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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Manual Therapy and Quality of Life in People with Headache: Systematic Review and Meta-analysis of Randomized Controlled Trials

Luca Falsiroli Maistrello[1] · Marco Rafanelli[2] · Andrea Turolla[3]

Abstract

Purpose of Review People with headache usually experienced significantly lower health-related quality of life (HRQoL) than the healthy subjects. The goal of this systematic review was to evaluate the effectiveness of manual therapy on HRQoL in patients with tension-type headache (TTH), migraine (MH) or cervicogenic headache (CGH).

Recent Findings We searched randomized controlled trials (RCTs) on MEDLINE, COCHRANE and PEDro databases. Treatment was manual therapy compared to usual care or placebo. The outcome was the HRQoL that could be measured by Headache Impact Test (HIT-6), Headache Disability Inventory (HDI), Migraine Disability Assessment Questionnaire (MIDAS) and Short Form Health Survey 12/36 (SF-12/36). For the RCT internal validity, we used the Cochrane risk of bias (RoB) tool. For the level of evidence, we used the Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE). We identified a total of 10 RCTs, 7 of which were included into the meta-analysis. For HIT-6 scale, meta-analysis showed statistically significant differences in favour to manual therapy both after treatment (mean difference (MD) − 3.67; 95% CI from − 5.71 to − 1.63) and at follow-up (MD − 2.47; 95% CI from − 3.27 to − 1.68). For HDI scale, meta-analysis showed statistically significant differences in favour to manual therapy both after treatment (MD − 4.01; 95% CI from − 5.82 to − 2.20) and at follow-up (MD − 5.62; 95% CI from − 10.69 to − 0.54). Other scales provided inconclusive results.

Summary Manual therapy should be considered as an effective approach in improving the quality of life in patients with TTH and MH, while in patients with CGH, the results were inconsistent. Those positive results should be considered with caution due to the very low level of evidence. Researchers should in future design primary studies using valid and reliable disease-specific outcome measures.

Keywords Tension-type · Migraine · Cervicogenic headache · Manual treatment · Physical therapy · HRQoL

Introduction

It is known that the quality of life in people suffering from headache is worse than in healthy subjects [1–3]; in addition, this high prevalence disorder has negative health consequences in terms of occupational, economic and social factors [4]. The first-line approach to the treatment of headaches is pharmacological; however, the chronicity of the disorder may increase the risk of incurring in drug abuse [5] or to develop a medication-overuse headache (MOH) [6, 7]. For these reasons, the use of non-pharmacological alternative practices like aerobic physical activity [8], behavioural interventions [9–11], physiotherapy and manual therapy [12–20] should also be considered [12, 17] even if the level of evidence is still low [21, 22].

All recent literature reviews focused on the effectiveness of manual treatment in reducing the frequency, intensity and duration of attacks in headaches, especially on migraine (MH), tension-type headache (TTH) and cervicogenic headache (CGH) [13, 17–19, 23–25]; however, none of the aforementioned reviews performed a quantitative analysis of the results of manual treatments on patients' quality of life. Considering

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✉ Luca Falsiroli Maistrello
ft.luca.maistrello@gmail.com

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Campus of Savona, Savona, Italy

[2] Cosenza, Italy

[3] Laboratory of Neurorehabilitation Technologies, Fondazione Ospedale San Camillo IRCCS, Venice, Italy

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the multifactorial nature of headache, it would be more correct to adopt a broader approach, evaluating the effects of treatments also on other factors such as pharmacological consumption, stress, patient satisfaction or expectations, disability and impact on the quality of life [3, 26].

The aim of this systematic review was to research and summarize in a meta-analysis the results obtained on the quality of life in patients with headache when treated with manual therapy techniques compared to the pharmacological usual care or placebo.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) [27]. Review protocol was registered on PROSPERO [28], code CRD42018106999.

Inclusion Criteria

Only randomized controlled trials (RCTs) in Italian, English and Spanish were considered.

The studies had to refer to adult subjects with TTH, MH or CGH diagnosis; the treatment had to be based on the manual therapy compared to pharmacological usual care or placebo.

The studies had to report results on quality of life measured by at least one of the following scales: Headache Impact Test (HIT-6), Headache Disability Inventory (HDI), Migraine Disability Assessment Questionnaire (MIDAS), Short Form Health Survey 12 (SF-12) or 36 (SF-36).

Exclusion Criteria

Studies that included only pharmacological treatment, botulinum toxin treatment, physiotherapy treatment without manual therapy or that compared two active treatments were excluded.

Search Strategy

The literature search was performed by two independent authors (FML and RM) on MEDLINE, COCHRANE library and PEDro databases without any filter regarding author and year of publication (last search January 31, 2019). We considered any systematic reviews only to identify any primary study to be included in our review.

The keywords used were Headache, Migraine Disorders, Tension-Type Headache, Post-Traumatic Headache, Cervicogenic Headache, Musculoskeletal Manipulations, Physical Therapy Modalities, Physiotherapy, Manual Therapy, Soft Tissue*, Quality of Life, Dry needling, Acupressure and Clinical Trial, appropriately combined in the following search strings:

Medline (PubMed): ((("Headache"[Mesh]) OR "Migraine Disorders"[Mesh] OR "Tension-Type Headache"[Mesh] OR "Tension-Type Headache" OR "Post-Traumatic Headache"[Mesh] OR "Cervicogenic Headache")) AND ("Musculoskeletal Manipulations"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR Physiotherapy OR "Manual Therapy" OR "Soft Tissue*" NOT ("dry needling" OR "acupressure")) AND ("Quality of Life"[Mesh] OR Health) AND Clinical Trial [Publication Type]

Cochrane (in trials): ((("Headache") OR "Migraine Disorders" OR "Tension-Type Headache" OR "Tension-Type Headache" OR "Post-Traumatic Headache" OR "Cervicogenic Headache")) AND ("Musculoskeletal Manipulations" OR "Physical Therapy Modalities" OR Physiotherapy OR "Manual Therapy" OR "Soft Tissue*" NOT ("dry needling" OR "acupressure")) AND ("Quality of Life" OR Health)

PEDro (simply search): "Headache" AND "Manual Therapy"

Study Selection

Two independent authors (FML, RM) screened the records by title and abstract applying the eligibility criteria. At the end of the screening process, full-text articles were retrieved and assessed for their eligibility in the qualitative and/or quantitative synthesis. Any disagreement was resolved by consensus.

Data Collection

Two authors (FML, RM) independently collected information from the included trials by ad hoc extraction form. The extracted data were organized in synoptic tables, including the following: author, year, design, duration, follow-up, sample size calculation, diagnosis, intervention, control, outcome (related to the quality of life), results. Any disagreements between reviewers were resolved by consensus.

Measured results in the studies at the baseline and different follow-up were extracted; if necessary, the authors of the studies included were contacted [29–31].

Risk of Bias Assessment

The internal validity of the studies was independently assessed by two authors (FML, RM) using the Cochrane risk of bias (RoB) assessment tool [32]. The RoB for each study was assessed considering the following domains: selection bias (generation of random sequences and concealment of assignments), performance bias (blindness of participants and personnel), detection bias (blindness of evaluators), attrition bias (incomplete outcome data), reporting bias (selective reporting) and

other sources of bias (sample size calculated on a different or unspecified outcome) [32]. Each domain could be classified as "high", "low" or "unclear" risk of bias according to study reporting, and any disagreement was resolved by consensus.

Level of Evidence

We used the Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE) to evaluate the overall quality of evidence based on the methodological quality of included trials [33]. The highest quality rating is for evidence based on high-quality RCTs; however, it is possible to downgrade this level of evidence if one of these factors is found in the included studies: study limitation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias [34]. Two authors (FML, RM) independently assessed the quality of the evidence; any disagreement between the authors was resolved by consensus. The GRADEPro GDT software was used [35].

Analysis and Synthesis of Results

Treatment effects for continuous outcome measures were evaluated by using the pooled mean difference (MD). The variance was expressed with 95% confidence intervals (95% CI). For the analysis, the studies were grouped according to the diagnostic class and outcome measure. The results from individual trials were combined in the meta-analysis using the fixed-effects models in case of absence of heterogeneity or random-effects models in the presence of heterogeneity [36]. Heterogeneity was analysed by the I^2 statistic and the chi^2 test; a value $P < 0.05$ indicated a statistically significant heterogeneity [37].

For the meta-analyses, we firstly entered the mean values and standard deviations (SDs) measured after the intervention (post-treatment); secondly, we consider the values measured at the last available follow-up. To explore the influence of studies with high risk of bias that could lead to errors in the interpretation of the results of the meta-analysis [38], a sensitivity analysis was performed, excluding studies with at least two domains with high risk of bias. Studies that did not provide usable results for the quantitative assessment of outcomes were included in the review but excluded from the meta-analysis; the results of these studies have been treated in a descriptive way. When a trial presented multiple comparisons [39•, 40–42], the participants of the intervention or the comparison groups were equally distributed in two or more groups with smaller sample size, but equal means and SDs as suggested by Higgins et al. [43] in order to avoid a unit-of-analysis error. The Cochrane Review Manager V5.3 software was used for meta-analysis [44].

Results

Study Selection

We identified 206 records through database searching. After removing the duplicates, a total of 179 records were selected for screening. A total of 140 records were excluded after reading title and abstract. Of the 39 remaining articles, 29 were excluded after reading the full-text, while 10 articles were eligible for inclusion in the review [29–31, 39•, 40–42, 45–47]. Of these, 7 articles were included in the quantitative synthesis [30, 39•, 40–42, 45, 47] while 3 were excluded from the quantitative synthesis [29, 31, 46] (Fig. 1).

General Study Characteristics

We included 10 studies: 7 concerned TTH [29, 30, 39•, 40–42, 45], 2 MH [31, 47] and 1 involved a group of patients with mixed headaches (MH, TTH and CGH) [46] (Table 1).

Population

The pooled population consisted of 728 subjects (mean age 40.9 ± 10.4 years) with a significant majority of women (582 out of 728, 80%).

The TTH subgroup consisted of 518 subjects (71.2% of the whole population) with a significant majority of women (423 out of 518, 81.7%). Three RCT concerned chronic TTH [29, 30, 46], four concerned episodic and chronic TTH [40–42, 45] and one considered both frequent-episodic and chronic TTH [39•]. The MH subgroup consisted of 160 subjects (22.0% of the whole population) with a majority of women (124 out of 160 77.5%). One RCT concerned MH with and without aura [31] and two chronic MH [46, 47]. In one trial [46], 4 subjects with CGH and 6 subjects with non-specified mixed headache were evaluated.

Diagnosis

Headaches were diagnosed using the International Classification of Headache Disorders criteria (IHS) [48] except in one trial [31] that adopted the International Classification of Disease (ICD-10) criteria for the CGH subgroup. The diagnosis was usually performed by a neurologist; in one case, diagnosis was performed by a general practitioner [29] and one trial did not specify who made the diagnosis [31].

Treatment and Sessions

The number of treatments ranged from 4 sessions in 4 weeks up to a maximum of 14 sessions in 6 months; the duration of the session ranged from 15′ to 50′. The post-treatment/follow-

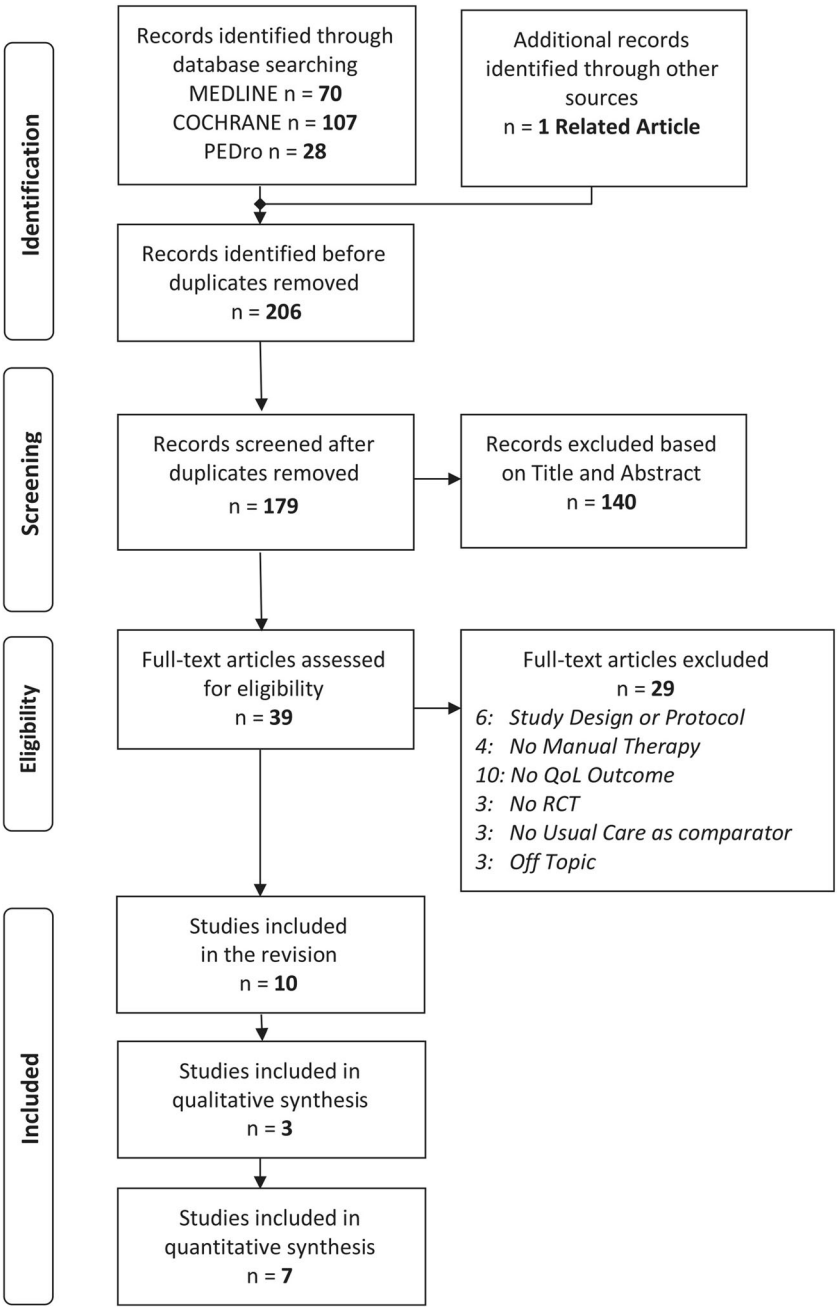

Fig. 1 PRISMA flow diagram for trial inclusion

up period ranged from a minimum of 2 weeks to a maximum of 9 months after the end of treatment.

Treatment Techniques

The treatments proposed in the studies included different techniques of manual therapy: articular mobilizations [30, 46], treatment of myofascial trigger points [29, 42], sub-occipital inhibitory pressures and manipulations of upper cervical levels [40, 41, 45], soft tissue techniques [31, 39, 47] and neuro-dynamic techniques [39•].

Outcome Measure

Five trials used the HIT-6 scale [30, 39•, 40, 42, 47], four used the HDI scale [30, 40–42], one used the MIDAS scale [31], three used the SF-36 scale [29, 31, 46] and one used the SF-12 scale [45].

Risk of Bias Within Studies

No attrition bias was detected in any study, but the blindness of the participants and personnel could not be achieved in any study, due to the nature of the manual treatment. Five studies

Table 1 General study characteristics

Author, year	Design/duration, follow-up	Sample diagnosis	Intervention control	Scale (HRQoL)	Results
Berggren 2012 [29]	RCT B/L: 4 weeks TR: 10 weeks R/O: 4 weeks	*N* = 39 (39F) CTTH Mean age 40.4 years (± 11.5)	- GT: 1 TrPs manual treatment a week for 10 weeks - GC: usual care	SF-36	No significant difference between GT and GC groups at both post-treatment and F/U
Castien 2011 [30]	RCT B/L: 2 weeks TR: 8 weeks F/U: 26 weeks	*N* = 82 (64 F) CTTH Mean age 40.4 years (± 10.8)	9 sessions in 8 weeks; duration 30′ - GT (*n* = 41): cervico-thoracic mobilization, exercise and postural correction - GC (*n* = 41): usual care	HDI HIT-6	**
Cerritelli 2015 [47]	RCT TR: 24 weeks	N = 105 (69F) CMH Mean age 38.7 years (± 9.3)	8 sessions in 6 months; duration 30′ - GT (*n* = 35): myofascial and ligamentous release - GP (*n* = 35): placebo: sham treatment - GC (*n* = 35): usual care	HIT-6	**
Espi-Lopez 2016 [45]	RCT B/L: 1 month TR: 4 weeks F/U: 1 month	*N* = 76 (62F) ETTH/CTTH Mean age 39.9 years (± 10.9)	4 sessions for 4 weeks; duration 20′ - GT1 (*n* = 19): sub-occipital inhibitory pressure - GT2 (*n* = 19): sub-occipital manipulation - GT3 (*n* = 19): inhibitory pressure and manipulation - GC (*n* = 19): usual care (rest position)	SF-12	**
Espi-Lopez 2014a [41]	RCT TR: 4 weeks	N = 76 (62F) CTTH/ETTH Mean age 39.9 years (± 10.9)	4 sessions for 4 weeks; duration 20′ - GT1 (*n* = 19): sub-occipital inhibitory pressure - GT2 (*n* = 19): manipulation C0–C1, C1–C2 - GT3 (*n* = 19): pressure and manipulation - GC (*N* = 19): usual care (rest position)	HDI	**
Espi-Lopez 2014b [40]	RCT TR: 4 weeks F/U: 8 weeks	*N* = 84 (68F) CTTH/ETTH Mean age 39.7 years (± 11.4)	4 sessions for 4 weeks; duration di 20′ - GT1 (*n* = 20): sub-occipital inhibitory pressure - GT2 (*n* = 22): manipulation C0–C1, C1–C2 - GT3 (*n* = 20): pressure and manipulation - GC (*n* = 22): usual care (rest position)	HDI HIT-6	**
Ferragut- Garcias 2016 [39•]	RCT B/L: 2 weeks TR: 6 weeks F/U: - 2 weeks - 1 month	*N* = 97 (78F) FETTH/CTTH Mean age 39.7 years (± 11.5)	6 sessions for 6 weeks; duration 15′ - GT1 (*n* = 23): SSTM cranio-cervical muscles - GT2 (*n* = 25): neuro-dynamic technique - GT3 (*n* = 25): combination of the 2 - GP (*n* = 24): placebo: sham massage	HIT-6	**
Moraska 2015 [42]	RCT B/L: 4 weeks TR: 6 weeks F/U: 4 weeks	*N* = 62 (48F) ETTH/CTTH Mean age 33.4 years (± 11.1)	12 sessions for 6 weeks; duration 45′ - GT (*n* = 20): TrPs manual treatments, myofascial release, post-isometric relaxation - GP (*n* = 21): placebo: detuned US - GC (*n* = 20): usual care	HDI HIT-6	**
Uthaikhup 2017 [46]	RCT B/L: 1 week TR: 10 weeks R/O: 1 week F/U: - 6 months	*N* = 65 (56 F) - TTH: *n* = 2 - MH: *n* = 13 - CGH: *n* = 44 - Mixed: *n* = 6	14 sessions in 10 weeks (2 per week for the 1st 4 weeks, 1 for the last 6 weeks); duration 45′ - GT (*n* = 33): cervical mobilization and therapeutic exercise - GC (*n* = 32): usual care (no treatment)	SF-36 (PCS, MCS)	Only in GT: post-treatment improvement in PCS (25.3; 19.2 to 31.4) and MCS (23.4; 17.6 to 29.2); $P < 0.001$.

Table 1 (continued)

Author, year	Design/duration, follow-up	Sample diagnosis	Intervention control	Scale (HRQoL)	Results
	- 9 months	Mean age 60.7 years (± 0.9)			F/U 9 months: improvement in PCS (21.6; 16.0 to 27.2) and MCS (17.9; 11.6 to 24.2); $P < 0.001$.
Voigt 2011 [31]	RCT TR: 10 weeks F/U: 6 months	$N = 42$ (42F) MH Mean age 45.05 years (± 11.0)	5 sessions in 10 weeks; duration 50′ - GT ($n = 21$): cervical manipulation - GC ($n = 21$): usual care (no treatment)	SF-36 MIDAS	SF-36: improvement at F/U in GT only in vitality, mental health, fisic pain, role and physical activity items ($P < 0.05$). MIDAS: improvement at F/U only in GT ($P = 0.04$). Significative difference between groups at F/U.

RCT randomized controlled trial; *B/L* baseline duration; *F/U* follow-up; *R/O* run-out duration; *TR* treatment duration; *GT* treatment group; *GP* placebo group; *GC* control group; *TTH* tension-type headache; *MH* migraine; *CGH* cervicogenic headache; *TrPs* myofascial trigger point; *SF-36* short form health survey 36; *SF-12* short form health survey 12; *HDI* headache disability inventory; *HIT-6* headache impact test; *PCS* physical component summary score; *MCS* mental component summary score; *HRQoL* health-related quality of life

**Results reported in the meta-analysis

had more than one high-risk domain of bias [29–31, 42, 46]. One study did not achieve the concealment of the assignment [31] while in four studies, the same risk was uncertain [40, 41, 45, 47]. Two studies were at high risk for detection bias, not having ensured the blindness of the evaluators [31, 42], while in four studies, the same risk was uncertain [29, 30, 40, 41]. Two studies did not completely report the values measured on patients for the outcome investigated [30, 31]. Regarding other sources of bias, five studies calculated the sample size using different outcomes and where considered as having high risk of sample selection bias [29–31, 42, 46]. Similarly in three studies [40, 41, 45], the same risk of bias was uncertain because the outcome on which the sample size was calculated was not specified (Figs. 2 and 3).

Synthesis of the Results

The meta-analysis was conducted using the results obtained in the groups at the end of the treatment and at the follow-up; the studies were grouped by different scales and by clinical diagnosis (Figs. 4, 5, and 6).

Three studies that used the SF-36 scales were excluded from the meta-analysis because one used a customized version of the scale [46], one did not report the results [29] and one reported the values of the subscales but without the SDs [31]; the same study also used the MIDAS scale but without providing SD values.

Results on HIT-6 Scale

At the post-treatment, the meta-analysis included five studies for a total of 413 patients; two studies had high risk of bias on TTH [30, 42], two studies had low risk of bias on TTH [39•, 49] and one had low-risk of bias on MH [47]. In the TTH subgroup ($N = 308$), the analysis showed a significant difference in favour of the treatment but with high heterogeneity probably due to the different treatment techniques used, the different management of the control group and the presence of high risk of bias studies (MD − 2.85; 95% CI from − 4.90 at − 0.80; $P = 0.006$; $I^2 = 76\%$; Fig. 4a). The heterogeneity dropped to a non-significant value when the two high risk of bias studies were excluded from the analysis [30, 42] (MD − 4.40; 95% CI from − 6.33 to − 2.48; $P < 0.001$; $I^2 = 43\%$; Fig. 4b). In the MH subgroup ($N = 105$), the results showed a significant difference in favour of the treatment (MD − 7.48; 95% CI from − 10.57 to − 4.39; $P < 0.001$; $I^2 = 0\%$); despite the absence of heterogeneity, the level of evidence remains low due to the presence of a single study. The combined results between the two subgroups showed a significant difference in favour of the treatment (MD − 3.67; 95% CI from − 5.71 to − 1.63; $P < 0.001$; $I^2 = 78\%$; Fig. 4a); also in this case, the heterogeneity decreased to non-significant values when the two studies at high risk of bias were excluded from the analysis

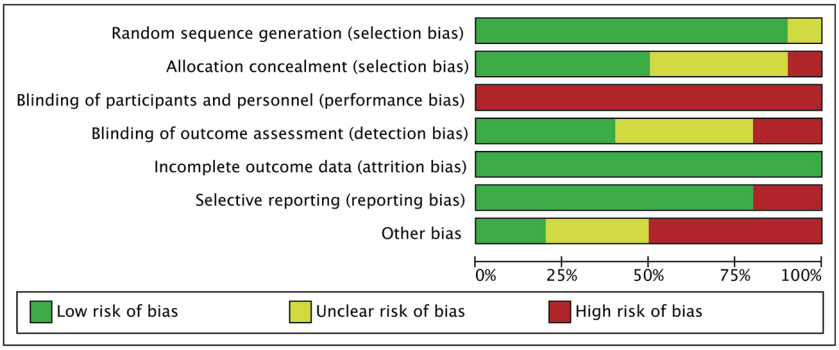

Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all studies

[30, 42] (MD − 5.26; 95% CI from − 6.90 to − 3.63; $P < 0.001$; $I^2 = 42\%$; Fig. 4b). Despite the more robust results obtained from the sensitivity analysis, the overall level of evidence remains very low due to the high risk of bias of the most influential studies.

At the follow-up, the meta-analysis included four studies, two had high risk of bias [30, 42] and two had low risk of bias [39•, 49] for a total of 308 patients with TTH; the study on MH [47] did not show follow-up. The analysis showed a significant difference in favour of the treatment (MD − 2.47; 95% CI from − 3.27 to − 1.68; $P < 0.001$; $I^2 = 22\%$) and low heterogeneity; however, the level of evidence remained very low due to the presence of two studies with high risk of bias (Fig. 4c).

Results on HDI Scale

At the post-treatment, the meta-analysis included four studies, two had high risk of bias [30, 42] and two had low risk of bias [40, 41] for a total of 287 patients with TTH. The analysis showed a significant difference in favour of the treatment (MD − 4.01; 95% CI from − 5.82 to − 2.20; $P = 0.02$; $I^2 = 38\%$) with a very low level of evidence (Fig. 5a).

At the follow-up, meta-analysis included three studies, two had high risk for bias [30, 42] and one had low risk of bias [40] for a total of 208 patients with TTH; one trial [40] did not present follow-up. The analysis showed a significant difference in favour of the treatment (MD − 5.62; 95% CI from − 10.69 to − 0.54; $P = 0.03$; $I^2 = 72\%$); the high heterogeneity was probably due to the different mechanism of action of joint mobilization techniques with respect to muscle techniques; the level of this evidence was very low (Fig. 5b).

Results on MIDAS Scale

Only one trial with high risk of bias [31] used the MIDAS scale on patients with MH. In the study, the comparison data between the groups at the follow-up for this outcome and the relative dispersion values (SD) are not reported; however, the authors found a significant decrease in the MIDAS score compared to the baseline only in the treatment group (from 37.6 to 24.8, $P < 0.05$) but not in the control group. The level of evidence is very low due to the high risk of bias and the presence of a single study.

Results on SF-36 Scale

Three trials with high risk of bias used SF-36 scale [29, 31, 46]. Uthaikhup et al. [46] analysed the results on a group of 65 elderly patients with mixed headaches, MH, TTH and CGH. The eight domains of the SF-36 scale were grouped into a physical component summary score (PCS) and mental component summary score (MCS). The measured PCS values showed a mean difference of 25.3 points (from 19.2 to 31.4; 95% CI; $P < 0.001$) to post-treatment and 23.4 points (from 17.6 to 29.2; 95% CI; $P < 0.001$) to the follow-up to 9 months for the treatment group. Similarly, the MCS showed a mean difference of 21.6 points (from 16.0 to 27.2; 95% CI; $P < 0.001$) to post-treatment and 17.9 points (from 11.6 to 24.2; 95% CI; $P < 0.001$) to the follow-up of 9 months. In contrast, the study conducted on 39 subjects with TTH by Berggren et al. [29] reported no significant difference between post-treatment and follow-up groups for any of the items on the scale, but the values were not reported in the study. Voigt et al. [31] on a sample of 42 subjects with MH reported significant improvements in the treatment group only in the vitality, mental health, physical pain, role and physical activity items ($P < 0.05$) while the results on the other items did not reach significance statistics; the data reported by the authors did not allow a comparison between the results obtained to the post-treatment due to the lack of dispersion indices. The level of this evidence was very low.

Results on SF-12 Scale

Only one trial with high risk of bias [45] conducted on 76 subjects with TTH did not report significant differences in the SF-12 score between the groups neither to post-

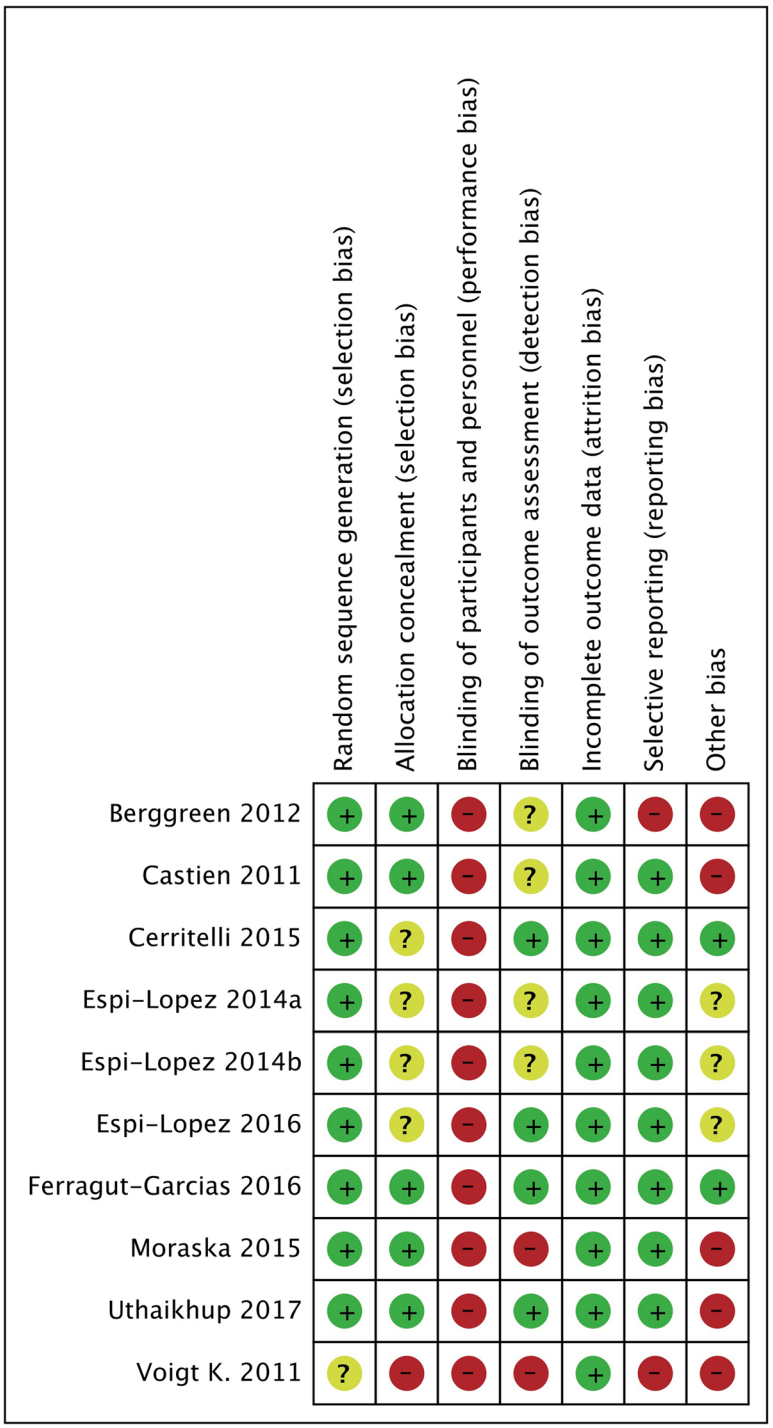

Fig. 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

treatment (Fig. 6a) nor to follow-up (Fig. 6b). The authors found a significant improvement with respect to baseline only in the group receiving sub-occipital inhibition while separate analyses for domains revealed different results depending on the item considered. The best results were observed in the group receiving the combined treatment, both post-treatment and follow-up. The authors concluded that the manual techniques applied to the sub-occipital region for a minimum of 4 weeks could offer a positive improvement only in some aspects of the quality of life of the patient's life, but the level of evidence was very low because of presence of a single study.

Discussion

The purpose of this review was to investigate the effectiveness of manual therapy on the health-related quality of life in

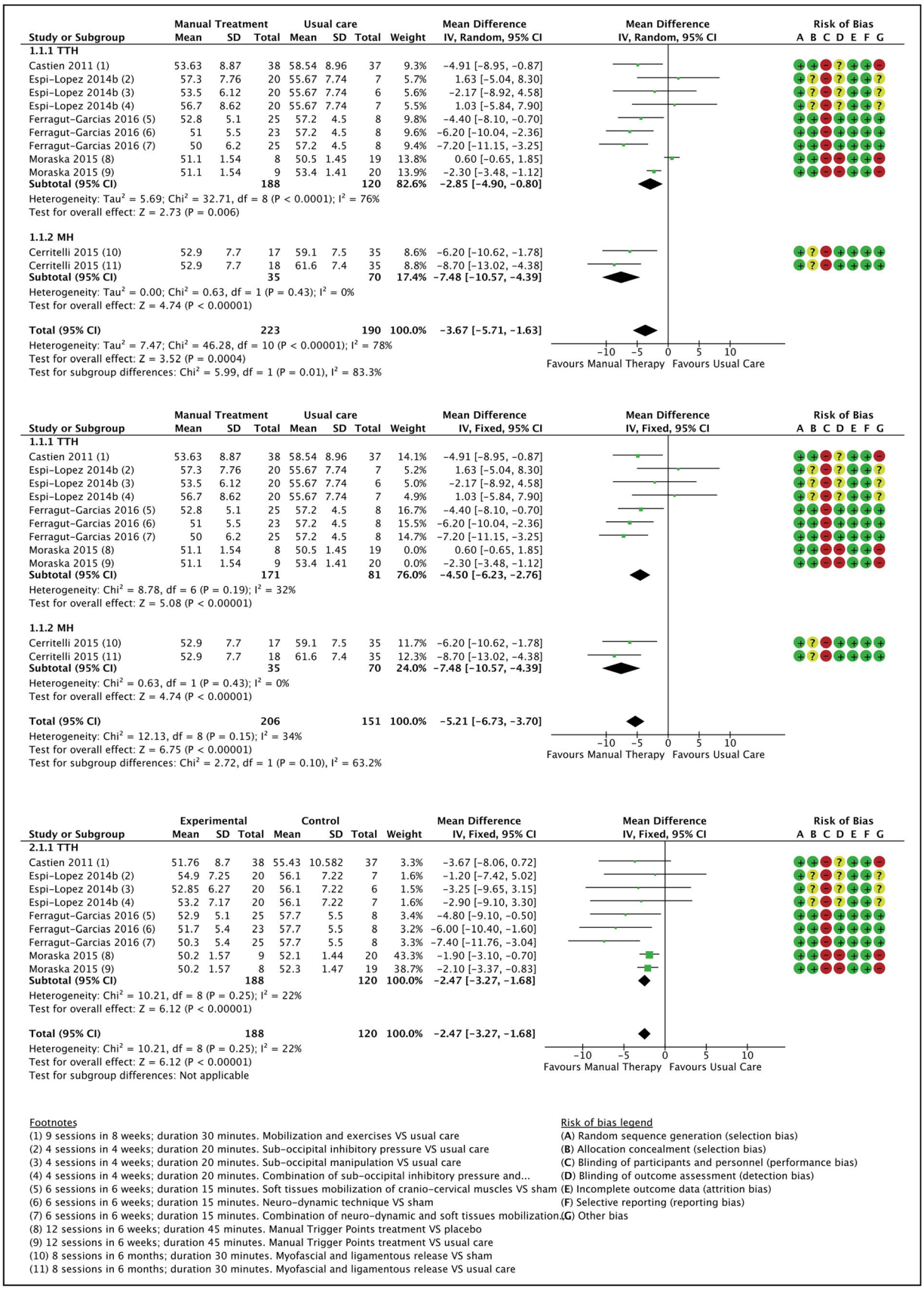

Fig. 4 **a**–**c** Forest plot of comparison, scale HIT-6. Results obtained at post-treatment (top); results of comparisons excluding studies with high risk of bias (middle); results obtained at follow-up (bottom). TTH tension-type headache, MH migraine, CI confidence interval, SD standard deviation

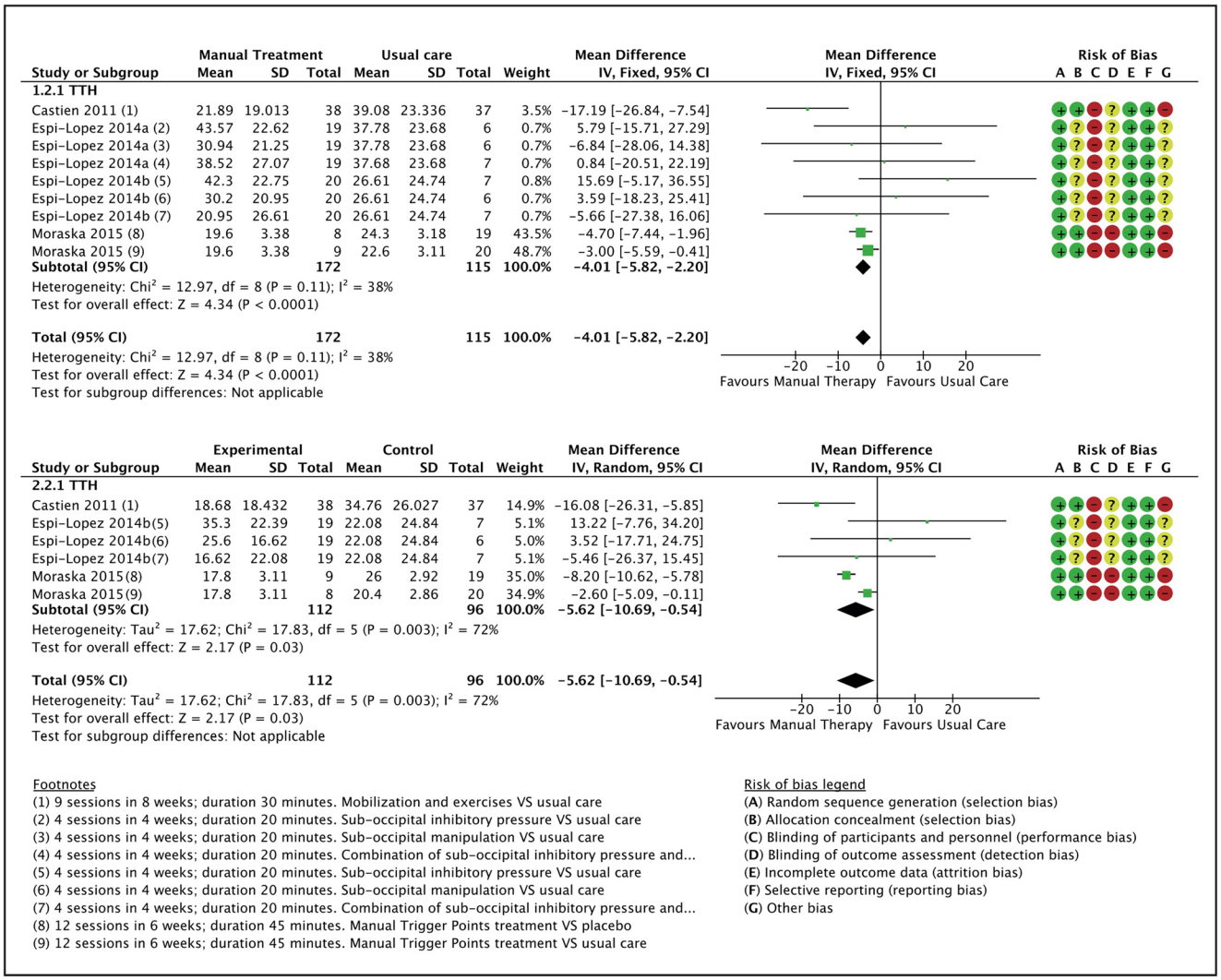

Fig. 5 **a**, **b** Forest plot of comparison, scale HDI. Results obtained at post-treatment (top); results obtained at follow-up (bottom). TTH tension-type headache, CI confidence interval, SD standard deviation

patients with headache. On a total of 10 included studies, 7 concerned TTH [29, 30, 39•, 40–42, 45], 2 MH [31, 47] and 1 involved a group of patients with mixed headaches, MH, TTH and CGH [46]. The entire sample consisted of 728 subjects, 80% of whom were women; this data could make the results less generalizable; however, several studies have confirmed that the female gender could constitute a risk factor for the headaches, in particular for MH and TTH [50, 51].

Except for a few exceptions, manual therapy obtained more positive effect on quality of life compared to usual care or placebo when measured by the HIT-6 and HDI disease-specific scales in patients with TTH or MH [39•, 47]; however, only the HIT-6 scale results reached the minimal clinical important difference [52–54]. These positive results are consistent with those obtained in a previous narrative review that investigated the general effects of manual therapy on patients with TTH [20]. Instead, the results obtained on CGH are to be taken with reserve: in fact, his type of disorder was included only in one study [46] where groups were composed by patients with different types of headache (MH, TTH, CGH and mixed). Authors reported a general improvement in the treatment group compared to control, but the results obtained on the CGH subgroup could not be extracted.

In some cases, a trend in favour of the control group has been noted. Moraska et al. reported better results in the group that received the placebo but this trend was noted only post treatment and was not statistically significant [42]; this positive trend was not maintained at follow-up. In three trials conducted by Espi Lopez et al. [40, 41, 45], all treatment and control groups reported significant improvement with respect to baseline but between-group differences were not significant. Unlike the other studies included in the review that used classical placebo groups [39•, 42, 47], in those cases, authors have tried to

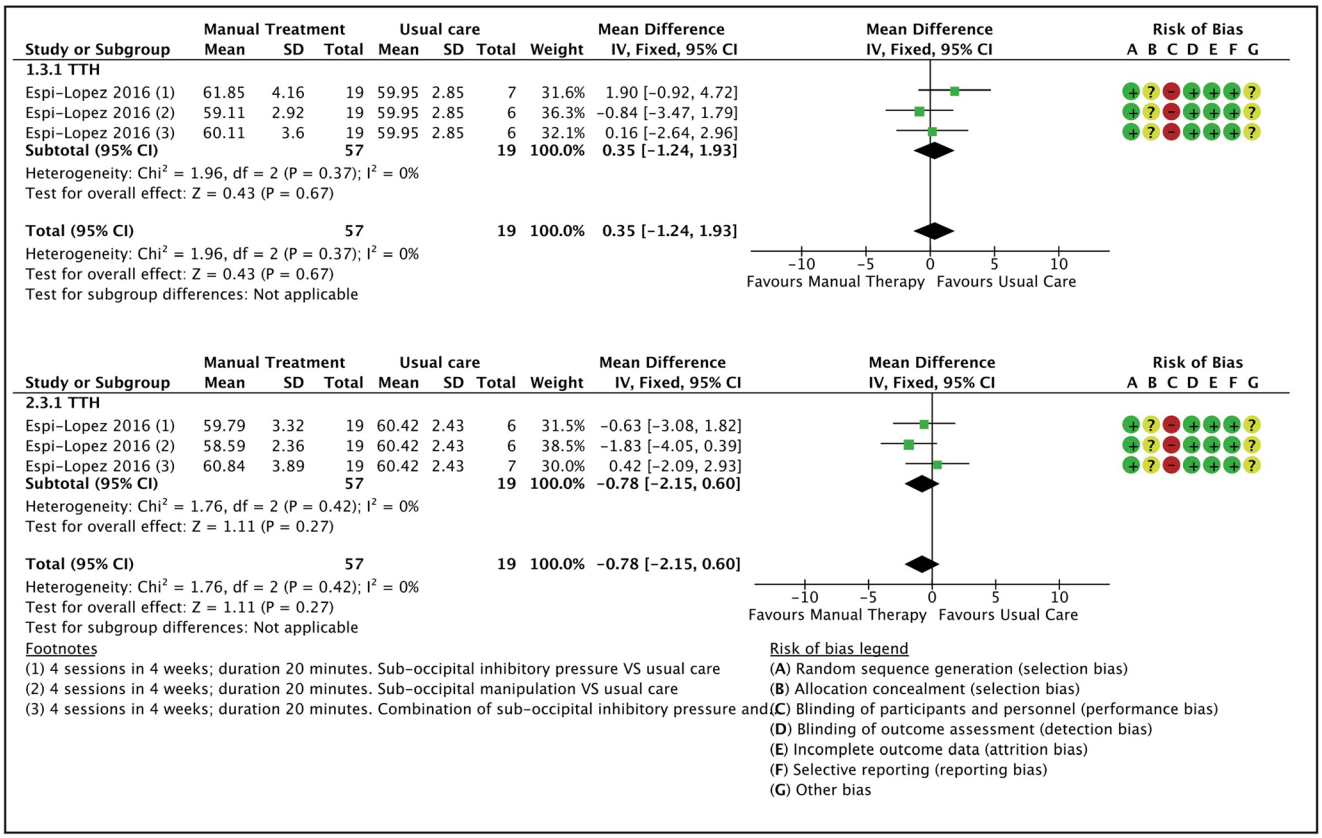

Fig. 6 **a**, **b** Forest plot of comparison, scale SF-12. Results obtained at post-treatment (top) and follow-up (bottom). TTH tension-type headache, CI confidence interval, SD standard deviation

guarantee a rigorous control of contextual factors, giving to the control group (who received no active treatment or placebo) the same conditions of the treatment group in terms of number of sessions, frequency and duration. These particular types of control group (sometimes called attention control groups [55]) seemed to be as effective as conventional placebo [40]. These apparently inconclusive results could be explained not only by the different effectiveness of the manual therapy techniques adopted, but also by the different management of the contextual conditions, supporting the idea that not only the nature of intervention but also the setting in which the treatment is performed is important, due to the influence of the context on manual treatments. Factors like the time dedicated to the patient, interaction and human relationship [42, 56] should be adequately balanced among all the groups of subjects involved in the studies [57]; an adequate control of contextual factors could actually affect the overall effect of manual therapy, which is sensitive to both the placebo and the nocebo effect [58••].

The results obtained by the MIDAS and SF-36 scales have been tendentially positive compared to the baseline values for most of the groups; also in this case, manual therapy techniques seem to have a certain influence on different aspects of quality of life in people with TTH, especially in functional aspects. However, only one study reported clearly beneficial effects of treatment [46] while data from the other studies were not comparable in the meta-analysis [29, 31]. Regarding the SF-12 scale, between-group comparisons showed no significant differences even if the trend was positive for both when compared to the baseline [45]. These conditions and the lack of data do not allow us to claim with any certainty that manual therapy, in this case, was more effective than usual care or placebo.

It seems that the measure of the effectiveness of manual techniques could depend on the method used to evaluate the quality of life, as the best results were found when disease-specific scales were used. According to Haywood et al. [59••], the use of valid and specific scales like HIT-6 should be considered both in research studies and in clinical approaches; in fact, generic assessment scales like SF-12 or SF-36 may not be appropriate for evaluating patients with TTH and MH headaches [60–62] even if they could represent a valid support to the disease-specific scales. Combining generic and disease-specific tools would make possible to obtain a general overview of the impact of the disease on patients, making the results comparable with other disorders [26].

Limitations

The present review has some limitations: first, the inclusion criteria were limited to only three languages; secondly, in the studies with more than two comparisons, the need to split the shared group into two or more groups with smaller sample size (in order to avoid a double-counting error according to the indications of the Cochrane Handbook [43]) may have reduced the power of the meta-analysis results.

Conclusions

Manual therapy has shown better effects compared to usual care and placebo in terms of quality of life patients with TTH and MH, but the results should be taken with caution due to the very low level of evidence and high risk of bias of the most influential studies. In patients with CGH, the results are inconsistent, and there is a need to make new specific studies for this type of headache. In the face of significant improvements compared to baseline and the absence of adverse effects, manual therapy should, therefore, be considered as a valid approach, being able to positively affect the quality of life of patients with headache. To increase the level of evidence, researchers should in future design primary studies that provide appropriate control groups and follow-up periods, using valid and reliable disease-specific outcome measures.

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Compliance with Ethical Standards

Conflict of Interest Luca Falsiroli Maistrello, Marco Rafanelli and Andrea Turolla declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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