] Findings were displayed in forest plots.[39] The risk of publication bias was assessed analyzing the symmetry present in the funnel plot,[40] with Egger's test (where $p < 0.1$ suggests risk of publication bias)[40] and with the Trim-and-fill method.[41] Heterogeneity was analyzed with the degree of inconsistency (I^2) (small < 25%, medium 25% to 50%, or large > 50%); the Cochrane-Q test and *p*-value for this test ($p < .1$ indicates the presence of heterogeneity).[42,43]

Sensitivity analysis was performed using the *leave-one-out method* with the aim of assessing the contribution of each study to the overall pooled effect in each analysis.[44] In addition, subgroup analysis was performed to assess the effect of exercise therapy when it was used alone or with other therapies and in different specific comparisons (exercise therapy vs no intervention; exercise therapy vs splints; exercise therapy + splints vs splints; exercise therapy vs physiotherapy (manual therapy and electrotherapy); and exercise therapy + counselling education vs counselling education).

Results

Initially, 1942 references were retrieved from databases and 6 from other sources. We excluded 861 studies as duplicate and other 686 studies by title/abstract. Three hundred eighty-nine studies were screened for eligibility and 375 were excluded for not meet the inclusion criteria (reasons in Figure 1). Finally, 16 studies[45–60] were included in this meta-analysis. The PRISMA flow chart (Figure 1) displays the study selection process.

The studies included were carried out between 2001 and 2021 in Europe, Asia, America and Australia. These studies provided data from 812 participants (29.01±7.64 years old and 77% female) with different temporomandibular disorders, being the most frequent temporomandibular disc displacement with or without reduction[45,50–52,54–56,59] and orofacial pain.[49,53,58,60] The experimental group was comprised by 416 participants (29.01±7.64 years old and 77% female) who performed temporomandibular exercise therapy as unique therapy or combined with others (splints, physiotherapy or counselling education). By contrast, the comparison group was integrated by 396 participants (29.16±8.17 years old and 75% female) that carried out one of the following control therapies: splints, counselling education, physiotherapy (placebo, manual physiotherapy, usual care, electrotherapy) or no intervention. The duration of temporomandibular exercise therapy was heterogeneous due to the different temporomandibular exercise therapies in the studies included (details in Table 2). All assessments were carried out in short-term. Related with finance support, 7 RCTs[47,49–51,53,59,60] received external funding, 2 did not receive finance[48,55] and in others 7 this information is not available.[45,46,52,54,56–58] All these characteristics are carefully detailed in Table 1.

The risk of bias scores for 13 RCTs[46–58] was obtained in the PEDro database, and for 3 RCTs[45,59,60] it was assessed manually. All included RCTs obtained 3 points or more. The mean PEDro score was 5.68±1.57 points. Eight RCTs showed good quality,[45,48,50,51,55,58–60] 7 moderate[46,49,52–54,56,57] and one low quality.[47] Table 2 shows the PEDro assessment.

Pain

Fifteen studies[45,46,48–60] with 18 independent comparisons provided data to assess the effect of temporomandibular exercise therapy on temporomandibular pain. An overall analysis, with a moderate-quality evidence showed a medium effect favors temporomandibular exercise therapy (SMD -0.58; 95% CI -1.01 to -0.12; *p* 0.014) in reducing pain (Table 3, Figure 2). In addition, our results showed that temporomandibular exercise therapy reduced temporomandibular pain in Visual Analogue Scale or Numeric Pain Rating Scale 1 point (95% CI -1.67 to -0.29; *p* 0.005). The funnel plot was slightly asymmetric (*p* for Egger test, 0.1) and variation after Trim and Fill estimation was 16% respect original pooled effect (adjusted SMD = -0.69). Heterogeneity level was low (I^2, 8%; df, 17; *Q*, 16.86; *p* 0.4639) was found. Sensitivity analysis did not report substantial variations respect the original pooled effect.

When subgroup analysis was performed, we found that temporomandibular exercise therapy is better that no intervention (SMD -0.77; 95% CI -1.18 to -0.36; p <0.001), reducing temporomandibular pain in 1.71 points. In addition, in comparison with other therapies, when temporomandibular exercise therapy was combined with other therapies, the effect was higher (SMD -0.5; 95% CI -0.73 to -0.26; p <0.001) that when temporomandibular exercise therapy is used alone (SMD -0.32; 95% CI -0.53 to -0.12; p <0.001).

More specifically, a medium effect was found favors temporomandibular exercise therapy more counselling vs counselling (SMD -0.48; 95% CI -1.07 to -0.21; *p* 0.001). The effect was similar when temporomandibular exercise therapy was used alone (SMD -0.6; 95% CI -0.86 to -0.33; p <0.001) or combined with splints (SMD -0.56; 95% CI -1.07 to -0.06; *p* 0.029), both in comparison to splints. However, not statistical significant differences were found between temporomandibular exercise therapy and physiotherapy (SMD 0.36; 95% CI -0.06 to 0.72; *p* 0.054).

Pain pressure threshold

Four studies[47,49,53,55] with 11 independent comparisons provided data to assess the effect of temporomandibular exercise therapy to increase pain pressure threshold in temporalis, masseter and medial and lateral pterygoid. Low-quality evidence of a medium effect favors temporomandibular exercise therapy (SMD 0.45; 95% CI 0.14 to 0.76; *p* 0.005) was found to increase pain pressure threshold (Table 3, Figure 2). Symmetric funnel plot (*p* for Egger test = 0.11) and no variation showed in Trim-and-fill estimation reduced the risk of publication bias. No heterogeneity was present (I^2, 5.86%; df, 10; *Q*, 10.62; *p* 0.4145) and sensitivity analysis did not report substantial variations respect original pooled effect.

Subgroup analysis showed that temporomandibular exercise therapy alone is better than other therapies to increase pain pressure threshold (SMD 0.51; 95% CI 0.15 to 0.86; *p* 0.005). However, no effect was found when temporomandibular exercise therapy was used in combination with other therapies (SMD 0.22; 95% CI -0.5 to 0.94; *p* 0.56).

Finally, temporomandibular exercise therapy is better than physiotherapy (SMD 0.48; 95% CI 0.09 to 0.87; *p* 0.017), but not better than counselling education when it is used in combination with counselling education (SMD 0.21; 95% CI -0.53 to 0.97; *p* 0.574).

Active maximum mouth opening

Ten studies[45,47,49–52,55–58] with 12 independent comparisons reported data to assess the effect of temporomandibular exercise therapy to improve the active maximum mouth opening. Our findings showed with moderate-quality evidence a medium effect of temporomandibular exercise therapy (SMD 0.43; 95% CI 0.14 to 0.71; *p* 0.003) to increase the active maximum mouth opening (Table 3, Figure 3). No risk of publication bias was found (*p* for Egger test = 0.2 and no variation after Trim-and-fill estimation). The level of heterogeneity was low (I^2, 9.83%; df, 11; *Q*, 12.19; *p* 0.3495) and the sensitivity analysis did not report variations greater to 17% with respect to the original effect.

When subgroup analysis was performed, only significant statistical differences were found when temporomandibular exercise therapy was used alone (SMD 0.44; 95% CI 0.04 to 0.85; *p* 0.032), and no when was used in combination with other therapies (SMD 0.32; 95% CI -0.02 to 0.65; *p* 0.06).

According specific therapy comparisons, the combined use of temporomandibular exercise therapy more splints are better that splints (SMD 1.14; 95% CI 0.22 to 2.07; *p* 0.015). However not statistical significant differences were found between temporomandibular exercise therapy more counselling education vs counselling education (SMD 0.03; 95% CI -0.67 to 0.73; *p* 0.94), and between temporomandibular exercise therapy vs physiotherapy (SMD 0.41; 95% CI -0.12 to 0.94; *p* 0.13) and temporomandibular exercise therapy vs splints (SMD 0.48; 95% CI -0.1 to 1.06; *p* 0.1).

Passive maximum mouth opening

Seven studies[45,46,50,54–57] with 8 independent comparisons provided data to assess the effect of temporomandibular exercise therapy to increase the passive maximum mouth opening. Our results reported with low-quality evidence a medium effect favors temporomandibular exercise therapy (SMD 0.4; 95% CI 0.06 to 0.75; *p* 0.022) to increase the passive maximum mouth opening (Table 3, Figure 3). No risk of publication bias was found (*p* for Egger test = 0.3 and no variation after Trim and Fill estimation) and meta-analysis did not show heterogeneity (I^2, 0%; df, 7; *Q*, 6.1; *p* 0.5281). One study removed analysis suggested 35% of variation respect original effect size excluding Haketa, T.

Not statistical significant differences were found when temporomandibular exercise therapy was used alone (SMD = 0.52; 95% CI = -0.1 to 1.12; *p* = .1) or in combination with other therapies (SMD = 0.14; 95% CI = -0.22 to 0.5; *p* = .45).

According specific therapy comparison, only significant differences were found favors temporomandibular exercise therapy more splints vs splints (SMD = 0.56; 95% CI = 0.06 to 1.06; *p* = .027). Not statistical significant differences were found between temporomandibular exercise therapy more counselling education vs counselling education (SMD = -0.09; 95% CI = -0.46 to 0.3; *p* = .66).

Discussion

Differences between previous published reviews[27–30] does not allow to establish a robust and combined effect of exercise therapy on temporomandibular disorders respect other therapies. For example, Armijo-Olivo (2016), Dickerson (2017) and Zhang (2021) included patients with different temporomandibular disorders and La-Touche, R (2020) only included patients with temporomandibular joint disc displacement without reduction and without meta-analysis. These reviews present controversial findings about pain, due to in the reviews of Dickerson and Zhang, exercise therapy did not show differences in reducing pain. We consider that it is necessary to perform a more complete meta-analysis to collect all available evidence with the aim to assess the effect of exercise therapy on pain and mouth opening, in comparison with others therapies commonly used. Thus, to date, our review is the meta-analysis that includes more studies (n=16), and may increase the evidence and robustness of the results in comparison to previous reviews.

Our meta-analysis reported a medium effect of exercise therapy in reducing pain. One strength of this meta-analysis is that reports that exercise therapy reduces the pain 1 point, overcoming the minimum change important difference for temporomandibular pain (0.9 points[61]), that translates in a moderate reduction. For pain intensity, our findings disagree with the meta-analysis of Dickerson, S (2017), and our meta-analysis suggests that exercise therapy is effective to reduce pain in comparison with no intervention, but not respect manual physiotherapy. One interesting result, in contrast to the findings of Zhang, L (2021), is that exercise alone or combined with occlusal splints is more effective that occlusal splints alone. On the one hand, exercise therapy-based training could help to increase the masticatory muscle strength and resistance and, on the other hand, splints maintain temporomandibular joint in functional postures free to pain and correct muscle disequilibrium. Finally, our meta-analysis is the first that assess the effect of exercise therapy more counselling education, showing statistical significant differences favors exercise more education vs. education in reducing pain. Counselling education provides cognitive strategies to reduce pain based in the re-education of parafunctional habits, that can increase hyperactivity in oral muscles producing temporomandibular pain. These results can help physiotherapists to take clinical decisions on how to apply temporomandibular exercise therapy to achieve better results.

Our meta-analysis also reported that exercise therapy is be able to increase pain pressure threshold in some temporomandibular muscles with medium effect. This outcome has been assessed for first time in our meta-analysis that assess this outcome, although these findings must be taken into account with caution due to the low number of studies included that reduce the level of evidence. Subgroup analyses revealed that exercise therapy is better that physiotherapy, but exercise more counselling is not better than counselling, probably explained because only one study (Craane et al 2012) provided 2 independent comparisons to assess this outcome and would be important to carry out more RCTs comparing the effect of exercise plus counselling vs. counselling in order to implement a future meta-analysis. Previous studies reported that exercise therapy in masticatory and neck muscles can reduce the sensitivity to painful stimuli producing analgesia or hypoalgesia, possibly due to stimulated release of analgesic peptides,[49,62] that could improve neuromuscular activation patterns and mandibular function.

Regarding active and passive maximum mouth opening, our meta-analysis reported a medium effect of exercise therapy to improve it. No differences were found between exercise more others vs. others, and it can be explained because findings are in limit to statistical significance (p 0.06) and if more studies could be included, our findings could change. Our findings showing a large and medium effect of exercise therapy more splints vs. splints on active and passive maximum mouth opening, respectively. The results of the individual studies, in which the exercise group improves more in some and the counselling group in others, are responsible for not having a significant result in one of the directions in these both outcomes. These results are in line with previous reviews, and underlying the results of La-Touche,[28] although our meta-analysis included more temporomandibular disorders. Pain may be responsible of the reduction of temporomandibular joint movements due to hypoactivity of agonistic and antagonistic temporomandibular during jaw opening.[63] Probably the reduction of pain of the exercise therapy during jaw movements may be responsible of the improvement in mouth opening. In addition, recent studies have shown gray matter alterations of the anterior medial cingulate in frontal lobe in temporomandibular disorders.[64] The main function of this area is produce autonomic and endocrine responses to emotion, and is possible that its alteration favors the presence of negative emotions and its poor regulation in temporomandibular disorders related with pain that restrict movement.[65] In this sense, exercise therapy is an active therapy that could break with monotonous passive therapies, increasing motivation and adherence of patient to the muscle training therapy that could increase gray matter in this area and in sensori-motor cortex.

In light of the results of this review, clinicians should consider the use of exercise therapy to reduce pain and increase maximum mouth opening in these patients. However, it is important consider some limitations. Firstly, the low number of studies included and participants reported in some comparisons can reduce the robustness, quality evidence and generalization of our findings. Secondly, all assessments were carried out to short-time, so no conclusions could be obtained of the effectiveness in the medium and long term. Thirdly, risk of publication bias and the variations found in sensitivity analyses in some meta-analysis must be taken into account.

In conclusion, exercise therapy is effective to reduce pain and increase pain pressure threshold, active and passive maximum mouth opening. On pain, exercise therapy is better than no intervention and occlusal splints, and its effect was major when was combined with occlusal splints or counselling education. To increase pain pressure threshold, exercise therapy is better when it is used alone, specifically in comparison to passive conventional physiotherapy. Finally, to increase active and passive maximum mouth opening, exercise therapy more splints is better than splints.

Clinical messages:

- Exercise therapy reduces temporomandibular pain and increase pain pressure threshold in patients with temporomandibular disorders.
- Exercise therapy increases active and passive mouth opening in patients with temporomandibular disorders.
- Exercise therapy in combination with splints is better than splints to reduce pain and increase mouth opening.

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Table 1. Characteristics of the Studies Included in the Meta-Analysis (N=16), in Alphabetical Order

Study and Participants, *n*	**Groups, *n***	**Experimental Intervention Characteristics**	**Control Intervention Characteristics**	**Outcomes**	**Test**
Alajbeg, IZ et al 2015 (Croatia). RCT, parallel-2 arms. 12 patients with anterior disc displacement without reduction. Diagnostic criteria: RDC/TMD-Axis I and confirmed by MRI. Setting: University Funding: NR	-EG: 6 patients, 31.5y; 5F:1M -CG: 6 patients; 29.5y; 4F:2M	Physiotherapy including exercises such as mobilizations, trans1lations and tractions at home more stabilization splints. Exercises were prescribed 2/3 times a day.	Stabilization splints	Pain	VAS
				AMMO PMMO	Distance (mm) between the maxillary and mandibular incisal edges
Bae, Y et al 2013 (Korea), RCT, parallel-3 arms. 41 patients with pain in temporomandibular joint and limited ROM. Diagnostic criteria: Clinical experience Setting: NR Funding: NR	-EG$_1$: 16 patients; 22.6y; 13F:3M -EG$_2$: 14 patients; 23.1y; 10F:4M -CG: 11 patients; 22.4y; 8F:3M	-EG$_1$: Therapeutic exercise (opening and closing movements). 10 minutes, 3 times per week for 4 weeks -EG$_2$: Relaxation exercises of masticator muscle, 10 minutes, 3 times per week for 4 weeks	No therapy	Pain	VAS
				PMMO	Distance (mm) between the median clefs of the upper and lower teeth
Barbosa, MA et al 2019 (Brazil). Single blinded RCT, parallel-2 arms. 34 patients with chronic orofacial pain and TMD. Diagnosis criteria: The RDC/TMD-Axis I Setting: University Funding: Yes	-EG: 17 patients, 30y; 17F -CG: 17 patients; 26y; 17F	Biting endurance exercises, controlled by biofeedback. 16 sessions, twice a week for 8 weeks	Placebo (simulated laser therapy)	Pain	VAS
				PPT	Algometer
Bas, B et al 2018 (Turkey). Prospective RCT 27 patients (33y and 92,5% females) with disc displacement without reduction. Diagnosis criteria: The RDC/TMD-Axis II Setting: University Funding: NR	-EG: 13 patients -CG: 14 patients	Self-administered active and relaxation exercises of the shoulders, jaw, tongue with and without resistance over 6 weeks, 3 times in a day. All patients used stabilization splints	Stabilization splints	Pain	VAS
				PMMO	Distance (mm) between the incisal edges of the upper and lower incisors
Craane, B et al 2012 (Belgium). RCT, parallel-2 arms. 49 patients with anterior disc displacement without reduction. Diagnosis criteria: The RDC/TMD-Axis II Setting: University Funding: No	-EG: 23 patients, 34.7y; 23F -CG: 26 patients; 38.5y; 26F:2M	Physiotherapy program that included therapeutic exercises and mobilizations more counselling education. Nine sessions for 6 weeks.	Counselling Education	Pain	NPRS
				AMMO	Distance (mm) between the maxillary and mandibular incisal edges
				PMMO	
				PPT	Algometer
Haketa, T et al 2010 (Japan). Single blinded RCT, parallel-2 arms. 44 patients with anterior disc displacement without reduction. Diagnosis criteria: The RDC/TMD-Axis II and confirmed by MRI. Setting: University Funding: NR	-EG: 19 patients, 38.8y; 19F -CG: 25 patients; 38.6y; 21F:4M	General self-care protocol based in therapeutic exercises (active, passive and stretching movements). Four sets per day for 8 weeks.	Stabilization splints	Pain	VAS
				AMMO PMMO	Distance (mm) between the incisal edges of the upper and lower central incisors in TMJ affected side.
Ismail, F et al 2007 (Germany). Prospective RCT, parallel-2 arms. 26 patients with acute arthrogenous TMD. Diagnosis criteria: Diagnosed by MRI and classified in RDC/TMD-Axis III	-EG: 13 patients; 41y; 13F -CG: 13 patients; 44.5y; 10F:3M	Physiotherapy program integrating mobilizations, tractions and exercises of jaw	Michigan splint therapy	Pain	VAS
				AMMO PMMO	Distance (mm) between the maxillary and

Setting: Medical School Funding: NR		elevator muscles. Therapy for 12 weeks, 45 min, twice a week.			mandibular incisal edges
Kalamir, A et al 2013 (Australia). RCT, parallel-2 arms. 46 patients with peri-auricular myogenous chronic pain. Diagnosis criteria: The RDC/TMD-Axis I Setting: Private dental clinic Funding: NR	-EG: 23 patients; 26.8y; 15F:8M -CG: 23 patients; 28.2y; 14F:9M	Mobilizations, jaw self-care exercises and diaphragmatic breathing exercises 2 sessions per week for 5 weeks	Intraoral myofascial passive physiotherapy	Pain	VAS
				AMMO	Distance (mm) between the maxillary and mandibular incisal edges
Magesty, RA et al 2021 (Brazil). Single-blinded RCT, parallel-2 arms. 70 patients (22.8y and 68.4% females) with disc displacement with reduction. Diagnosis criteria: The RDC/TMD-Axis II Setting: University Funding: Yes	-EG: 35 patients -CG: 35 patients	Opening and closing jaw exercises more counselling education. Three times a week, all days for 1 month	Counselling Education	Pain	Physical pain dimension of the OHIP-14
Mulet, M et al 2007 (United States). Double blinded RCT, parallel-2 arms. 42 patients with masticatory myofascial pain. Diagnosis criteria: The RDC/TMD-Axis I Setting: University Funding: Yes	-EG: 20 patients; 25.1y; 19F:1M -CG: 22 patients; 23.4y; 21F:1M	Rocabado's 6x6 exercises more counselling education. Six times per day for 4 weeks. Each exercise was repeated 6 times	Counselling education	Pain	NPRS
Patil, SR et al 2017 (Saudi Arabia). RCT, parallel-2 arms. 36 patients with heterogeneous TMD. Diagnosis criteria: The RDC/TMD. Axis not specified Setting: University Funding: Yes	-EG: 18 patients; 34y; 12F:6M -CG: 18 patients; 32.9y; 11F:7M	Exercise program comprising opening and closing mouth exercises, and isometric, stretching and resistive jaw exercises. Twice a day for 4 weeks	TENS	PPT	VAS in masseter, pterygoids and temporalis muscles
				AMMO	Distance (mm) between the maxillary and mandibular incisal edges
Shousha, TM et al 2018 (Egypt). Single blinded RCT, parallel-2 arms. 112 patients with myogenic TMD. Diagnosis criteria: The RDC/TMD-Axis I Setting: University Funding: No	-EG: 56 patients; 21.8y; 33F:23M -CG: 56 patients; 21.6y; 29F:27M	Physiotherapy based-masseter and medial pterygoid stretching and jaw relaxation exercises. Six weeks, twice per week and 15 minutes per session	Stabilization splints	Pain	VAS
Tanhan, A et al 2021 (Turkey). RCT, parallel-3 arms. 59 patients with orofacial and neck pain from TMD. Diagnosis criteria: The RDC/TMD-Axis I Setting: University Funding: Yes	-EG: 20 patients; 20.4y; 13F:7M -CG$_1$: 17 patients; 21.4y; 13F:4M -CG$_2$: 22 patients; 20.9y; 20F:2M	Stretching, resistance and relaxation exercises more body posture correction). Three days a week for 4 weeks.	-CG$_1$: Low-level laser therapy -CG$_2$: Manual pressure release	Pain	VAS
				AMMO	Distance (mm) between the maxillary and mandibular incisal edges
				PPT	Algometer in masseter and temporalis muscles
Wahlund, K et al 2021 (Sweden). RCT, parallel-2 arms. 64 patients (15.6y and 83% females) with disc displacement with reduction. Diagnosis criteria: The RDC/TMD-Axis II Setting: University Funding: Yes	-EG: 33 patients -CG: 31 patients	Jaw exercises (opening and mobilizations) and stretching more counselling for 4 months, 3 times per day	Counselling education	Pain	VAS
				AMMO PMMO	Distance (mm) between the maxillary and mandibular incisal edges
Wänman, A et al 2020 (Sweden). RCT, parallel-3 arms. 90 patients with disc displacement with reduction. Diagnosis criteria: The RDC/TMD-Axis II	-EG$_1$: 30 patients; 37.1y; 19F:11M -EG$_2$: 30 patients; 38.5y; 24F:6M	-EG$_1$: Warm-up, jaw opening-closing movements and resistance exercises. Ten sessions and 15 minutes per session.	Stabilization splints	Pain	VAS
				AMMO	Distance (mm) between the maxillary and

Setting: University Funding: Yes	-CG: 30 patients; 40.4y; 20F:10M	-EG_2: Jaw exercises (opening and closing movements) and isometric exercises according to Au and Klineberg at home.			mandibular incisal edges
Yuasa, H et al 2001 (Japan). RCT, parallel 2-arms. 60 patients with disc displacement without reduction. Diagnosis criteria: The RDC/TMD-Axis II Setting: University Funding: NR	-EG: 30 patients; 25.5; 22F:8M -CG: 30 patients; 28y; 26F:4M	Range of motion exercises (mouth opening and lateral and anterior mandibular movements) more Ampiroxicam for 4 weeks	No therapy	Pain	VAS
				AMMO	Distance (mm) between the maxillary and mandibular incisal edges

N= participants; RCT, randomized controlled trial; EG, experimental group; CG, control group; F, female; M, male; y, years; AMMO, active maximum mouth opening; PMMO; passive maximum mouth opening; VAS, Visual Analogue Scale; mm, millimeters, TMD, te mporomandibular disorders, NR, not reported; NPRS, Numeric Pain Rating Scale; OHIP, Oral Health Impact Profile short form; RDC/TMD, Research Diagnostic Criteria for Temporomandibular Disorders; MRI; Magnetic resonance imaging.

Table 2. Methodological Quality and Risk of Bias (PEDro Scores) of the Studies Included in the Meta-Analysis (N=16), in Alphabetical order

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total**	**Quality**
Alajbeg, IZ et al 2015	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	7/10	Good
Bae, Y et al 2013*	N	Y	N	Y	N	N	N	N	N	Y	Y	4/10	Moderate
Barbosa, MA et al 2019*	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5/10	Moderate
Bas, B et al 2018*	Y	Y	N	Y	N	N	N	N	N	Y	Y	4/10	Moderate
Craane, B et al 2012*	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10	Good
Haketa, T et al 2010*	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5/10	Moderate
Ismail, F et al 2007*	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10	Moderate
Kalamir, A et al 2013*	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10	Good
Magesty, RA et al 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8/10	Good
Mulet, M et al 2007	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8/10	Good
Patil, SR et al 2017*	N	Y	N	Y	N	N	N	N	N	Y	N	3/10	Low
Shousha, TM et al 2018*	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6/10	Good
Tanhan, A et al 2021*	N	Y	N	Y	N	N	N	N	N	Y	Y	4/10	Moderate
Wahlund, K et al 2021*	N	Y	Y	Y	N	N	N	Y	N	Y	Y	6/10	Good
Wänman, A et al 2020*	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	6/10	Good
Yuasa, H et al 2001*	N	Y	N	Y	N	N	N	Y	N	Y	Y	5/10	Moderate

1= Eligibility criteria, 2= Random allocation, 3= Concealed allocation, 4= Baseline comparability, 5= Blind subjects, 6= Blind therapists, 7= Blind assessors= 8. Adequate follow-up, 9= Intention-to-treat analysis, 10= Between-group comparisons, 11= Point estimates and variability. Note= Eligibility criteria item does not contribute to total score, Y = Yes, N = No, * = Score confirmed in PEDro database

Table 3. Main findings in meta-analyses and Quality of evidence assessment (GRADE)

Summary of Findings									
Outcomes	**Pooled Effect**					**Het.**	**Publication Bias**		
	S	***K***	***N***	**SMD**	**95% CI**	**I^2 *(p)***	**Funnel Plot Egger Test *(p)***	**Trim and Fill**	
								Adj SMD	**% of var**
TMJ Pain	15	18	776	-0.58	-1.01 to -0.12	8% (0.46)	Asym. (0.1)	-0.69	16%
PPT	4	11	178	0.45	0.14 to 0.76	5.9% (0.41)	Sym. (0.11)	0.45	0%
AMMO	10	12	486	0.43	0.14 to 0.71	9.8% (0.35)	Sym. (0.2)	0.43	0%
PMMO	7	8	263	0.4	0.06 to 0.75	0% (0.53)	Sym. (0.3)	0.4	0%

Quality of Evidence (GRADE)						
Outcomes	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality**
TMJ Pain	Medium	No	No	No	Probably	Moderate
PPT	Medium	No	No	Yes	No	Low
AMMO	Medium	No	No	No	No	Moderate
PMMO	Medium	No	No	Yes	No	Low

TMJ, Temporomandibular Joint; PPT, Pain pressure threshold; AMMO, Active maximum mouth opening; PMMO, Passive maximum mouth opening; GRADE, Grading Of Recommendations Assessment Development And Evaluation; Het, heterogeneity; S, Number of studies included; K, number of comparisons; N, number of participants in each meta-analysis; SMD, Cohen's standardized mean difference; CI, confidence interval; I^2, Higgins degree of inconsistency; *p*, *p*-value; Adj, adjusted; % var, percentage of variation; Sym, symmetric; Asym, asymmetric

FIGURES

Figure 1. PRISMA Flow Chart

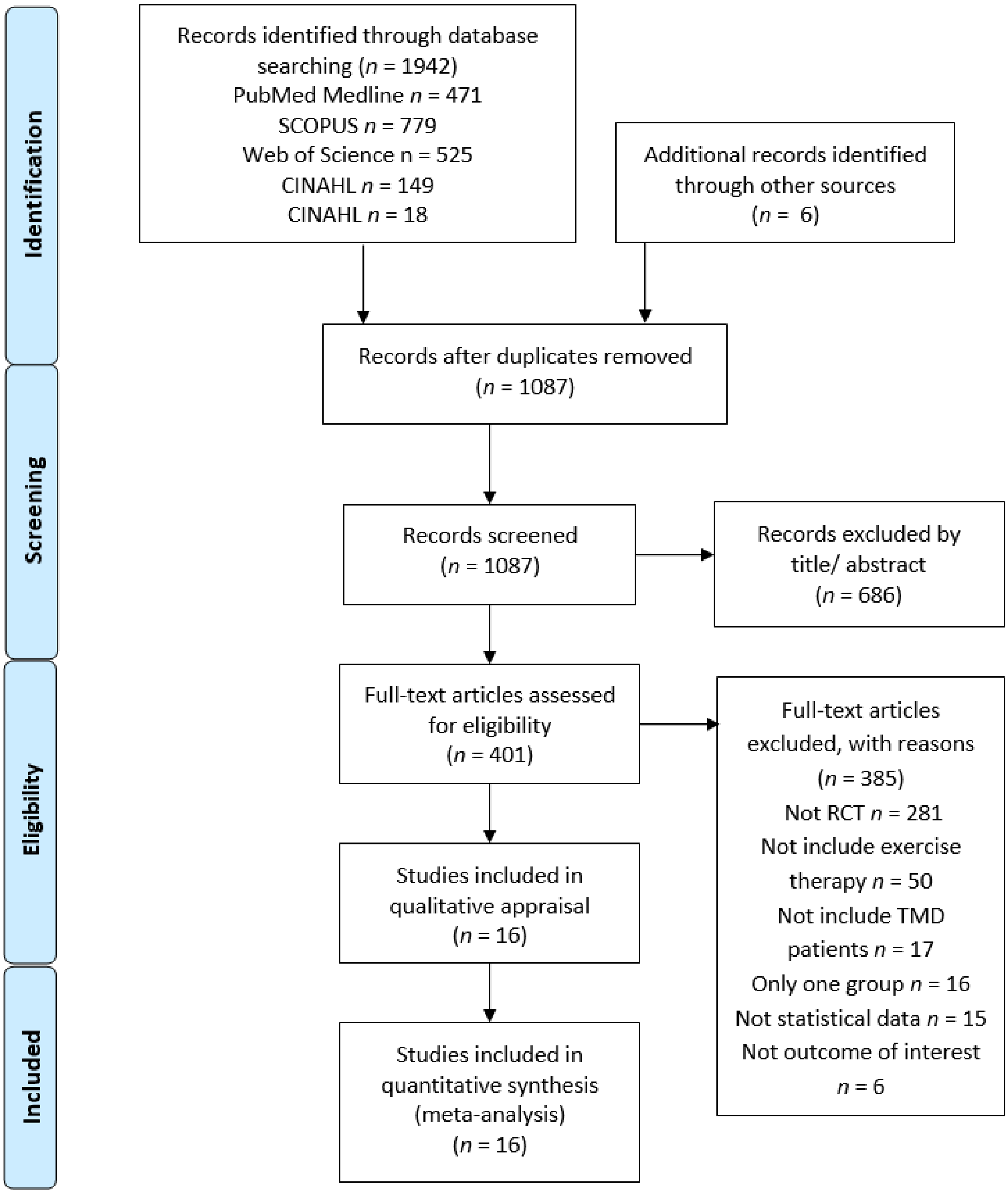
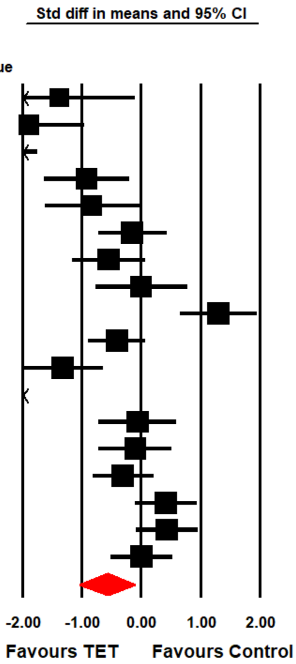


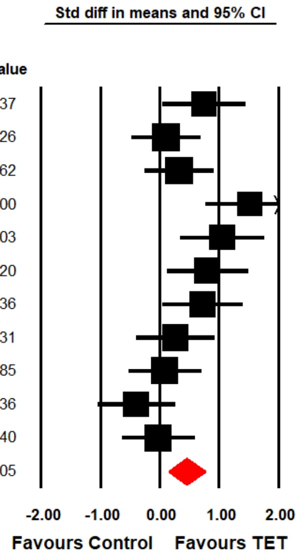
Figure 2. Forest Plot of the Effect of Temporomandibular Exercise Therapy on Pain (A) and on Pain Pressure Threshold (B)

Outcome	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
		Statistics for each study						
TMJ Pain	Alajbeg, IZ et al 2015(1)	-1.380	0.642	0.413	-2.639	-0.121	-2.148	0.032
TMJ Pain	Bae, Y et al 2013(1)	-1.888	0.468	0.219	-2.806	-0.970	-4.030	0.000
TMJ Pain	Bae, Y et al 2013(2)	-2.882	0.573	0.328	-4.005	-1.758	-5.028	0.000
TMJ Pain	Barbosa, MA et al 2019(1)	-0.924	0.361	0.130	-1.632	-0.217	-2.562	0.010
TMJ Pain	Bas, B et al 2018(1)	-0.833	0.402	0.161	-1.620	-0.046	-2.076	0.038
TMJ Pain	Craane, B et al 2012(1)	-0.151	0.292	0.085	-0.724	0.422	-0.517	0.605
TMJ Pain	Haketa, T el al 2010(1)	-0.548	0.310	0.096	-1.155	0.059	-1.768	0.077
TMJ Pain	Ismail, F et al 2007(1)	0.000	0.392	0.154	-0.769	0.769	0.000	1.000
TMJ Pain	Kalamir, A et al 2013(1)	1.296	0.328	0.108	0.653	1.939	3.950	0.000
TMJ Pain	Magesty, RA et al 2021(1)	-0.416	0.242	0.058	-0.890	0.058	-1.722	0.085
TMJ Pain	Mulet, M et al 2007(1)	-1.319	0.341	0.116	-1.987	-0.651	-3.871	0.000
TMJ Pain	Shousha, TM et al 2018 (1)	-2.571	0.255	0.065	-3.072	-2.071	-10.068	0.000
TMJ Pain	Tanhan, A et al 2021(1)	-0.063	0.330	0.109	-0.710	0.583	-0.192	0.847
TMJ Pain	Tanhan, A et al 2021(2)	-0.104	0.309	0.096	-0.710	0.501	-0.338	0.735
TMJ Pain	Wahlund, K et al 2021(1)	-0.313	0.258	0.066	-0.818	0.192	-1.213	0.225
TMJ Pain	Wänman, A et al 2020(1)	0.413	0.261	0.068	-0.098	0.925	1.583	0.113
TMJ Pain	Wänman, A et al 2020(2)	0.433	0.261	0.068	-0.079	0.945	1.658	0.097
TMJ Pain	Yuasa, H et al 2001(1)	0.000	0.258	0.067	-0.506	0.506	0.000	1.000
		-0.581	0.237	0.056	-1.045	-0.117	-2.455	0.014



A

Outcome	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
		Statistics for each study						
PPT	Barbosa, MA et al 2019(2)	0.740	0.355	0.126	0.045	1.435	2.087	0.037
PPT	Craane, B et al 2012(2)	0.102	0.292	0.085	-0.470	0.675	0.350	0.726
PPT	Craane, B et al 2012(3)	0.330	0.294	0.086	-0.246	0.905	1.122	0.262
PPT	Patil, SR et al 2017(1)	1.518	0.378	0.143	0.777	2.260	4.013	0.000
PPT	Patil, SR et al 2017(2)	1.051	0.356	0.126	0.354	1.748	2.955	0.003
PPT	Patil, SR et al 2017(3)	0.805	0.347	0.120	0.125	1.484	2.321	0.020
PPT	Patil, SR et al 2017(4)	0.720	0.344	0.118	0.046	1.394	2.092	0.036
PPT	Tanhan, A et al 2021(3)	0.261	0.331	0.110	-0.388	0.910	0.788	0.431
PPT	Tanhan, A et al 2021(4)	0.084	0.309	0.096	-0.522	0.690	0.272	0.785
PPT	Tanhan, A et al 2021(5)	-0.395	0.333	0.111	-1.048	0.258	-1.186	0.236
PPT	Tanhan, A et al 2021(6)	-0,023	0,309	0,095	-0,629	0,582	-0,075	0,940
		0,447	0,157	0,025	0,138	0,756	2,837	0,005

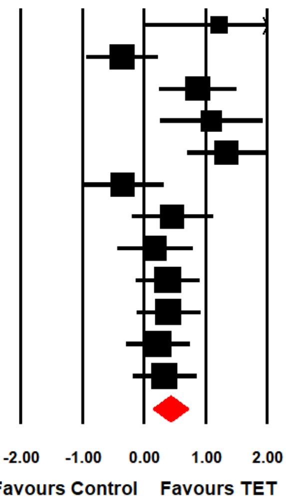


B

Figure 3. Forest Plot of the Effect of Temporomandibular Exercise Therapy on Active Maximum Mouth Opening (A) and on Passive Maximum Mouth Opening (B)

Outcome	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
AMMO	Alajbeg, IZ et al 2015(2)	1.221	0.629	0.395	-0.011	2.454	1.942	0.052
AMMO	Craane, B et al 2012(4)	-0.352	0.294	0.086	-0.929	0.224	-1.199	0.231
AMMO	Haketa, T el al 2010(3)	0.872	0.318	0.101	0.248	1.496	2.740	0.006
AMMO	Ismail, F et al 2007(3)	1.098	0.421	0.177	0.273	1.922	2.609	0.009
AMMO	Kalamir, A et al 2013(2)	1.344	0.326	0.107	0.704	1.984	4.117	0.000
AMMO	Patil, SR et al 2017(5)	-0.350	0.336	0.113	-1.008	0.309	-1.041	0.298
AMMO	Tanhan, A et al 2021(7)	0.458	0.334	0.112	-0.197	1.113	1.370	0.171
AMMO	Tanhan, A et al 2021(8)	0.173	0.310	0.096	-0.434	0.780	0.559	0.576
AMMO	Wahlund, K et al 2021(2)	0.384	0.258	0.067	-0.123	0.890	1.485	0.137
AMMO	Wänman, A et al 2020(3)	0.398	0.261	0.068	-0.113	0.909	1.525	0.127
AMMO	Wänman, A et al 2020(4)	0.226	0.259	0.067	-0.282	0.734	0.872	0.383
AMMO	Yuasa, H et al 2001(2)	0.335	0.260	0.068	-0.175	0.844	1.287	0.198
		0.426	0.144	0.021	0.144	0.709	2.957	0.003

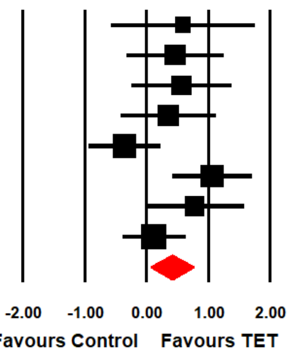
Std diff in means and 95% CI



A

Outcome	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
PMMO	Alajbeg, IZ et al 2015(3)	0.588	0.590	0.348	-0.567	1.744	0.998	0.318
PMMO	Bae, Y et al 2013(3)	0.462	0.397	0.157	-0.315	1.240	1.165	0.244
PMMO	Bae, Y et al 2013(4)	0.566	0.411	0.169	-0.239	1.371	1.378	0.168
PMMO	Bas, B et al 2018(2)	0.350	0.388	0.151	-0.411	1.111	0.902	0.367
PMMO	Craane, B et al 2012(5)	-0.358	0.294	0.087	-0.935	0.218	-1.218	0.223
PMMO	Haketa, T el al 2010(4)	1.065	0.325	0.106	0.429	1.702	3.279	0.001
PMMO	Ismail, F et al 2007(4)	0.779	0.407	0.166	-0.018	1.576	1.915	0.056
PMMO	Wahlund, K et al 2021(4)	0.121	0.256	0.066	-0.381	0.624	0.473	0.636
		0.402	0.176	0.031	0.057	0.748	2.283	0.022

Std diff in means and 95% CI



B