BMJ Open

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019040
Article Type:	Research
Date Submitted by the Author:	09-Aug-2017
Complete List of Authors:	Carnes, Dawn; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Plunkett, Austin ; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Ellwood, Julie; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, National Council for Osteoapthic Research, Centre for Primary Care and Public Health Miles, Clare; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Complementary medicine
Keywords:	manual therapy, PAEDIATRICS, 'colic', excessive crying, infants

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review.

Dawn Carnes[a,c], Austin Plunkett[a], Julie Ellwood[b], Clare Miles[a]

Affiliations:

[a] Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Centre for Primary Care and Public Health, London, UK

[b] National Council for Osteoapthic Research, London, UK

[c] Universtiy of Applied ciences, Western Switzerland, Faculty of Health, Fribourg, Switzerland

Address correspondence to:

Dawn Carnes

Email: d.carnes@qmul.ac.uk,

Author contribution

Dawn Carnes conceptualised and designed the study, contributed to the data selection, extraction and analysis, drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript submitted.

Clare Miles managed the data, contributed to the data selection, extraction and did the meta-analyses, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Austin Plunkett contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Julie Ellwood contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

PROSPERO Registration Number: 37353

Funding: This research received no specific grant from any funding agency in the public, commercial or 'not-for-profit sectors.

This study was Crowd funded from public donations.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors, except Julie Ellwood, had

financial support from the National Council for Osteopathic Research from crowd funded donations for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing: Full datasets, analyses and all full searches are available on request from the corresponding author at d.carnes@qmul.ac.uk. No individual patient level data was used in this study.

Abstract

Objective: To conduct a systematic review to assess the effect of manual therapy interventions for healthy but unsettled, distressed and excessively crying infants, to provide information to help clinicians and parents inform decisions about care.

Methods: We reviewed published peer-reviewed primary research articles in the last 26 years from 9 databases (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL). Our inclusion criteria were: manual therapy (by regulated or registered professionals) of unsettled, distressed and excessively crying babies or children who were otherwise healthy and treated in a primary care setting. Outcomes of interest were: crying, feeding, sleep, parent-child relations, parent experience/satisfaction and parent-reported global change.

Results: Nineteen studies were selected for full review: 7 randomised controlled trials, 7 case series, 3 cohort studies, 1 service evaluation study, and 1 qualitative study.

We found moderate strength evidence for the effectiveness of manual therapy on: reduction in crying time (favourable: -1.27 hours per day (95% CI -2.19, -0.36)); sleep (inconclusive); parent-child relations (inconclusive); and global improvement (no effect). The risk of reported adverse events was low: 7 non-serious events per 1,000 infants exposed to manual therapy (n= 1308).

Conclusions: Some small benefits were found but whether these are meaningful to parents remains unclear as does the mechanisms of action. Manual therapy appears relatively safe.

Strengths and limitations

Meaningful outcomes for parents with distressed, unsettled and excessively crying infants were investigated to help inform their decisions about seeking manual therapy care for their infants.

Compiling evidence for distressed unsettled and excessively crying infants based on multiple 'clinical' diagnoses' using varied definitions is difficult.

The mechanism of action of complex interventions was not explained by the pragmatic research investigations used in this review.

Low to moderate quality studies limited the certainty of outcomes, which are liable to change with more research.

Introduction

Unsettled infant behaviour and colic are terms used to describe a range of behaviours in infants aged up to twelve months which include prolonged episodes of crying, difficulties with sleeping and/or feeding [1]. Reports suggest a prevalence of approximately twenty percent [2] and the incidence is equal between sexes [3]. The problems are found more commonly in first-borns and infants who have siblings who also had this condition [4-6]. High levels of multiple health service use have been found in the post-partum period, including visits to emergency departments [1, 4]. A cost burden analysis found that the annual cost to the UK National Health Service of infant crying and sleeping problems in the first twelve weeks of life was £65 million [5]. There are associations between unsettled infant behaviour and high maternal depression scores [6] and the natural crying peak at 6 weeks coincides with the peak age for severe infant injury or death as a result of child abuse [7].

Many aetiological factors for unsettled infant behaviour have been explored including digestive, musculoskeletal, breastfeeding and parenting problems [8-22]. Medicalising these symptoms is controversial as they are seen as self-limiting with infants normally settling after twelve weeks. However coping with these infants during this period can be very difficult.

Manual therapists offer a mix of health screening, education, advice, psychological support and touch therapy for these infants. Manual treatment is based upon the premise that infants may have musculoskeletal strains or limitations affecting comfort, feeding and gut motility causing distress. A previous Cochrane review of manual therapy and colic, meta-analysed data from six randomised controlled trial (RCT) and found small positive (statistically significant) changes in crying time outcomes overall. However a sensitivity analysis of data from only RCT studies where parents were blinded to treatment did not show beneficial effects [23].

There are some concerns around the safety of manual techniques in the treatment of infants but published data of cases of serious adverse events are rare [24]. No reviews to our knowledge have explored qualitative research and non-specific effects such as parental confidence and satisfaction. In this review we aimed to update the Cochrane review of RCTs for crying time and investigate non RCT studies and outcomes that are important to parents, rather than bio-medical markers alone that might be of more interest to primary researchers exploring aetiology, as our selected population were babies that were considered healthy.

METHOD

Types of studies

We included the following types of peer reviewed studies in our search: RCTs, prospective cohort studies, observational studies, case control studies, case series, questionnaire surveys, and qualitative studies. We excluded single case studies and non-peer reviewed literature (editorials, letters, Masters and undergraduate theses). Systematic reviews were identified to inform our research and for citation tracking. There were no language restrictions in our search criteria.

Types of participants

Participants were aged between 0-12 months (infants) when they received manual therapy treatment. They were healthy, thriving and not receiving other medical interventions. Their presenting symptoms were excessive crying, distress, and unsettledness: they might also be decribed as having colic, constipation, breastfeeding/feeding difficulties and, or gastroesophageal reflux/discomfort.

'Colic' was determined using the Wessel 'rule of three' [25] or Rome III [26] criteria. Infants were considered to have colic if he or she was thriving and healthy, but had paroxysms of irritability, fussing or crying lasting for a total or more than three hours a day and occurring on more than three days a week for more than one week [26].

We excluded studies that included infants requiring treatment for conditions that required specialist or hospital based clinical care for conditions such as: respiratory disorders, developmental disorders (learning and motor), cystic fibrosis, cerebral palsy, otitis media, neuralgia, congenital torticolis or musculoskeletal trauma. We also excluded studies about plagiocephaly or brachycephaly.

The intervention

We included studies where the manual therapy intervention was delivered in primary care by statutorily registered or regulated professional(s). This included osteopaths, chiropractors, physiotherapists and any other discipline using manual contact as the primary therapeutic component. The intervention or therapy had to involve physical and/or manual contact with the patient for therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aids/products/procedures. We excluded mixed or multidisciplinary interventions where the response to the manual therapy elements would have been unclear/undeterminable. Studies where the professional trained a non-professional to deliver the therapy or where parents delivered the therapy were excluded also.

Types of outcome measures

Outcomes of interest were unsettled behaviours, experience/satisfaction and global change scores. Unsettled behaviours included, for example, excessive crying, lack of sleep, displays of distress or discomfort (back arching, drawing up of legs) and difficulty feeding. Adverse events data were also collected.

Selection of articles

Nine electronic databases were searched from 1990 to January 2017: the last 26 years (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL).

The main search string (modified for the different engines) is included in the electronic appendices, it included the key terms: musculoskeletal, manipulation, manual and physical therapy, physiotherapy, osteopathy and chiropratic with infant baby and new borns. We updated the search to end of January 2017 using Medline Ovid and search alerts from EMBASE, Cochrane and WOS. We also located articles through peer networks. Four reviewers (the authors in two teams of two) reviewed the titles and abstracts, then the full texts independently. Where there was disagreement a third reviewer from the other team

arbitrated the final decision to include or exclude. Review articles retrieved in the search were citation-tracked to identify additional studies. Covidence software was used to organise and classify the articles [27]. See Figure 1 for a flowchart of the search process.

Quality appraisal of included studies

Two reviewers rated the quality of each included study (either CM/JE or DC/AP). We used the appropriate quality appraisal tools for each type of study design [28-30]. An overall quality score for each study was assigned by summing the number of present quality criteria. For RCTs: 6 quality criteria were assessed (0-2 =low, 3-4=moderate, 5-6=high quality). For cohorts: 11 quality criteria were assessed (0-3=low, 4-7=moderate, 8-11=high quality). For case series: 9 quality criteria were assessed (0-2=low, 3-5=moderate, 6-9=high quality). For qualitative studies: 10 criteria were assessed (0-3=low, 4-7=moderate, 8-10=high quality).

Data extraction and synthesis

The study characteristics extracted are shown in Table 1 and the data in Table 2. One reviewer extracted the data and another checked the data extractions (all authors).

Analyses

We aimed to meta-analyse data for RCTs and matched or paired cohort studies. For RCTs, we planned to extract final value scores for each group and convert them to standardised mean differences (SMD) and weighted mean differences for comparison of treatment effects. Where there was a majority of either change or final value scores we planned sensitivity analysis to check 'consistency' / meaning of the meta-analyses. We planned to extract Risk Ratios (RR) for comparison of adverse events between treatment and control groups. I^2 was used to calculated heterogeneity. REVMAN software (version 5.3) was used to conduct the meta-analyses.

For non-RCTs studies analyses were descriptive, but change scores and RRs were extracted where possible. If there were a sufficient number of qualitative studies, we proposed to organise and synthesise findings from the qualitative data, by identifying emergent themes and sub-themes.

Strength of evidence

We rated the strength of evidence across studies for each outcome, into either high, moderate or low, taking note of the quality and overall direction of results (inconclusive, favourable or unfavourable)[31]. Strength of evidence was considered as follows:

High: Consistent results from at least two high quality RCTs, or other well-designed studies, conducted in representative populations where the conclusion is unlikely to be strongly affected by future studies

Moderate: Available evidence from at least one higher quality RCT or two or more lower quality RCTs but constrained by: number, size, quality, inconsistency in findings and limited generalisability to clinical practice. The conclusions are likely to be affected by future studies.

Low: Evidence was insufficient with limitations in data provision, number, power, quality, inconsistency in results and findings not generalisable to clinical practice. All low quality rated studies were rated as inconclusive regardless of author findings.

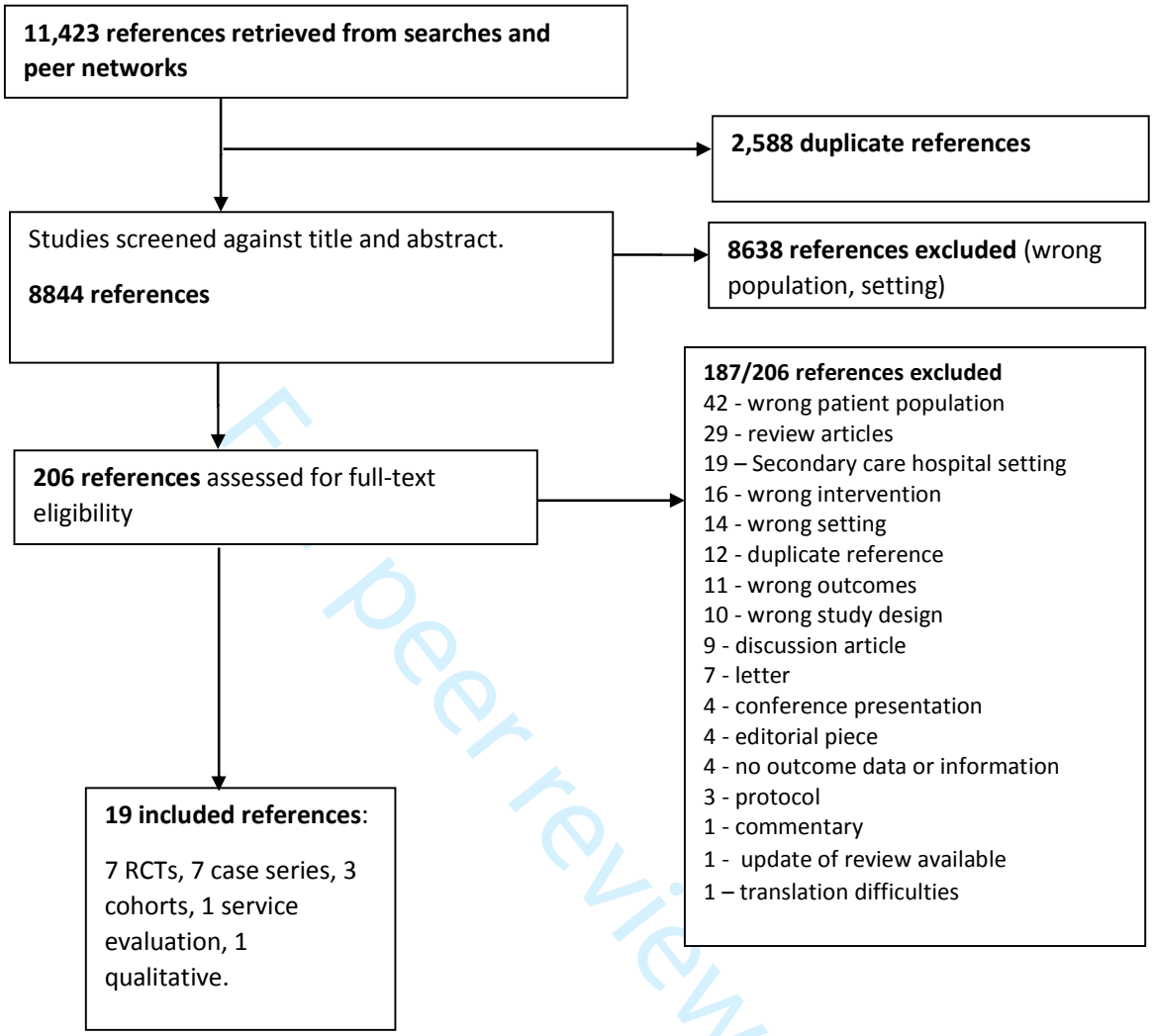
Two reviewers rated the quality and strength of evidence, and a consensus vote was used in cases of disagreement.

RESULTS

Search results

A total of 11,423 studies were retrieved. After duplicate removal, 8,844 remained. There were 8,638 references excluded by title and abstract predominantly because the population was not appropriate for example the children were too old and, or treatment settings were not primary care. We acquired full text for 206 references and 19 of these fulfilled our inclusion criteria. Reasons for exclusion are listed in Figure 1.

Figure 1: Flowchart of search process for the review



There were 19 primary studies included: seven RCTs [32-38], seven case series [39-45], three cohort studies [46-48], one service evaluation survey [49], and one qualitative study [50]. One other primary study was excluded due to translation difficulties of technical terms in chinese medicine [51]. All studies were published between 1990 and Jan 2017. Countries represented across the studies were the UK [32-34, 41-43, 46, 47, 49], USA [35, 40, 48], Canada [38], Australia [39, 44, 50], Norway [36], Denmark [37, 45]. The following conditions were represented in the studies: colic (n=11) [32-34, 36, 37, 39, 40, 43, 45-47]; gastroesophageal reflux (n=2) [35, 40]; breastfeeding difficulties (n=5) [38, 42, 44, 48, 49], and infant signs of distress (described as headache) (n=1) [41]. With the exception of four studies, all used

chiropractic intervention. The other four studies used massage therapy [35], and osteopathic intervention [33, 38, 49]. Eight studies used control groups [32, 33, 34, 35, 36, 38, 46, 47]. The controls varied across studies, from no physical treatment [33, 34, 36, 46, 47, 51], to a sham treatment [35, 38] or drug [37]. See Table 1 for characteristics of included studies.

In the few cases where there was uncertainty with selection choice these were all resolved after discussion with a third reviewer.

Table 1 Characteristics, study design and quality rating of included studies.

Author/ year	Country of study	Participants reported condition	Type of study design and follow up period (FU)	Intervention	Outcomes reported	Quality appraisal
Browning 2008 [32]	UK	Colic	RCT (spinal manual therapy vs occipital decompression (SMT vs OSD)) FU: 4 weeks post treatment.	Chiropractic	Sleep Resolution of symptoms	**High**
Cornall 2015 [50]	Australia	Breastfeeding difficulties	Qualitative study FU: None	Osteopathic	Observation regarding "the osteopathic therapeutic cycle".	**High**
Davies 2007 [39]	Australia	Irritable bowel syndrome (IBS)	Case series FU: over 30 days	Chiropractic	Resolution of symptoms	**Mod**
Elster 2009 [40]	USA	Acid reflux and/or colic	Retrospective case series FU: over 2 weeks – 6 months	Chiropractic	Resolution of symptoms	**Low**
Hayden 2006 [33]	UK	Colic	RCT Osteopathic treatment vs no treatment FU: 4 weeks	Osteopathic	Parents involvement Sleep Crying	**Mod**
Herzhaft-Le Roy 2017 [38]	Canada	Breastfeeding difficulties	RCT Groups : Osteopathic treatment vs sham FU: over 10 days	Osteopathic + lactation consultant	Feeding Nipple pain Global improvement:	**High**
Marchand 2009 [41]	UK	Headache behaviours	Retrospective case series FU: None	Chiropractic	Improvement of Symptoms	**Low**
Miller 2012a [34]	UK	Colic	RCT: Treatment blinded (TB) vs treatment not blinded (TNB) vs No treatment blinded (NTB) FU: 10 days	Chiropractic	Crying Improved Global change	**High**
Miller 2016 [49]	UK	Breastfeeding difficulties	Service evaluation (survey) FU: 6-12 weeks after attending clinic	Chiropractic and midwife	Breastfeeding	**Mod**
Miller 2008 [43]	UK	Colic	Retrospective review FU: over 2 year period	Chiropractic	Adverse events	**Mod**
Miller 2009a [47]	UK	Colic	Controlled Cohort study FU : At 2-3 years of age	Chiropractic	Sleep Temper tantrums	**Low**
Miller 2009b [42]	UK	Breastfeeding difficulties	Prospective case series FU: within a 2 week period	Chiropractic	Improvement in feeding Number of treatments	**Mod**

Miller 2012b [46]	UK	Colic	Prospective cohort study FU: End of treatment (duration, not reported)	Chiropractic	Consolability, Crying Personal stress, Sleep	**Low**
Neu 2014 [35]	USA	Gastro-oesophageal reflux	PILOT RCT: Massage vs no massage FU: 6 weeks	Massage therapists	Improvement in symptoms	**High**
Olafsdottir 2001 [36]	Norway	Colic	RCT: Chiropractic vs no treatment FU: over 8-14 days	Chiropractic	Crying hours Improvement of symptoms	**Mod**
Stewart 2012 [44]	Australia	Breastfeeding difficulties	Before and after study FU: At end of treatment (duration, not reported)	Chiropractic	Improvement feeding behaviour	**Low**
Vallone 2004 [48]	USA	Breastfeeding difficulties	Cohort study: Infants with breastfeeding difficulties vs infants without difficulties FU: over 6-8 weeks	Chiropractic	Feeding	**Low**
Wiberg 1999 [37]	Denmark	Colic	RCT : Chiropractic vs dimethicone FU: between 8-11 days	Chiropractic	Daily hours of infantile colic	**Low**
Wiberg 2010 [45]	Denmark	Colic	Retrospective review of clinical records FU: 11 years.	Chiropractic	Crying time	**Mod**

2

Quality assessment

The methodological quality of the studies varied (Table 1). Five studies were rated as high quality: four RCTs (low risk of bias) [32, 34, 35, 38] and a qualitative study [50]. Seven were rated as low with severe methodological flaws (for example: small samples, the treating clinician observed and reported outcomes) [37, 39, 41, 44, 46, 47, 48]. The remainder were of moderate quality [33, 36, 39, 42, 43, 45, 49]

Review findings

Table 2 shows the results from studies reporting similar outcomes. Six studies reported outcomes related to improvement in feeding [38, 42, 44, 48-50]. Seven, reduction in crying time [32-34, 36, 37, 45, 46], five reported global improvement in symptoms [32, 34, 36, 39, 40], four reported sleep outcomes [32, 33, 38, 46] and three reported outcomes about parent – child relations [33,35,46]. The remaining outcomes were from one study only.

Table 2: Findings from included studies by similar outcomes

Author/year/ (Quality rating)	Participants, n and age	Outcomes and Findings /results (parent reported outcomes unless otherwise stated)	Magnitude or direction of effect: Moderate to high quality studies only
Improvement in feeding : Overall Strength of Evidence LOW			
Herzhaft-Le Roy 2017* [38] (High)	N = 97 Age: mean 15 days	Ability to latch improved more in the treatment group (Time 3, mean score = 9.22, SD = 0.92) than in the control group (Time 3, mean score = 8.18, SD = 1.60); p = 0.001.	Significant favourable effect in those having osteopathic treatment
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks	7% (n = 5) reported no difference in feeding after attending the clinic. 86% reported exclusive breastfeeding at follow-up (compared to the 26% at start of the study). Relative RR of exclusive breastfeeding after attending the clinic was 3.6 (95% CI =2.4-5.4).	Significant favourable effect in those attending the clinic
Miller 2009b [42] (Moderate)	N = 114 Age: 2 days-12 weeks	All showed improvement. 78% (n=89) were able to be exclusively breastfed after 2-5 treatments, within a 2-week time period. 20% (n=23) required at least some bottle-feeding.	Inconclusive Descriptive statistics only. No control group. Favourable findings.
Stewart 2012 [44] (Low)	N = 19 Age: not reported	Improvements in breastfeeding behaviour = 100% Improved attachment to breast =100%, Reduced extension/arching = 94% Reduced side shaking =88%, Reduced overall stress of feeding = 84%, Reduced pain when feeding = 77%, Reduced side preference = 64%. (treating chiropractor reported data)	Inconclusive (low quality)
Vallone 2004 [48] (Low)	N = 25 Age: not reported	Improvement in latching and ability to breastfeed = >80%. 4 withdrew/were discharged from the study to seek other treatment. (Mixed patient and treating chiropractor reported data)	Inconclusive (low quality)
Cornall 2015 [50] (High)	N = 13 Mothers/ Osteopath dyads Age: mothers: median =32 years and newborns	Findings support optimal breastfeeding through a progressive, transitional cycle process, which is supported by four inter-related categories: i) connecting; ii) assimilating; iii) rebalancing; and iv) empowering. The findings outline contextual determinants that shaped women's views and experiences, osteopaths' professional identity and health care as a commodity.	Qualitative data affirming the need for a structured, yet creative and individualised approach to infant manual therapy, with the goal of helping the mother to achieve optimal breastfeeding.
Reduction in crying : Overall strength of evidence MODERATE			
Miller 2012a	N = 104	Mean crying times all groups decreased by day 10, mean decrease was:	Significant favourable effect in

[34] * (High)	Age: < 8 weeks	Treatment blinded (TB) 44.4% (P < .001), Treatment not blinded (TNB) 51.2% (P < .001), and No treatment blinded (NTB) 18.6% (P < .05) 1) TB vs. NTB: using cut-off of 2 or less hours of crying per day and more than 30% change, respectively. Day 10: 12.0 (95% CI: 2.1-68) and 3 (95% CI: 0.8-9). 2) TB vs. NTB: Reduction -1.4 hours of mean crying time (95% CI: -2.5 to -0.3) at day 10 3) TB vs. TNB: No significant difference between blinded treatment groups Adjusted ORs, 0.7 [95% CI, 0.2-2.0] and 0.5 [95% CI, 0.1-1.6] at days 8 and 10, respectively).	treatment group of -1.4 hours less hours of crying
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms (inc crying) in 18/22 infants in the spinal manual therapy (SMT) group and in 14/21 in the Occipital decompression group (OSD) as perceived by the parent, (rate ratio of 1.23 (95% CI:0.86—1.76). Infants treated with SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	No difference between groups, both treatment groups improved. Head to head trial.
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a statistically significant difference between the 2 groups in the mean reduction in crying time of 1.0 (95% CI: 0.14, 2.19) hours/24 hr. Overall reduction in crying time from weeks 1-4 was 63% in the treatment compared to 23% in the control group.	Significant favourable effect in treatment group of 1 less hour of crying
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	There was no difference between those treated and not treated (student's t-test, p=0.982). A reduction in crying hours per day in both groups was seen during the study, from a mean of 5.1 to 3.1 hours per day in the treatment group and 5.4 to 3.1 hours in the control group.	No difference between groups, both treatment groups improved
Wiberg 2010 [45] (Moderate)	N = 276 Age: 0-3 months	No apparent link between the clinical effect of chiropractic treatment and a natural decline in crying was found.	No clinical difference between treatment and natural decline.
Miller 2012b [46] (Low)	N = 158 Age: mean 5-6.7 weeks	Mean change reported by parents on 1-10 scale was 3.7 for all infants. p<0.001. (Calculations derived from Table 5 in paper)	Inconclusive (low quality)
Wiberg 1999[37]* (Low)	N=45 Age: mean 5.4 weeks	There was a significantly larger reduction in colic symptoms from pre-treatment to days 8-11 in the manipulation group (-1.0 hr/day, +/- 0.4 SE) compared to the dimethicone group (-2.7 hr/day, +/-0.3 SE).	Inconclusive (low quality)

Sleeping time: Overall strength of evidence MODERATE			
Herzhaft-Le Roy 2017 [38]* (High)	N = 97 Age: mean 15 days	16.5% of mothers in the osteopathic treatment group, reported that their infants slept better, appeared soothed, or better enjoyed lying on their back, in the days that followed treatment.	Inconclusive: Favourable outcome but only reported in the treatment group
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At day 14, the mean hours of sleep per day were significantly increased in both groups (SMT, by 1.66 hr/day, p<0.01; OSD, by 1.03 hr day, p<0.01).	No difference between groups, both treatment groups improved
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a significant difference between treated and control groups: mean increase in sleeping time of 1.17 hrs/24hr more (95% CI: 0.29- 2.27) (p<0.05). Overall improvement in sleeping time by wk 4 was 11% for the treated group and less than 2% in the control group (mean % change).	Significant favourable effect in treatment group of 1 .17 hours of more sleeping
Miller 2012b [46] (Low)	N = 158 Age: 5-6.7 weeks	Mean change reported by parents on 1-10 scale was 3.3 for all infants. p<0.001. (Calculations derived from Table 5 in paper)	Inconclusive (low quality)
Parent-child relations : Overall strength of evidence MODERATE			
Neu 2014 * [35] (High)	N = 43 Age: 4-12 weeks	Effect Size (ES) massage group relative to the non-massage group for Sensitivity to Cues, Social-Emotional Growth Fostering, Cognitive Growth and Fostering (0.24 to 0.56 - small to moderate. Not significant) Response to Distress (ES -0.18) in unintended direction (not significant)	Inconclusive: Non-significant favourable effects in the treatment group
Hayden 2006 [33]* (Moderate)	N = 28 Age: 10-83 days	The mean difference in contact time between week 1 and 4 for the treated group was 1.3hr (p<0.015) and 2 hrs for the control group.	Significant favourable effects with less contact time required for the treated group, compared to control.
Miller 2012b [46] (Low)	N = 158 Age: mean 5-6.7 weeks	Mean change reported by parents on 1-10 scale was 3.6. p<0.001. (Calculations derived from Table 5 in paper)	Inconclusive (low quality)
Global improvement / resolution of symptoms: Overall strength of evidence MODERATE			
Miller 2012a [34]* (High)	N = 104 Age: < 8 weeks	Treatment Group Blinded vs Non-blinded treatment group (Adjusted Odds Ratios [95% CI), 44.3 (7.7-253).	Significant favourable effect in change with treatment
Browning 2008 [32]* (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms in 18/22 infants in the SMT group and in 14/21 in the OSD group as perceived by the parent, (rate ratio of 1.23 (95% CI 0.86—1.76). Infants treated with	No difference between groups, both treatment groups improved

		SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	
Davies 2007 [39] (Moderate)	N = 52 Age: Median 7 weeks	45 of 52 improved. 1 in 4 infants required only 1 adjustment. (treating chiropractor reported data)	Inconclusive: Favourable descriptive statistics only. No control group.
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	69.9% of Treatment groups vs 60% Control showed some degree of improvement) (Fisher's exact test, p=0.374).	No difference between groups, both treatment groups improved
Elster 2009 [40] (Low)	N = 16 Age: 2 weeks - 11 months	9/9 patients were reported as symptom free after chiropractic treatment. 7/7 patients were symptom free after chiropractic treatment. (chiropractor reported)	Inconclusive (low quality)
Resolution of gastric symptoms: Overall strength of evidence LOW			
Elster 2009 [40] (Low)	N = 16 Age: 2 weeks -11 months	9/9 patients were reported as symptom free after chiropractic treatment. (chiropractor reported)	Inconclusive (low quality)
Maternal satisfaction: Overall strength of evidence LOW			
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks.	98% (n=83) planned to continue breastfeeding their baby, and would recommend the clinic to friends.	Inconclusive: Favourable descriptive statistics only. No control group.
Nipple pain: Overall strength of evidence LOW			
Herzhaft-Le Roy 2017 [38] * (High)	N = 97 Age: mean 15 days	VAS mean scores over time (p = .713). No statistical difference between groups.	No difference between groups.
Temper tantrum frequency: Overall strength of evidence LOW			
Miller 2009a [47] (Low)	N = 117 Age: <12 weeks	Treatment group twice as likely to fall into the never or rarely group for frequency of temper tantrums) RR for temper tantrums 2.0 (CI 95% 1.3-3.0).	Significant difference favouring treatment.
Improvement in headache associated behaviours: Overall strength of evidence LOW			
Marchand 2009 [41] (Low)	N = 13 Age: 2 days to 8.5 months	Headache improved or resolved after chiropractic treatment 100%. (chiropractor reported)	Inconclusive (low quality)
Adverse events			
Miller 2008 [43]	N = 697	7/697 of those attending treatment at clinic reported adverse reactions to	Adverse events are minimal and

(Moderate)	Age: 75% <12weeks	treatment, 5 of these were treated for colic. Reactions reported mild, transient and no medical care required.	transient

*RCT

Meta-analysis

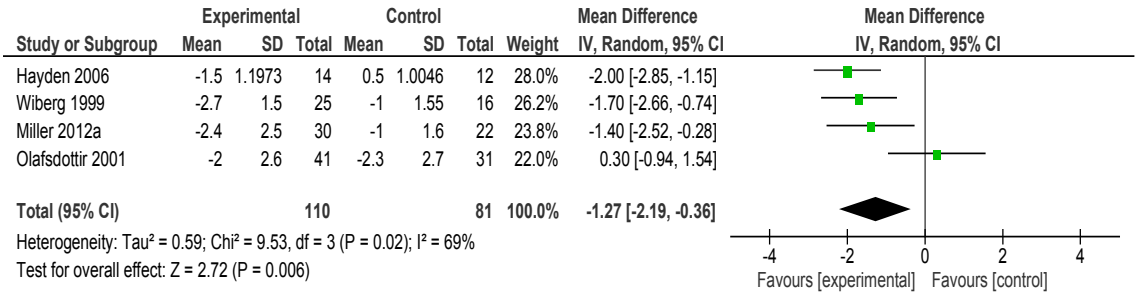
Meta-analysis was only possible for the RCTs with outcomes measuring reduction in crying time and for adverse events.

Meta-analyses for global improvement in symptoms, parent-child relations, sleeping time and feeding was not possible because: several studies did not have a 'no-treatment' control group [32, 39, 40, 42, 44, 48-50], did not present data at their primary endpoints [34, 36], did not collect enough data, or the data and outcomes were too heterogeneous.

Reduction in crying time

Seven studies reported data on crying time: [32-34, 36, 37, 45, 46]. There were sufficient data from four studies in the form of final value scores for the outcome of reduced crying time that could be meta-analysed for comparison of treatment effects. This replicated a previous meta-analysis [23]. Our replicated meta-analysis gave a slightly different but still significant outcome for reduced crying time of -1.27 (95% CI -2.19, -0.36) hours per day (Figure 2). The difference is due to apportioned weighting given by the different versions of REVMAN. One study [37] used dimethicone as a comparison, the other studies' controls were no treatment or placebo. We classified dimethicone as a placebo control (See Figure 2). Parents were blinded to their child's treatment in only two of studies included in the meta-analyses [34, 36].

Figure 2: Reduction in crying: RCTs mean difference



*Like Dobson et al 2012[23] we were unable to determine the standard deviations for the Olafsdottir 2001 data [36]. The Dobson review assigned the standard deviation of change scores based on the correlation coefficient of other, similar, studies, because personal correspondence was not successful with the author. We used the data from the Dobson 2012 review.

**Miller 2012a is the same study labelled Miller 2010 in the Dobson review which was a conference report in advance of the 20102 publication.

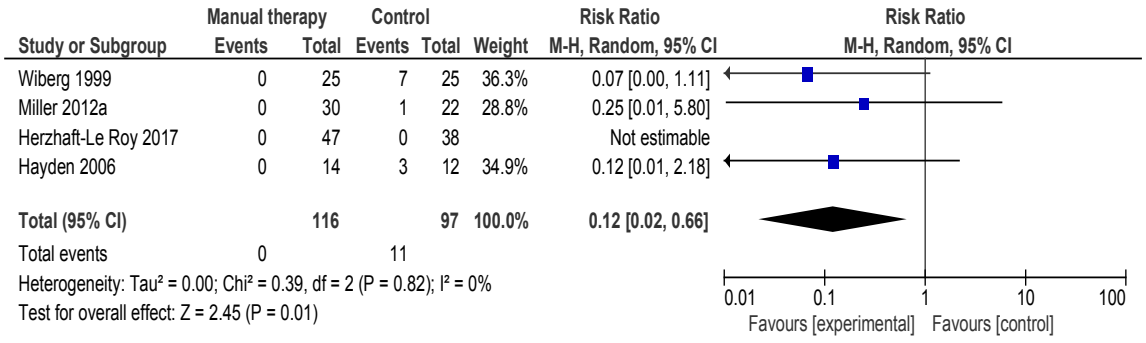
Adverse events

We were able to extract dichotomous data for adverse events and calculate RRs for meta-analysis. Of the nine studies that reported presence or absence of adverse events [33, 34, 37-39, 42, 43, 45], three studies reported there were no adverse events [38, 42, 45], two reported adverse events after manual therapy [39, 43] and three reported adverse events (worsening symptoms) in the control group [33, 34, 37].

Using data from all the studies reporting adverse events there were 1,308 infants exposed to manual therapy and nine non-serious adverse events recorded, giving an incidence rate of seven non serious events per 1,000 infants.

Figure 3 shows the meta-analysis for the RCTs, which was possible for four studies [33, 34, 37, 38]. There was an overall RR of 0.12 (95% CI: 0.12, 0.66), i.e. those who had manual therapy had 0.12 times the risk of having an adverse events compared to those who did not have manual therapy, i.e. a reduced risk (see Figure 3).

Figure 3: Adverse events meta-analysis: RCTs Relative Risk



Discussion

In this systematic review we searched for both RCT and non-RCT evidence. We found seven RCTs and 12 non-RCTs investigating the effects of manual therapy on healthy but unsettled, distressed and excessively crying infants treated in primary care.

Using the quantitative study designs we found moderate strength evidence for the effectiveness of manual therapy on reduction in crying time (favourable), sleep (inconclusive), parent-child relations (inconclusive) and global improvement (no effect).

Previous systematic reviews from 2012 and 2014 [23, 57] giving data specifically on this topic concluded there was favourable but inconclusive evidence for manual therapy for infantile colic. Since 2014, two new RCTs have been published: one pilot study RCT (n=18) [35] and one high quality RCT (n=97) [38] but neither presented new data on crying time for the meta-analysis. The Cochrane review by Dobson *et al* (2012) [23] included two studies that we excluded because they were not peer-reviewed: one a Masters thesis [58] and one from conference proceedings [59]. We repeated the Dobson *et al* sensitivity meta-analysis for peer-reviewed studies only, using Dobson's imputed standard deviation for one study [36]. The data extracted were the same but the meta-analysis results were slightly different due the different versions of REVMAN assigning different weights (we used REVMAN version 5.3 whilst Dobson *et al* used REVMAN 5.1) . Both showed a significant reduction in the weighted mean difference of just over one hour in daily crying time (-1.01 hours (95%CI -1.78, -0.24) [23] vs -1.27 hours (95%CI -2.19, -0.36). Using Brontfort et al's (2010) approach to overall evidence rating we classified one RCT as low risk of bias [34], two moderate risk [33, 36] and one high risk [37] which overall indicated a moderate level of evidence of

effectiveness for reduced crying time. Whether the reduction of around one hour of daily crying is meaningful to parents remains to be answered.

We anticipated that there would be more measurement of outcomes related to parent satisfaction and confidence or parent-child relations, but only five studies reported these outcomes [33, 35, 46, 49, 50]. This paucity of information about the reciprocity of parent-infant psychosocial development indicates a gap in the literature considering the importance of the parent-infant dyad in positive bonding [52] and the relationship between parent mood and psychosocial development of infants [53-56].

Results in context with other research

Our searches found 19 references to systematic reviews of manual therapy paediatric care. Most of these included conditions that were not the focus of our review, *e.g.,* otitis media, asthma, cerebral palsy, motor development. We noticed considerable overlap of studies included in these reviews. No new RCTs have been published in this field since 2012, therefore our review inevitably draws similar conclusions to the last review *i.e.* more high quality RCTs are needed, but methodological problems with research might preclude researchers taking on this challenge. The gold standard to test effectiveness is the RCT, but RCT designs have inherent problems. Double-blinding is not possible, one cannot blind the treating therapist and some parents are reluctant to blinding and being separated from their child. Other issues particular to allied, complementary and alternative therapies include: definitions of the condition and hence recruitment, describing the intervention and determining the active components of the intervention. These problems are further compounded by the self-limiting nature of many childhood conditions.

These methodological issues may help explain the equivocal findings, small numbers recruited and low quality assessments presented in systematic reviews.

It was anticipated that this review would present data about non-specific effects of treatment such as the impact on parental confidence, and the type of support given by clinicians and perceived by parents. There may be many reasons for non-specific improvements and these are difficult to assess as direct, indirect or completely independent of the study, for example, better subsequent parenting and parental bonding. In a study [36] using an attention control arm for the manual therapy component of their intervention, all infants and parents (unblinded) received the same support, advice and non-manual therapy care. They found no difference in outcomes between groups, and both groups improved over time. The authors of this study suggested that the counselling, support and natural progression of the condition played a more powerful role than the manual therapy.

It remains unclear what the active component of a manual therapy consultation and intervention is. It may be the psychological and self-management support given to parents by the clinician, or the hands-on therapy. It would be valuable to understand why parents seek manual therapy, despite the presence of other healthcare providers who provide similar support without the manual therapy component.

Safety

The safety data we extracted regarding adverse events indicated that manual therapy is a relatively low risk intervention, reflecting similar findings in other studies [24]. We did not find any prospective cohort studies specifically focused on adverse events in children.

Strengths and limitations

This was a comprehensive and rigorously conducted review that included studies in all languages, including a growing number of articles published from China, and all types of study designs. We acknowledged the value of non RCT evidence to inform this review.

Inclusion criteria were specific to our population of interest *i.e.* thriving infants who were inexplicably unsettled, distressed and excessively cried who were treated in primary care. This symptom-based approach permitted the inclusion of studies relating to various diagnoses, for example breastfeeding, gastric and behavioural problems. However, this latitude could also be interpreted as a weakness, since definitions of unsettledness, distress and excessive crying and otherwise healthy were not always clear. Perhaps a more stringent universally accepted definition of 'colic' is required. We may have failed to include some studies due to the authors' descriptions of their populations

Future research

Outcomes for parental satisfaction and confidence were under-researched and we did not find much data about these. Collecting parent outcomes may provide more informative data about the active components of care.

A well-powered RCT with parental blinding, blinded assessment of reported outcomes, testing both non-specific and manual therapy effects of manual therapist care is needed to supplement research in this area.

Conclusions

We found moderate favourable evidence for the reduction in crying time in infants receiving manual therapy care (around 1 hour per day), but this may change with further research evidence. For other outcomes the strength of evidence was low and inconclusive.

References

1. Don N, McMahon C, Rossiter C. Effectiveness of an individualized multidisciplinary programme for managing unsettled infants. *J Paediatr Child Health* 2002; 38(6):563-567.
2. Hiscock H, Jordan B. Problem crying in infancy. *Med J Aust* 2004; 181(9):507-512.
3. Johnson JD, Cocker K, Chang E: Infantile Colic: Recognition and Treatment. *Am Fam Physician* 2015; 92(7):577-582.
4. McCallum SM, Rowe HJ, Gurrin L, Quinlivan JA, Rosenthal DA, Fisher JR. Unsettled infant behaviour and health service use: a cross-sectional community survey in Melbourne, Australia. *J Paediatr Child Health* 2011; 47(11):818-823.
5. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child* 2001; 84(1):15-19.
6. Vik T, Grote V, Escribano J, Socha J, Verduci E, Fritsch M, Carlier C, von Kries R, Koletzko B. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatr* 2009; 98(8):1344-1348.
7. Overpeck MD, Brenner RA, Trumble AC, Trifiletti LB, Berendes HW. Risk factors for infant homicide in the United States. *N Engl J Med* 1998; 339(17):1211-1216.
8. Miller JJ, McVeagh P, Fleet GH, Petocz P, Brand JC. Breath hydrogen excretion in infants with colic. *Arch Dis Child* 1989; 64(5):725-729.
9. Rao MR, Brenner RA, Schisterman EF, Vik T, Mills JL. Long term cognitive development in children with prolonged crying. *Arch Dis Child* 2004; 89(11):989-992.
10. Stahlberg MR. Infantile colic: occurrence and risk factors. *Eur J Pediatr* 1984; 143(2):108-111.
11. Douglas PS, Hiscock H. The unsettled baby: crying out for an integrated, multidisciplinary primary care approach. *Med J Aust* 2010, 193(9):533-536.
12. Vandenplas Y, Koletzko S, Isolauri E, Hill D, Oranje AP, Brueton M, Staiano A, Dupont C. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Arch Dis Child* 2007; 92(10):902-908.
13. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet* 2001; 14(5):359-363.
14. Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J Pediatr* 1988; 113(6):979-984.
15. Chau K, Lau E, Greenberg S, Jacobson S, Yazdani-Brojeni P, Verma N, Koren G. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938. *J Pediatr* 2015; 166(1):74-78.
16. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, Roos S, Matteuzzi D. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. *Pediatrics* 2010; 126(3):e526-533.
17. Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML, Satzke C, Heine RG, Stock A, Barr RG, Wake M. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* 2014; 348:g2107.
18. Carey WB. "Colic"--primary excessive crying as an infant-environment interaction. *Pediatr Clin North Am* 1984; 31(5):993-1005.
19. Illingworth RS. Infantile colic revisited. *Arch Dis Child* 1985, 60(10):981-985.
20. Miller AR, Barr RG: Infantile colic. Is it a gut issue? *Pediatr Clin North Am* 1991; 38(6):1407-1423.

21. Dihigo SK. New strategies for the treatment of colic: modifying the parent/infant interaction. *J Pediatr Health Care* 1998; 12(5):256-262.
22. Wolke D, Gray P, Meyer R: Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics* 1994; 94(3):322-332.
23. Dobson D, Lucassen Peter LBJ, Miller Joyce J, Vlieger Arine M, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database of Systematic reviews.2012; 12. Art. No.: CD004796
24. Todd AJ, Carroll MT, Robinson A, Mitchell EK. Adverse Events Due to Chiropractic and Other Manual Therapies for Infants and Children: A Review of the Literature. *J Manipulative Physiol Ther* 2015; 38(9):699-712.
25. Wessel MA, Cobb JC, Jackson EB, Harris GS, Jr., Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954; 14(5):421-435.
26. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006; 130(5):1519-1526.
27. Software. Csr: Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org
28. Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. 2011.
29. CASP: Critical Appraisal Skills Programme (CASP) 2014. CASP Checklists (URL used) Oxford. CASP. 2014.
30. National Institutes of Health (NIH). Quality Assessment Tool for Case Series Studies. 2014. Available online at https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series.
31. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropractic & Osteopathy* 2010; 18(3):Epub.
32. Browning M, Miller J. Comparison of the short-term effects of chiropractic spinal manipulation and occipito-sacral decompression in the treatment of infant colic: A single-blinded, randomised, comparison trial. *Clin Chiropr* 2008; 11(3):122-129.
33. Hayden C, Mullinger B. A preliminary assessment of the impact of cranial osteopathy for the relief of infantile colic. Complementary Therapy in Clinical Practice. 2006; (12): 83-90.
34. Miller J, Newell N, Bolton J. Efficacy of manual therapy in infant colic: A pragmatic single-blind randomised controlled trial. J. of Manip. and Physiological Therapeutics 2012a; 35 (8): 600-607
35. Neu M, Schmiege SJ, Pan Z, Fehringer K, Workman R, Marcheggianni-Howard C, Furuta GT. Interactions during feeding with mothers and their infants with symptoms of gastroesophageal reflux. *Journal of Alternative & Complementary Medicine* 2014; 20(6):493-499.
36. Olafsdottir E, Forshei S, Fluge G, Markestad T. Randomised controlled trial of infantile colic treated with chiropractic spinal manipulation. *Archives of Disease in Childhood* 2001; 84(2):138-141.
37. Wiberg JM, Nordsteen J, Nilsson N. The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer. J. of Manip. and Physiological Therapeutics. 1999;22 (8); 1999: 517-522.
38. Herzhaft-Le Roy J, Xhignesse M. Efficacy of an Osteopathic Treatment Coupled With Lactation Consultations for Infants' Biomechanical Sucking Difficulties: A Randomized Controlled Trial. *Journal of Human Lactation* 2017; 33 (1):165-172.

39. Davies NJ, Jamison JR. Chiropractic management of irritable baby syndrome. *Chiropr J Aust* 2007; 37(1):25-29.
40. Elster E. Sixteen infants with acid reflux and colic undergoing upper cervical chiropractic care to correct vertebral subluxation: A retrospective analysis of outcome. *J Pediatr Matern & Fam Health - Chiropr* 2009;(2).
41. Marchand AM, Miller JE, Mitchell C. Diagnosis and chiropractic treatment of infant headache based on behavioral presentation and physical findings: a retrospective series of 13 cases. *J Manipulative Physiol Ther* 2009, 32(8):682-686.
42. Miller JE, Miller L, Sulesund AK, Yevtushenko A. Contribution of Chiropractic Therapy to Resolving Suboptimal Breastfeeding: A Case Series of 114 Infants. *Journal of Manipulative and Physiological Therapeutics* 2009b; 32(8):670-674.
43. Miller JEB, K. Adverse effects of spinal manipulative therapy in children younger than 3 years: a retrospective study in a chiropractic teaching clinic. *Journal of Manipulative & Physiological Therapeutics* 2008; 31(6):419-423.
44. Stewart A. Paediatric chiropractic and infant breastfeeding difficulties: A pilot case series study involving 19 cases. *Chiropr J Aust* 2012; 42(3):98-107.
45. Wiberg KR, Wiberg JM. A Retrospective Study of Chiropractic Treatment of 276 Danish Infants With Infantile Colic. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(7):536-541 536p.
46. Miller J, Newell D: Prognostic significance of subgroup classification for infant patients with crying disorders: A prospective cohort study. *J Can Chiropr Assoc* 2012b, 56(1):Online access only.
47. Miller JE, Phillips HL: Long-Term Effects of Infant Colic: A Survey Comparison of Chiropractic Treatment and Nontreatment Groups. *Journal of Manipulative and Physiological Therapeutics* 2009a; 32(8):635-638.
48. Vallone S. Chiropractic Evaluation and Treatment of Muskuloskeletal Dysfunction in Infants Demonstrating. *J Clin Chiro Pediatrics* 2004; 6(1):349-368.
49. Miller J, Beharie MC, Taylor AM, Simmenes EB, Way S. Parent Reports of Exclusive Breastfeeding After Attending a Combined Midwifery and Chiropractic Feeding Clinic in the United Kingdom: A Cross-Sectional Service Evaluation. *J Evid Based Complementary Altern Med* 2016; 21(2):85-91.
50. Cornall D. Promoting optimal breastfeeding through the osteopathic therapeutic cycle. 2015.PhD thesis. Victoria University, Australia.
51. Hu WQ. [Clinical observation on manipulation without syndrome differentiation in treating infantile diarrhea]. *Zhong Xi Yi Jie He Xue Bao/Journal of Chinese Integrative Medicine* 2004; 2(3):220-221.
52. Costa R, Figueiredo B. Infant's psychophysiological profile and temperament at 3 and 12 months. *Infant Behav Dev* 2011; 34(2):270-279.
53. Barr RG: Colic and crying syndromes in infants. *Pediatrics* 1998; 102(5 Suppl E):1282-1286.
54. Canivet CA, Ostergren PO, Rosen AS, Jakobsson IL, Hagander BM. Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. *Scand J Public Health* 2005; 33(1):26-34.
55. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ* 1993; 307(6904):600-604.
56. Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. *Pediatrics* 2001; 108(4):893-897.
57. Clar C, Tsertsvadze A, Court R, Hundt GL, Clarke A, Sutcliffe P: Clinical effectiveness of manual therapy for the management of musculoskeletal and non-

musculoskeletal conditions: systematic review and update of UK evidence report. *Chiropr Man Therap* 2014; 22(1):12.

58. Heber A, Senger U. [DIE OSTEOPATHISCHE BEHANDLUNGBEI3–MONATSKOLIK IM VERGLEICHZURKONVENTIONELLENTHERAPIE]. Osteopathic Treatment Of Infantile Colic *Masters thesis* 2003; Germany: Akademie für Osteopathie (AFO).
59. Mercer C. A Study to Determine the Efficacy of Chiropractic Spinal Adjustments as aTreatment Protocol in the Management of Infantile Colic. *Thesis* 1999, Durban, SA: Technikon Natal, Durban University.

Supplementary Appendix

Search strategy MEDLINE (Ovid). Searched on 20/3

1	Musculoskeletal Manipulations/	1113
2	Chiropractic/ or Manipulation, Chiropractic/	3748
3	Osteopathic Medicine/ or Manipulation, Osteopathic/	3458
4	Physical Therapy Modalities/ or Physical Therapy Specialty/	33016
5	osteopath*.tw.	4428
6	osteopathic medicine.tw.	447
7	manual therap*.tw.	1513
8	manual medic*.tw.	194
9	chiropract*.tw.	4817
10	physiotherap*.tw.	17644
11	physical therap*.tw.	15693
12	manipulat* therap*.tw.	864
13	OMT*.tw.	1048
14	Pediatrics/	45050
15	Child, Preschool/ or Infant/ or Infant, Newborn/	1367091
16	Infant, Premature/	44779
17	(pediatric* or paediatric*).tw.	247751
18	(baby* or babies or infant* or infancy).tw.	397831
19	(newborn or neonat* or preterm* or premature*).tw.	406003
20	pre-school*.tw.	3997
21	(toddler* or nursery school* or kindergar*).tw.	12720
22	preschool*.tw.	20817
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	66104
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1797322
25	23 and 24	5198
26	limit 25 to (humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)") and humans and (case reports or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or government publications or guideline or journal article or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews or validation studies))	**3788**
	Nb: adding "." to a two word phrase does not reduce the hits.	

Search strategy EMBASE searched 23/3

1	Musculoskeletal Manipulations/	9520
2	physiotherapy/	70,576
3	chiropractic/	4070
4	Manipulative medicine/	30
5	Osteopathic medicine/	69
6	osteopath*.ab.ti	6628
7	osteopathic medicine.ab.ti	551
8	manual therap*.ab.ti	2181
9	chiropract*.ab.ti	4837
10	Physiotherap*.ab.ti	34,098
11	manipulat* therap*.ab.ti	1012
12	Physical therapy:ab,ti	19,848
13	OMT.ti.ab	1729
14	Child/	1,518,179
15	Prematurity/	87,967
16	Newborn/	513,711
17	Preschool child/	332829
18	Pediatric*.ab.ti OR paediatric*.ab.ti	378,867
19	Baby*.ab.ti OR babies.ab.ti OR infant*:ab.ti OR infancy:ab.ti	543,298
20	Newborn*:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti	546,221
21	Toddler*:ab,ti OR nursery school:ab,ti or kindergar*:ab,ti	8760
22	Pre-school*:ab,ti	5996
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	108,853
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2,604,523
25	23 AND 24	11443
26	25 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim)	**1642**

Search strategy WOS searched 28/3

# 1	TS="manipulative therap*"	670
#2	TS="manual therap*"	1518
#3	TS="manual medic*"	158
#4	TS= (osteopath*)	2539
#5	TS="osteopathic medicine*"	274
#6	TS="musculoskeletal manipulat*"	117
#7	TS= (chiropract*)	3763
#8	TS= (physiotherap*)	15,228
#9	TS= ("physical therap*")	14,452
#10	TS=OMT	1006
#11	TS=(pediatric* OR paediatric*)	258,801
#12	TS=(baby* or babies or infant* or infancy)	389,506
#13	TS=(newborn* or neonat* or preterm* or premature*)	404,386
#14	TS=pre-school*	3780
#15	TS=preschool*	39,891
#16	TS=(toddler* OR "nursery school*" OR kindergar*)	20,504
#17	TS=child*	1,260,094
#18	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	35,258
#19	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11	1,867,978
#20	#18 AND #19 Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	3890
#21	(#20) *AND* DOCUMENT TYPES: (Article OR Abstract of Published Item OR Discussion OR Proceedings Paper OR Review) Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	**3603**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes P5-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes P1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes P6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes P7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes Supp file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes P7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes P8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes P8 Tables 1&2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes P8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes P8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Yes P8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes P8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes P10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes T1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes T1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes P20-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Yes P20-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes P20-21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes T2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes P25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes P26
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes P1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	4
Hypothesis statement	Yes	5
Description of Study Outcome(s)	Yes	7
Type of exposure or intervention used	Yes	7
Type of study design used	Yes	6
Study population	Yes	6
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	8
Search strategy, including time period included in the synthesis and keywords	Yes	7
Effort to include all available studies, including contact with authors	Yes	7
Databases and registries searched	Yes	7
Search software used, name and version, including special features used (eg, explosion)	Yes	8
Use of hand searching (eg, reference lists of obtained articles)	No	
List of citations located and those excluded, including justification	Yes	9
Method for addressing articles published in languages other than English	Yes	6
Method of handling abstracts and unpublished studies	Yes	7
Description of any contact with authors	No	
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8-9
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	8-9
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	8

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	9
Assessment of heterogeneity	Yes	21 &22
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	8-9
Provision of appropriate tables and graphics	Yes	11, 13-14, 16-2
Reporting of Results		
Table giving descriptive information for each study included	Yes	13-14
Results of sensitivity testing (eg, subgroup analysis)	No	
Indication of statistical uncertainty of findings	Yes	23
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	23
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	24
Assessment of quality of included studies	Yes	24
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	25
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	26
Guidelines for future research	Yes	26
Disclosure of funding source	Yes	1

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

BMJ Open

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019040.R1
Article Type:	Research
Date Submitted by the Author:	13-Oct-2017
Complete List of Authors:	Carnes, Dawn; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Plunkett, Austin ; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Ellwood, Julie; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, National Council for Osteoapthic Research, Centre for Primary Care and Public Health Miles, Clare; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Complementary medicine
Keywords:	manual therapy, PAEDIATRICS, 'colic', excessive crying, infants

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses.

Dawn Carnes[a,c], Austin Plunkett[a], Julie Ellwood[b], Clare Miles[a]

Affiliations:

[a] Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Centre for Primary Care and Public Health, London, UK

[b] National Council for Osteoapthic Research, London, UK

[c] Universtiy of Applied Sciences, Western Switzerland, Faculty of Health, Fribourg, Switzerland

Address correspondence to:

Dawn Carnes

Email: d.carnes@qmul.ac.uk,

Author contribution statement

Dawn Carnes conceptualised and designed the study, contributed to the data selection, extraction and analysis, drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript submitted.

Clare Miles managed the data, contributed to the data selection, extraction and did the meta-analyses, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Austin Plunkett contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Julie Ellwood contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

PROSPERO Registration Number: CRD42016037353

Funding: This research received no specific grant from any funding agency in the public, commercial or 'not-for-profit sectors.

This study was Crowd funded from public donations.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors, except Julie Ellwood, had

financial support from the National Council for Osteopathic Research from crowd funded donations for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing: Full datasets, analyses and all full searches are available on request from the corresponding author at d.carnes@qmul.ac.uk. No individual patient level data was used in this study.

Word count: 3984

Tables: 3

Figures: 3

Abstract

Objective: To conduct a systematic review and meta-analyses to assess the effect of manual therapy interventions for healthy but unsettled, distressed and excessively crying infants, to provide information to help clinicians and parents inform decisions about care.

Methods: We reviewed published peer-reviewed primary research articles in the last 26 years from 9 databases (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL). Our inclusion criteria were: manual therapy (by regulated or registered professionals) of unsettled, distressed and excessively crying babies or children who were otherwise healthy and treated in a primary care setting. Outcomes of interest were: crying, feeding, sleep, parent-child relations, parent experience/satisfaction and parent-reported global change.

Results: Nineteen studies were selected for full review: 7 randomised controlled trials, 7 case series, 3 cohort studies, 1 service evaluation study and 1 qualitative study.

We found moderate strength evidence for the effectiveness of manual therapy on: reduction in crying time (favourable: -1.27 hours per day (95% CI -2.19, -0.36)); sleep (inconclusive); parent-child relations (inconclusive); and global improvement (no effect). The risk of reported adverse events was low: 7 non-serious events per 1,000 infants exposed to manual therapy (n= 1308) and 110 per 1,000 in those not exposed.

Conclusions: Some small benefits were found but whether these are meaningful to parents remains unclear as does the mechanisms of action. Manual therapy appears relatively safe.

Word count 235

Strengths and limitations

Meaningful outcomes for parents with distressed, unsettled and excessively crying infants were investigated to help inform their decisions about seeking manual therapy care for their infants.

Compiling evidence for distressed unsettled and excessively crying infants based on multiple 'clinical diagnoses' using varied definitions is difficult.

The mechanism of action of complex interventions was not explained by the pragmatic research investigations used in this review.

Low to moderate quality studies limited the certainty of conclusions, suggesting they are liable to change with further research.

Introduction

Unsettled infant behaviour and colic are terms used to describe a range of behaviours in infants aged up to twelve months which include prolonged episodes of crying, difficulties with sleeping and/or feeding [1]. Reports suggest a prevalence of approximately twenty percent [2] and the incidence is equal between sexes [3]. The problems are found more commonly in first-borns and infants who have siblings who also had this condition [4-6]. High levels of multiple health service use have been found in the post-partum period, including visits to emergency departments [1, 4]. A cost burden analysis found that the annual cost to the UK National Health Service of infant crying and sleeping problems in the first twelve weeks of life was £65 million [5]. There are associations between unsettled infant behaviour and high maternal depression scores [6] and the natural crying peak at 6 weeks coincides with the peak age for severe infant injury or death as a result of child abuse [7].

Many aetiological factors for unsettled infant behaviour have been explored including diet, feeding and digestive issues [8, 9, 10, 11], musculoskeletal strains and disorders [12, 13,], developmental progress [14, 15, 16, 17] and parenting [18, 19, 20, 21, 22]. Despite extensive research, causative factors and effective treatment remain elusive.

Medicalising these symptoms is controversial as they are seen as self-limiting with infants normally settling after twelve weeks. However coping with these infants during this period can be very difficult.

Manual therapists offer a mix of health screening, education, advice, psychological support and touch therapy for these infants. Manual treatment is based upon the premise that infants may have musculoskeletal strains or limitations affecting comfort, feeding and gut motility causing distress. A previous Cochrane review (2012) of manual therapy and colic meta-analysed data from six randomised controlled trial (RCT) and found small positive (statistically significant) changes in crying time outcomes overall. However a sensitivity

analysis of data from only RCT studies where parents were blinded to treatment did not show beneficial effects [23]. Other analyses showed a small beneficial effect for sleep but not for 'recovery'. The studies included in this review were generally small and methodologically prone to bias, so definitive conclusions could not be drawn and effects were downgraded accordingly [23].

There are some concerns around the safety of manual techniques in the treatment of infants but published data of cases of serious adverse events are rare [24]. No reviews to our knowledge have explored qualitative research and non-specific effects such as parental confidence and satisfaction. In this review we aimed to update the Cochrane review [23] of RCTs for crying time and investigate non RCT studies and outcomes that are important to parents, rather than bio-medical markers alone that might be of more interest to primary researchers exploring aetiology, as our selected population was babies that were considered healthy.

METHOD

Types of studies

We included the following types of peer reviewed studies in our search: RCTs, prospective cohort studies, observational studies, case control studies, case series, questionnaire surveys, and qualitative studies. We excluded single case studies and non-peer reviewed literature (editorials, letters, Masters and undergraduate theses). Systematic reviews were identified to inform our research and for citation tracking. There were no language restrictions in our search criteria.

Types of participants

Participants were aged between 0-12 months (infants) when they received manual therapy treatment. They were healthy, thriving and not receiving other medical interventions. Their presenting symptoms were excessive crying, distress, and unsettledness: they might also be decribed as having colic, constipation, breastfeeding/feeding difficulties and, or gastroesophageal reflux/discomfort.

'Colic' was determined using the Wessel 'rule of three' [25] or Rome III [26] criteria. The latter considers infants to have colic if they were thriving and healthy, but had paroxysms of irritability, fussing or crying lasting for a total or more than three hours a day and occurring on more than three days a week for more than one week [26].

We excluded studies that included infants requiring treatment for conditions that needed specialist or hospital based clinical care for conditions such as: respiratory disorders, developmental disorders (learning and motor), cystic fibrosis, cerebral palsy, otitis media, neuralgia, congenital torticolis or musculoskeletal trauma. We also excluded studies about plagiocephaly or brachycephaly.

The intervention

We included studies where the manual therapy intervention was delivered in primary care by statutorily registered or regulated professional(s). This included osteopaths, chiropractors, physiotherapists and any other discipline using manual contact as the primary therapeutic component. The intervention or therapy had to involve physical and/or manual contact with the patient for therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aids/products/procedures. We excluded mixed or multidisciplinary interventions where the response to the manual therapy elements would have been unclear/undeterminable. Studies where the professional trained a non-professional to deliver the therapy or where parents delivered the therapy were excluded also.

Types of outcome measures

Outcomes of interest were unsettled behaviours, experience/satisfaction and global change scores. Unsettled behaviours included, for example, excessive crying, lack of sleep, displays of distress or discomfort (back arching, drawing up of legs) and difficulty feeding. Adverse events data were also collected.

Selection of articles

Nine electronic databases were searched from January 1990 to January 2017: the last 26 years (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL). We selected this timeframe because our scoping work revealed that most papers prior to January 1990 were theory driven position papers on the manual therapy care of infants and for pragmatic reasons in terms of access to full text original articles.

The main search string (modified for the different engines) is included in the electronic supplementary appendices. It included the key terms: musculoskeletal, manipulation, manual and physical therapy, physiotherapy, osteopathy and chiropratic with infant baby and new borns. We updated the search to end of January 2017 using Medline Ovid and search alerts

from EMBASE, Cochrane and WOS. We also located articles through peer networks. Four reviewers (the authors in two teams of two) reviewed the titles and abstracts, then the full texts independently. Where there was disagreement between the reviewers, a third reviewer from the other team arbitrated the final decision to select reject. Review articles retrieved in the search were citation-tracked to identify additional studies. Covidence software was used to organise and classify the articles [27]. See Figure 1 for a flowchart of the search process.

Quality appraisal of included studies

Two reviewers independently rated the quality of each included study (either CM/JE or DC/AP). We used the appropriate quality appraisal tools for each type of study design [28-30]. An overall quality score for each study was assigned by summing the number of quality criteria which were present. For RCTs: 6 risk of bias criteria were assessed [28] (5-6 quality criteria evaluated as present indicated low risk of bias = high quality, 3-4 = moderate quality and 1-2 = low quality). For cohorts: 11 quality criteria were assessed [29] (8-11 quality criteria evaluated as present = high quality, 4-7 = moderate quality, 0-3 = low quality). For case series: 9 quality criteria were assessed [30] (if 7-9 quality criteria were present = high quality, if 3-6 = moderate quality and 0-3 = low quality). For qualitative studies: 10 criteria were assessed [29] (if 8-10 quality criteria were present = high quality, 4-7 = moderate quality and 0-3 = low quality). All low quality cohort and case series studies were regarded as severely methodologically flawed and were not included in the final analyses.

Data extraction and synthesis

One reviewer extracted the data and another checked the data extractions (all authors).

Analyses

We aimed to meta-analyse data for RCTs and matched or paired cohort studies. For RCTs, we planned to extract final value scores for each group and convert them to standardised mean

differences (SMD) and weighted mean differences for comparison using a random effects model due to the expected differences in treatment protocols and effects between studies. Where there was a majority of either change or final value scores we planned sensitivity analysis to check 'consistency' / meaning of the meta-analyses. We planned to extract Risk Ratios (RR) for comparison of adverse events between treatment and control groups. I^2 was used to calculate heterogeneity. REVMAN software (version 5.3) was used to conduct the meta-analyses.

For non-RCTs studies, analyses proposed were descriptive and narrative but change scores and RRs were extracted where possible. If there were a sufficient number of qualitative studies, we proposed to organise and synthesise findings from the qualitative data, by identifying emergent themes and sub-themes.

Strength of evidence

We rated the strength of evidence across studies for each outcome, as either high, moderate or low, taking note of the quality and overall direction of results (inconclusive, favourable or unfavourable) [31]. Strength of evidence was considered as follows:

High: Consistent results from at least two high quality RCTs, or other well-designed studies, conducted in representative populations where the conclusion is unlikely to be strongly affected by future studies

Moderate: Available evidence from at least one higher quality RCT or two or more lower quality RCTs but constrained by: number, size, quality, inconsistency in findings and limited generalisability to clinical practice. The conclusions are likely to be affected by future studies.

Low: Evidence was insufficient with limitations in data provision, number, power, quality, inconsistency in results and findings not generalisable to clinical practice. All studies that were rated as low quality rated were treated as inconclusive regardless of author findings.

Two reviewers rated the quality and strength of evidence, and a consensus vote was used in cases of disagreement.

RESULTS

Search results

A total of 11,423 studies were retrieved. After duplicate removal, 8,844 remained. There were 8,638 references excluded by title and abstract predominantly because the population was not appropriate, for example, the children were too old and / or treatment settings were not primary care. We acquired full text for 206 references and 19 of these fulfilled our inclusion criteria. Reasons for exclusion are listed in Figure 1.

There were 19 primary studies included: seven RCTs [32-38], seven case series [39-45], three cohort studies [46-48], one service evaluation survey [49], and one qualitative study [50]. One other primary study was excluded due to translation difficulties of technical terms in chinese medicine [51]. All studies were published between January 1990 and January 2017. Countries represented across the studies were the UK [32-34, 41-43, 46, 47, 49], USA [35, 40, 48], Canada [38], Australia [39, 44, 50], Norway [36], Denmark [37, 45]. The following conditions were represented in the studies: colic (11 studies) [32-34, 36, 37, 39, 40, 43, 45-47]; gastroesophageal reflux (2 studies) [35, 40]; breastfeeding difficulties (5 studies) [38, 42, 44, 48, 49], and infant signs of distress (described as headache) (1 Study) [41]. With the exception of four studies, all used chiropractic intervention. The other four studies used massage therapy [35], and osteopathic intervention [33, 38, 49]. Eight studies used control groups [32, 33, 34, 35, 36, 38, 46, 47]. The controls varied across studies, from no physical treatment [33, 34, 36, 46, 47], to a sham treatment [35, 38] or drug [37]. See Table 1 for characteristics of included studies.

In the few cases where there was uncertainty with selection choice these were all resolved after discussion with a third reviewer.

1

Table 1. Characteristics, study design and quality rating of included studies.

Author/ year	Country of study	Participants reported condition	Type of study design and follow up period (FU)	Intervention	Outcomes reported	Quality appraisal
Browning 2008 [32]	UK	Colic	RCT (spinal manual therapy (SMT) vs occipital decompression (OSD) FU: 4 weeks post treatment.	Chiropractic	Sleep Resolution of symptoms	**High**
Hayden 2006 [33]	UK	Colic	RCT Osteopathic treatment vs no treatment FU: 4 weeks	Osteopathy	Parents involvement Sleep Crying	**Mod**
Herzhaft-Le Roy 2017 [38]	Canada	Breastfeeding difficulties	RCT Groups : Osteopathic treatment vs sham FU: over 10 days	Osteopathy + lactation consultant	Feeding Nipple pain Global improvement:	**High**
Miller 2012a [34]	UK	Colic	RCT: Treatment blinded (TB) vs treatment not blinded (TNB) vs no treatment blinded (NTB) FU: 10 days	Chiropractic	Crying Improved Global change	**High**
Neu 2014 [35]	USA	Gastro-oesophageal reflux	PILOT RCT: Massage vs no massage FU: 6 weeks	Massage therapy	Parent-child relations	**High**
Olafsdottir 2001 [36]	Norway	Colic	RCT: Chiropractic vs no treatment FU: over 8-14 days	Chiropractic	Crying hours Improvement of symptoms	**Mod**
Wiberg 1999 [37]	Denmark	Colic	RCT : Chiropractic vs dimethicone FU: between 8-11 days	Chiropractic	Daily hours of infantile colic	**Low**
Miller 2009a [47]	UK	Colic	Controlled Cohort study FU : Behaviour at 2-3 years of age	Chiropractic	Sleep Temper tantrums	**Low**
Miller 2012b [46]	UK	Colic	Prospective cohort study FU: End of treatment (duration, not reported)	Chiropractic	Consolability, Crying Personal stress, Sleep	**Low**
Miller 2016 [49]	UK	Breastfeeding difficulties	Service evaluation (survey) FU: 6-12 weeks after attending clinic	Chiropractic and midwife	Breastfeeding	**Mod**
Vallone 2004 [48]	USA	Breastfeeding difficulties	Cohort study: Infants with breastfeeding difficulties vs infants without difficulties FU: over 6-8 weeks	Chiropractic	Feeding	**Low**
Davies 2007	Australia	Irritable bowel	Case series	Chiropractic	Resolution of symptoms	**Mod**

[39]		syndrome (IBS)	FU: over 30 days			
Elster 2009 [40]	USA	Acid reflux and/or colic	Retrospective case series FU: over 2 weeks – 6 months	Chiropractic	Resolution of symptoms	**Low**
Marchand 2009 [41]	UK	'Headache' behaviours	Retrospective case series FU: none	Chiropractic	Improvement of Symptoms	**Low**
Miller 2008 [43]	UK	Colic	Retrospective case review FU: over 2 year period	Chiropractic	Adverse events	**Mod**
Miller 2009b [42]	UK	Breastfeeding difficulties	Prospective case series FU: within a 2 week period	Chiropractic	Improvement in feeding Number of treatments	**Mod**
Stewart 2012 [44]	Australia	Breastfeeding difficulties	Case review / Before and after study FU: at end of treatment (duration, not reported)	Chiropractic	Improvement feeding behaviour	**Low**
Wiberg 2010 [45]	Denmark	Colic	Retrospective review of clinical records FU: 11 years.	Chiropractic	Crying time	**Mod**
Cornall 2015 [50]	Australia	Breastfeeding difficulties	Qualitative study FU: none	Osteopathy	Observation regarding "the osteopathic therapeutic cycle".	**High**

2

Quality assessment

The methodological quality of the studies varied (Table 2). Five studies were rated as high quality: four RCTs (low risk of bias) [32, 34, 35, 38] and a qualitative study [50]. Seven were of moderate quality [33, 36, 39, 42, 43, 45, 49]. The remaining seven were rated as low quality due to severe methodological flaws (for example: small samples, the treating clinician observed and reported outcomes) [37, 39, 41, 44, 46, 47, 48] (Table 2). The non-RCT studies rated as low quality were excluded from further analyses.

Table 2. Quality appraisal of studies

	Neu 2014	Wiberg 1999	Hayden 2006	Miller 2012a	Olafsdottir 2001	Browning 2008	Herzalft-Le Roy 2017
RCTs*							
1. Sequence generation	L	L	L	L	U	L	L
2. Allocation concealment	L	U	U	L	L	U	L
3. Blinding of parents	L	H	H	L	L	L	L
4. Blinding of outcome assessors	L	L	H	L	L	L	L
5. Incomplete outcome data	L	H	L	H	U	L	L
6. Selective outcome reporting	L	U	L	L	U	L	H
Quality assessment	**High**	**Low**	**Mod**	**High**	**Mod**	**High**	**High**
Cohort Studies**	Vallone 2004	Miller 2009a	Miller 2012b	Miller 2016+			
1. Clear focused issue?	YES	YES	NO	YES			
2. Cohort recruitment acceptable?	CD	YES	CD	NO			
3. Exposure accurately measured?	NO	CD	NO	CD			
4. Outcome accurately measured?	NO	NO	NO	NO			
5a. Confounders identified?	NO	NO	CD	YES			
5b. Confounders considered appropriately?	NO	NO	NO	YES			
6a. Follow up complete enough?	CD	NO	CD	CD			
6b. Follow up long enough?	CD	YES	YES	CD			
9. Results believable?	NO	NO	CD	YES			
10. Results applicable?	NO	NO	CD	NO			
11. Results consistent with others?	CD	N/A	CD	YES			
Quality assessment	**Low**	**Low**	**Low**	**Mod**			
Case series***	Elster 2009	Miller 2009b	Stewart 2012	Miller & Benfield 2008	Wiberg 2010	Davies 2007	Marchand 2009
1. Question clearly stated?	YES	YES	NO	YES	YES	YES	YES
2. Population clearly described?	NO	YES	NO	YES	YES	YES	CD
3. Were cases consecutive?	CD	YES	CD	YES	YES	YES	CD
4. Were subjects comparable?	CD	YES	CD	YES	YES	YES	CD
5. Intervention clearly described?	NO	NO	NO	NO	NO	YES	NO
6. Outcomes consistent and appropriate across all participants?	NO	NO	NO	NO	NO	NO	NO
7. Follow-up adequate?	CD	CD	NO	CD	NO	CD	CD
8. Statistics described and appropriate?	NO	N/A	YES	YES	CD	N/A	N/A
9. Results clear?	NO	YES	NO	YES	NO	NO	NO
Quality assessment	**Low**	**Mod**	**Low**	**Mod**	**Mod**	**Mod**	**Low**
Qualitative studies**	Cornall 2015						
1. Clear research question?	YES						
2. Qual. Method appropriate?	YES						
3. Research design appropriate	YES						
4. Recruitment strategy appropriate?	YES						
5. Data collection appropriate?	YES						
6. Relationship between researchers and participants considered?	YES						

7. Ethics considered?	YES
8. Data analysis rigorous?	YES
9. Findings clear?	YES
10. Research valuable?	YES
Quality assessment	**High**

CD = can not determine * Cochrane Risk of bias tool (28) ** CASP checklist for cohort studies and qualitative studies (29) *** NIH Quality assessment tool for case series (30)

Review findings

Table 3 shows the results from studies reporting similar outcomes. Six studies reported outcomes related to improvement in feeding [38, 42, 44, 48-50], seven reported a reduction in crying time [32-34, 36, 37, 45, 46], five reported global improvement in symptoms [32, 34, 36, 39, 40], four reported sleep outcomes [32, 33, 38, 46] and three reported outcomes about parent – child relations [33,35,46]. The remaining outcomes were from one study only.

Table 3: Findings from included studies by similar outcomes

Author/year/ (Quality rating)	Participants, n and age	Outcomes and Findings /results (parent reported outcomes unless otherwise stated)	Magnitude or direction of effect: Moderate to high quality studies only
Reduction in crying : Overall strength of evidence MODERATE			
Miller 2012a [34] * (High)	N = 104 Age: < 8 weeks	Mean crying times all groups decreased by day 10, mean decrease was: Treatment blinded (TB) 44.4% (P < .001), Treatment not blinded (TNB) 51.2% (P < .001), and No treatment blinded (NTB) 18.6% (P < .05) 1) TB vs. NTB: using cut-off of 2 or less hours of crying per day and more than 30% change, respectively. Day 10: 12.0 (95% CI: 2.1-68) and 3 (95% CI: 0.8-9). 2) TB vs. NTB: Reduction -1.4 hours of mean crying time (95% CI: -2.5 to -0.3) at day 10 3) TB vs. TNB: No significant difference between blinded treatment groups Adjusted ORs, 0.7 [95% CI, 0.2-2.0] and 0.5 [95% CI, 0.1-1.6] at days 8 and 10, respectively).	Significant favourable effect in treatment group of -1.4 hours less hours of crying
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms (inc crying) in 18/22 infants in the spinal manual therapy (SMT) group and in 14/21 in the occipital decompression group (OSD) as perceived by the parent, (rate ratio of 1.23 (95% CI:0.86—1.76). Infants treated with SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	No difference between groups, both treatment groups improved. Head to head trial.
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a statistically significant difference between the 2 groups in the mean reduction in crying time of 1.0 (95% CI: 0.14, 2.19) hours/24 hr. Overall reduction in crying time from weeks 1-4 was 63% in the treatment compared to 23% in the control group.	Significant favourable effect in treatment group of 1 less hour of crying
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	There was no difference between those treated and not treated (student's t-test, p=0.982). A reduction in crying hours per day in both groups was seen during the study, from a mean of 5.1 to 3.1 hours per day in the treatment group and 5.4 to 3.1 hours in the control group.	No difference between groups, both treatment groups improved
Wiberg 2010 [45] (Moderate)	N = 276 Age: 0-3 months	No apparent link between the clinical effect of chiropractic treatment and a natural decline in crying was found.	No clinical difference between treatment and natural decline.
Wiberg 1999[37]* (Low)	N=45 Age: mean 5.4 weeks	There was a significantly larger reduction in colic symptoms from pre-treatment to days 8-11 in the manipulation group (-1.0 hr/day, +/- 0.4 SE) compared to the dimethicone group (-2.7 hr/day, +/-0.3 SE).	Inconclusive (low quality)

Sleeping time: Overall strength of evidence MODERATE			
Herzhaft-Le Roy 2017 [38]* (High)	N = 97 Age: mean 15 days	16.5% of mothers in the osteopathic treatment group, reported that their infants slept better, appeared soothed, or better enjoyed lying on their back, in the days that followed treatment.	Inconclusive: Favourable outcome but only reported in the treatment group
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At day 14, the mean hours of sleep per day were significantly increased in both groups (SMT, by 1.66 hr/day, p<0.01; OSD, by 1.03 hr day, p<0.01).	No difference between groups, both treatment groups improved
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a significant difference between treated and control groups: mean increase in sleeping time of 1.17 hrs/24hr more (95% CI: 0.29- 2.27) (p<0.05). Overall improvement in sleeping time by wk 4 was 11% for the treated group and less than 2% in the control group (mean % change).	Significant favourable effect in treatment group of 1 .17 hours of more sleeping
Parent-child relations : Overall strength of evidence MODERATE			
Neu 2014 * [35] (High)	N = 43 Age: 4-12 weeks	Effect Size (ES) massage group relative to the non-massage group for Sensitivity to Cues, Social-Emotional Growth Fostering, Cognitive Growth and Fostering (0.24 to 0.56 - small to moderate. Not significant) Response to Distress (ES -0.18) in unintended direction (not significant)	Inconclusive: Non-significant favourable effects in the treatment group
Hayden 2006 [33]* (Moderate)	N = 28 Age: 10-83 days	The mean difference in contact time between week 1 and 4 for the treated group was 1.3hr (p<0.015) and 2 hrs for the control group.	Significant favourable effects with less contact time required for the treated group, compared to control.
Global improvement / resolution of symptoms: Overall strength of evidence MODERATE			
Miller 2012a [34]* (High)	N = 104 Age: < 8 weeks	Treatment Group Blinded vs Non-blinded treatment group (Adjusted Odds Ratios [95% CI), 44.3 (7.7-253).	Significant favourable effect in change with treatment
Browning 2008 [32]* (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms in 18/22 infants in the SMT group and in 14/21 in the OSD group as perceived by the parent, (rate ratio of 1.23 (95% CI 0.86—1.76). Infants treated with SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	No difference between groups, both treatment groups improved
Davies 2007 [39] (Moderate)	N = 52 Age: Median 7 weeks	45 of 52 improved. 1 in 4 infants required only 1 adjustment. (treating chiropractor reported data)	Inconclusive: Favourable descriptive statistics only. No control group.
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	69.9% of Treatment groups vs 60% Control showed some degree of improvement) (Fisher's exact test, p=0.374).	No difference between groups, both treatment groups improved
Improvement in feeding : Overall Strength of Evidence LOW			

Herzhaft-Le Roy 2017* [38] (High)	N = 97 Age: mean 15 days	Ability to latch improved more in the treatment group (Time 3, mean score = 9.22, SD = 0.92) than in the control group (Time 3, mean score = 8.18, SD = 1.60); p = 0.001.	Significant favourable effect in those having osteopathic treatment
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks	7% (n = 5) reported no difference in feeding after attending the clinic. 86% reported exclusive breastfeeding at follow-up (compared to the 26% at start of the study). Relative RR of exclusive breastfeeding after attending the clinic was 3.6 (95% CI =2.4-5.4).	Significant favourable effect in those attending the clinic
Miller 2009b [42] (Moderate)	N = 114 Age: 2 days-12 weeks	All showed improvement. 78% (n=89) were able to be exclusively breastfed after 2-5 treatments, within a 2-week time period. 20% (n=23) required at least some bottle-feeding.	Inconclusive Descriptive statistics only. No control group. Favourable findings.
Cornall 2015 [50] (High)	N = 13 Mothers/ Osteopath dyads Age: mothers: median =32 years and newborns	Findings support optimal breastfeeding through a progressive, transitional cycle process, which is supported by four inter-related categories: i) connecting; ii) assimilating; iii) rebalancing; and iv) empowering. The findings outline contextual determinants that shaped women's views and experiences, osteopaths' professional identity and health care as a commodity.	Qualitative data affirming the need for a structured, yet creative and individualised approach to infant manual therapy, with the goal of helping the mother to achieve optimal breastfeeding.
Maternal satisfaction: Overall strength of evidence LOW			
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks.	98% (n=83) planned to continue breastfeeding their baby, and would recommend the clinic to friends.	Inconclusive: Favourable descriptive statistics only. No control group.
Nipple pain: Overall strength of evidence LOW			
Herzhaft-Le Roy 2017 [38] * (High)	N = 97 Age: mean 15 days	VAS mean scores over time (p = .713). No statistical difference between groups.	No difference between groups.
Adverse events			
Miller 2008 [43] (Moderate)	N = 697 Age: 75% <12weeks	7/697 of those attending treatment at clinic reported adverse reactions to treatment, 5 of these were treated for colic. Reactions reported were mild, transient and no medical care required.	Adverse events are minimal and transient

*RCT

Meta-analyses

A meta-analysis was only possible for the RCTs with outcomes measuring reduction in crying time and for adverse events.

Meta-analyses for global improvement in symptoms, parent-child relations, sleeping time and feeding were not possible because: several studies did not have a 'no-treatment' control group [32, 39, 40, 42, 44, 48-50], did not present data at their primary endpoints [34, 36], did not collect enough data, or the data and outcomes were too heterogeneous.

Reduction in crying time

Seven studies reported data on crying time: [32-34, 36, 37, 45, 46]. There were sufficient data from four studies in the form of final value scores for the outcome of reduced crying time that could be meta-analysed for comparison of treatment effects. This replicated a previous meta-analysis [23]. Our replicated meta-analysis (Figure 2) gave a slightly different but still significant outcome for reduced crying time of -1.27 (95% CI -2.19, -0.36) hours per day (Figure 2). The difference is due to apportioned weighting given by the different versions of REVMAN. One study [37] used dimethicone as a comparison, the other studies' controls were no treatment or placebo. We classified dimethicone as a placebo control (See Figure 2). Parents were blinded to their child's treatment in only two of the studies included in the meta-analysis [34, 36].

Adverse events

We were able to extract dichotomous data for adverse events and calculate RRs for meta-analysis (Figure 3). Of the eigth studies that reported presence or absence of adverse events [33, 34, 37-39, 42, 43, 45], three studies reported there were no adverse events [38, 42, 45], two reported adverse events after manual therapy [39, 43] and three reported adverse events (worsening symptoms) in the control group [33, 34, 37].

Using data from all the studies reporting adverse events there were 1,308 infants exposed to manual therapy and nine non-serious adverse events recorded, giving an incidence rate of seven non serious events per 1,000 infants. Conversely there were 11 non-serious adverse events in the infants not exposed to manual therapy (n= 97) giving an incidence rate of around 110 per 1,000 infants.

Figure 3 shows the meta-analysis for the RCTs, which was possible for four studies [33, 34, 37, 38]. There was an overall RR of 0.12 (95% CI: 0.12, 0.66), i.e. those who had manual therapy had an 88% reduced risk of having an adverse event compared to those who did not have manual therapy.

Discussion

In this systematic review we searched for both RCT and non-RCT evidence. We found seven RCTs and 12 non-RCTs investigating the effects of manual therapy on healthy but unsettled, distressed and excessively crying infants treated in primary care.

Using Brontfort *et al's* (2010) approach to overall evidence rating we found: moderate strength evidence for a small positive effective of manual therapy on reduction in crying time, inconclusive evidence for sleep and parent-child relations and no effects for global improvement (Table 3).

Previous systematic reviews from 2012 and 2014 [23, 52] concluded there was favourable but inconclusive and weak evidence for manual therapy for infantile colic. Since 2014, two new RCTs have been published: one pilot study RCT (n=18) [35] and one high quality RCT (n=97) [38] but neither presented new data on crying time for the meta-analysis. These two new RCTs blinded the parents to treatment but they reported outcomes on feeding and global

improvement and parent-child relations respectively. This meant we were unable to update the meta-analyses conducted by Dobson *et al* (2012).

We considered all methodological study types narratively and looked at: direction of effect, quality of the study and results presented (Table 3). However, because the low quality studies were so methodologically flawed we did not include their results in the final analyses (this indicates a need for more scientific rigour in this field of research). We were still able to review the effects of manual therapy on multiple outcomes in 12 of our 19 selected studies. With the exception of reduced crying time the findings were inconclusive and the absence of effect shown for global improvements might suggest that the reduction in crying time of just over one hour was not sufficient enough to be meaningful for parents.

We anticipated that there would be more measurement of outcomes related to parent satisfaction and confidence or parent-child relations, but only five studies reported these outcomes [33, 35, 46, 49, 50]. This paucity of information about the reciprocity of parent-infant psychosocial development indicates a gap in the literature considering the importance of the parent-infant dyad in positive bonding [53] and the relationship between parent mood and psychosocial development of infants [54-57].

Results in context with other research

The Cochrane review by Dobson *et al* (2012) [23] included two studies that we excluded because they were not peer-reviewed: one a Masters thesis [58] and one from conference proceedings [59]. We repeated the Dobson *et al* (2012) sensitivity meta-analysis for peer-reviewed studies only, using their imputed standard deviation for one study [36]. The data extracted were the same but the meta-analysis results were slightly different due the different versions of REVMAN assigning different weights (we used REVMAN version 5.3 whilst Dobson *et al* used REVMAN 5.1). Both showed a significant reduction in the weighted mean

difference of just over one hour in daily crying time (-1.01 hours (95% CI -1.78, -0.24) [23] vs -1.27 hours (95% CI -2.19, -0.36). As mentioned above whether this reduction of around one hour of daily crying is meaningful to parents remains to be answered.

The I^2 statistic in our meta-analysis and Dobson *et al* (2014) were 69% and 55% respectively, indicating heterogeneity between the studies analysed. This was not unexpected due to the potential variation in treatments (and hence effects), loose diagnostic criteria and power of the samples for the RCTs. Therefore the results have to be considered with this in mind and used to inform further research for well powered studies, flexible but protocolised treatment and parental blinding. Dobson *et al* (2012) conducted a sensitivity meta-analysis to explore parent blinding to their infant's treatment (Miller *et al* (2012) [34] and Olafsdottir *et al* (2001) [36]) and interestingly their results showed that there was no difference in crying time between groups with blinding.

Our searches also revealed 19 references to other systematic reviews of manual therapy paediatric care for conditions that were not the focus of our review, *e.g.,* otitis media, asthma, cerebral palsy and motor development. Our review draws similar conclusions to these other reviews *i.e.* more high quality RCTs are needed, but methodological problems with research in this field might preclude researchers taking on this challenge. The gold standard to test effectiveness is the RCT, but double-blinding is not possible (one cannot blind the treating therapist) and some parents are reluctant to blinding and being separated from their child. Other issues particular to allied, complementary and alternative therapies include: loose definitions and diagnostic criteria, describing and or protocolising interventions that are bespoke and determining the active elements of these multi-component interventions. These problems are further compounded by the self-limiting nature of many childhood conditions.

These methodological issues may help explain the equivocal findings, small numbers recruited and low quality assessments presented in systematic reviews.

Data about non-specific effects of treatment such as the impact of care on parental confidence, and clinician reassurance was not found, possibly because these are difficult to assess as direct, indirect or independent of the study intervention. In one study we reviewed [36] all infants and parents received the same support, advice and non-manual therapy care. They found no difference in outcomes between the group who had manual therapy in addition, and both groups improved over time. The authors of this study suggested that the counselling, support and natural progression of the condition played a more powerful role than the manual therapy.

It remains unclear what the active components of a manual therapy consultation are but we suggest that it would be valuable to understand why parents seek manual therapy care, despite the presence of other healthcare providers.

Safety

The safety data we extracted regarding adverse events indicated that manual therapy is a relatively low risk intervention, reflecting similar findings in other studies [24]. The definitions of adverse events recorded in the studies reviewed ranged from 'worsening symptoms' to seeking other forms of care: a comprehensive prospective cohort study specifically focused on adverse events in children is necessary to draw better conclusions.

Strengths and limitations

This was a comprehensive and rigorously conducted review that included studies in all languages, including a growing number of articles published from China (titles and abstracts were in English for indexing). There was one Chinese paper that was selected for full paper review. We translated this article but we were unable to fully interpret and understand the

treatment given and the outcomes which related to Chinese Traditional Medicine energy points [51]. In other words, the therapeutic paradigm presented was beyond our knowledge from a Western medicine perspective.

Inclusion criteria were specific to our population of interest *i.e.* thriving infants who were inexplicably unsettled, distressed and excessively crying who were treated in primary care. This symptom-based approach to selection permitted the inclusion of studies relating to various diagnoses, for example breastfeeding, gastric and behavioural problems. However, this latitude could also be interpreted as a weakness, since definitions of unsettledness, distress and excessive crying and otherwise healthy were not always clear. Perhaps a more stringent, universally accepted definition of 'colic' is required. We may have failed to include some studies due to the authors' descriptions of their populations.

Future research

Outcomes for parental satisfaction and confidence were under-researched and we did not find much data about these. Collecting parent outcomes may provide more informative data about the active components of care.

A well-powered RCT with: parental blinding, blinded assessment of reported outcomes, testing both non-specific and manual therapy effects of manual therapist care is needed to supplement research in this area.

Conclusions

We found moderate favourable evidence for the reduction in crying time in infants receiving manual therapy care (around one hour per day), but this may change with further research evidence. For other outcomes the strength of evidence was low and inconclusive.

Figure 1: Flowchart of search process for the review

Figure 2: Reduction in crying: RCTs mean difference

Footnote:

*Like Dobson et al 2012[23] we were unable to determine the standard deviations for the Olafsdottir2001 data [36]. The Dobson review assigned the standard deviation of change scores based on the correlation coefficient of other, similar, studies, because personal correspondence was not successful with the author. We used the data from the Dobson 2012 review.

**Miller 2012a is the same study labelled Miller 2010 in the Dobson review which was a conference report in advance of the 2012 publication

Figure 3: Adverse events meta-analysis: RCTs Relative Risk

References

1. Don N, McMahon C, Rossiter C. Effectiveness of an individualized multidisciplinary programme for managing unsettled infants. *J Paediatr Child Health* 2002; 38(6):563-567.
2. Hiscock H, Jordan B. Problem crying in infancy. *Med J Aust* 2004; 181(9):507-512.
3. Johnson JD, Cocker K, Chang E: Infantile Colic: Recognition and Treatment. *Am Fam Physician* 2015; 92(7):577-582.
4. McCallum SM, Rowe HJ, Gurrin L, Quinlivan JA, Rosenthal DA, Fisher JR. Unsettled infant behaviour and health service use: a cross-sectional community survey in Melbourne, Australia. *J Paediatr Child Health* 2011; 47(11):818-823.
5. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child* 2001; 84(1):15-19.
6. Vik T, Grote V, Escribano J, Socha J, Verduci E, Fritsch M, Carlier C, von Kries R, Koletzko B. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatr* 2009; 98(8):1344-1348.
7. Overpeck MD, Brenner RA, Trumble AC, Trifiletti LB, Berendes HW. Risk factors for infant homicide in the United States. *N Engl J Med* 1998; 339(17):1211-1216.
8. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J. Paediatr. Child health.2012; 48 (2): 128-37.
9. Miller J, Weber S. Is infant colic an allergic reaction to cow's milk: What is the evidence? J. Clin Chiro.Pediatr. 2013; 14(1) 1097-1102.
10. Sung V, CollettS, de Gooyer T et al. Probiotics to prevent or treat excessive infant crying: systematic review and meta-analysis. JAMA. 2013; 167(12):1150-1157
11. Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* 2014; 348:g2107.
12. Ernst E. Chiropractic spinal manipulation for infant colic: a systematic review of RCTs. Int. J. Clin. Prac. 2009; 63(9): 1351-1353
13. Langkau J, Miller J. An investigation of musculoskeletal dysfunction in infants includes a case series of KISS diagnosed children. J. Clin Chiro.Pediatr. 2012; 13(1) 958-967.
14. Rao MR, Brenner RA, Schisterman EF, Vik T, Mills JL. Long term cognitive development in children with prolonged crying. *Arch Dis Child* 2004; 89(11):989-992.
15. St James-Roberts I, Peachey E. Distinguishing infant prolonged crying from sleep-waking problems. Arch. Dis. Child. 2011; 96(4): 340-4.
16. Wolke D, Bilgin A, Samara M. Systematic review and meta-analyses: fussing and crying durations and prevalence of colic in infants. J.Pediatr. 2017; 185: 55-61
17. Barr R. Changing our understanding of infat colic (Editorial). Arch. Pediatr. Adolesc.Med. 2002; 156(12): 1172-1174
18. Douglas PS, Hiscock H. The unsettled baby: crying out for an integrated multidisciplinary primary care approach.
19. Talachian E, Bidari A, Rezaie MH. Incidence and risk factors for infantile colic in Iranian infants. World J. Gastroenterol. 2008; 14 (29): 4662-4666.
20. Kurth E, Spichager E, Cignacco E, Powell Kennedy H et al. Predictors of crying problems in the early postpartum period. JOGNN, 2010, 39: 250-262
21. Dihigo SK. New strategies for the treatment of colic: modifying the parent/infant interaction. *J Pediatr Health Care* 1998; 12(5):256-262.

22. Wolke D, Gray P, Meyer R: Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics* 1994; 94(3):322-332.
23. Dobson D, Lucassen Peter LBJ, Miller Joyce J, Vlieger Arine M, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database of Systematic reviews.2012; 12. Art. No.: CD004796
24. Todd AJ, Carroll MT, Robinson A, Mitchell EK. Adverse Events Due to Chiropractic and Other Manual Therapies for Infants and Children: A Review of the Literature. *J Manipulative Physiol Ther* 2015; 38(9):699-712.
25. Wessel MA, Cobb JC, Jackson EB, Harris GS, Jr., Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954; 14(5):421-435.
26. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006; 130(5):1519-1526.
27. Software. Csr: Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org
28. Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. 2011.
29. CASP: Critical Appraisal Skills Programme (CASP) 2014. CASP Checklists (URL used) Oxford. CASP. 2014.
30. National Institutes of Health (NIH). Quality Assessment Tool for Case Series Studies. 2014. Available online at https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series.
31. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropractic & Osteopathy* 2010; 18(3):Epub.
32. Browning M, Miller J. Comparison of the short-term effects of chiropractic spinal manipulation and occipito-sacral decompression in the treatment of infant colic: A single-blinded, randomised, comparison trial. *Clin Chiropr* 2008; 11(3):122-129.
33. Hayden C, Mullinger B. A preliminary assessment of the impact of cranial osteopathy for the relief of infantile colic. Complementary Therapy in Clinical Practice. 2006; (12): 83-90.
34. Miller J, Newell N, Bolton J. Efficacy of manual therapy in infant colic: A pragmatic single-blind randomised controlled trial. J. of Manip. and Physiological Therapeutics 2012a; 35 (8): 600-607
35. Neu M, Schmiege SJ, Pan Z, Fehringer K, Workman R, Marcheggianni-Howard C, Furuta GT. Interactions during feeding with mothers and their infants with symptoms of gastroesophageal reflux. *Journal of Alternative & Complementary Medicine* 2014; 20(6):493-499.
36. Olafsdottir E, Forshei S, Fluge G, Markestad T. Randomised controlled trial of infantile colic treated with chiropractic spinal manipulation. *Archives of Disease in Childhood* 2001; 84(2):138-141.
37. Wiberg JM, Nordsteen J, Nilsson N. The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer. J. of Manip. and Physiological Therapeutics. 1999;22 (8); 1999: 517-522.
38. Herzhaft-Le Roy J, Xhignesse M. Efficacy of an Osteopathic Treatment Coupled With Lactation Consultations for Infants' Biomechanical Sucking Difficulties: A Randomized Controlled Trial. *Journal of Human Lactation* 2017; 33 (1):165-172.
39. Davies NJ, Jamison JR. Chiropractic management of irritable baby syndrome. *Chiropr J Aust* 2007; 37(1):25-29.

40. Elster E. Sixteen infants with acid reflux and colic undergoing upper cervical chiropractic care to correct vertebral subluxation: A retrospective analysis of outcome. *J Pediatr Matern & Fam Health - Chiropr* 2009;(2).
41. Marchand AM, Miller JE, Mitchell C. Diagnosis and chiropractic treatment of infant headache based on behavioral presentation and physical findings: a retrospective series of 13 cases. *J Manipulative Physiol Ther* 2009, 32(8):682-686.
42. Miller JE, Miller L, Sulesund AK, Yevtushenko A. Contribution of Chiropractic Therapy to Resolving Suboptimal Breastfeeding: A Case Series of 114 Infants. *Journal of Manipulative and Physiological Therapeutics* 2009b; 32(8):670-674.
43. Miller JEB, K. Adverse effects of spinal manipulative therapy in children younger than 3 years: a retrospective study in a chiropractic teaching clinic. *Journal of Manipulative & Physiological Therapeutics* 2008; 31(6):419-423.
44. Stewart A. Paediatric chiropractic and infant breastfeeding difficulties: A pilot case series study involving 19 cases. *Chiropr J Aust* 2012; 42(3):98-107.
45. Wiberg KR, Wiberg JM. A Retrospective Study of Chiropractic Treatment of 276 Danish Infants With Infantile Colic. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(7):536-541 536p.
46. Miller J, Newell D: Prognostic significance of subgroup classification for infant patients with crying disorders: A prospective cohort study. *J Can Chiropr Assoc* 2012b, 56(1):Online access only.
47. Miller JE, Phillips HL: Long-Term Effects of Infant Colic: A Survey Comparison of Chiropractic Treatment and Nontreatment Groups. *Journal of Manipulative and Physiological Therapeutics* 2009a; 32(8):635-638.
48. Vallone S. Chiropractic Evaluation and Treatment of Muskuloskeletal Dysfunction in Infants Demonstrating. *J Clin Chiro Pediatrics* 2004; 6(1):349-368.
49. Miller J, Beharie MC, Taylor AM, Simmenes EB, Way S. Parent Reports of Exclusive Breastfeeding After Attending a Combined Midwifery and Chiropractic Feeding Clinic in the United Kingdom: A Cross-Sectional Service Evaluation. *J Evid Based Complementary Altern Med* 2016; 21(2):85-91.
50. Cornall D. Promoting optimal breastfeeding through the osteopathic therapeutic cycle. 2015.PhD thesis. Victoria University, Australia.
51. Hu WQ. [Clinical observation on manipulation without syndrome differentiation in treating infantile diarrhea]. *Zhong Xi Yi Jie He Xue Bao/Journal of Chinese Integrative Medicine* 2004; 2(3):220-221.
52 Clar C, Tsertsvadze A, Court R, Hundt GL, Clarke A, Sutcliffe P: Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: systematic review and update of UK evidence report. *Chiropr Man Therap* 2014; 22(1):12.
53. Costa R, Figueiredo B. Infant's psychophysiological profile and temperament at 3 and 12 months. *Infant Behav Dev* 2011; 34(2):270-279.
54. Barr RG: Colic and crying syndromes in infants. *Pediatrics* 1998; 102(5 Suppl E):1282-1286.
55. Canivet CA, Ostergren PO, Rosen AS, Jakobsson IL, Hagander BM. Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. *Scand J Public Health* 2005; 33(1):26-34.
56. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ* 1993; 307(6904):600-604.
57. Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. *Pediatrics* 2001; 108(4):893-897.

58. Heber A, Senger U. [DIE OSTEOPATHISCHE BEHANDLUNGBEI3–MONATSKOLIK IM VERGLEICHZURKONVENTIONELLENTHERAPIE]. Osteopathic Treatment Of Infantile Colic *Masters thesis* 2003; Germany: Akademie für Osteopathie (AFO).
59. Mercer C. A Study to Determine the Efficacy of Chiropractic Spinal Adjustments as aTreatment Protocol in the Management of Infantile Colic. *Thesis* 1999, Durban, SA: Technikon Natal, Durban University.

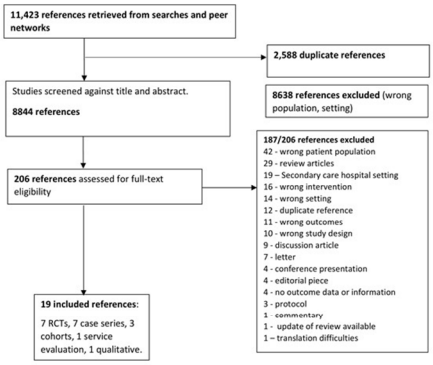


Figure 1: Flowchart of search process for the review

108x60mm (300 x 300 DPI)

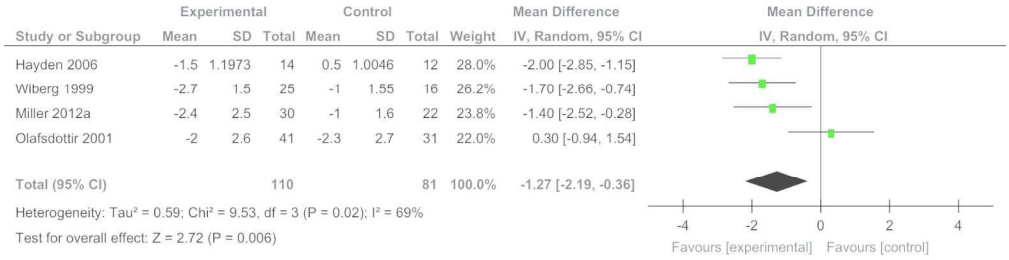


Figure 2: Reduction in crying: RCTs mean difference

184x49mm (300 x 300 DPI)

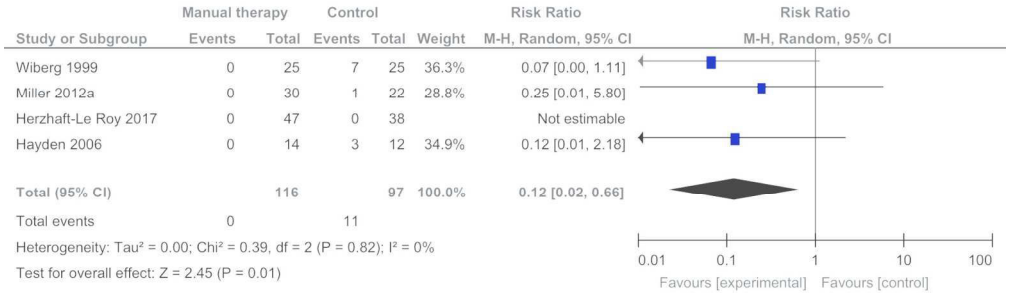


Figure 3: Adverse events meta-analysis: RCTs Relative Risk

184x54mm (300 x 300 DPI)

Supplementary Appendix

Search strategy MEDLINE (Ovid). Searched on 20/3

1	Musculoskeletal Manipulations/	1113
2	Chiropractic/ or Manipulation, Chiropractic/	3748
3	Osteopathic Medicine/ or Manipulation, Osteopathic/	3458
4	Physical Therapy Modalities/ or Physical Therapy Specialty/	33016
5	osteopath*.tw.	4428
6	osteopathic medicine.tw.	447
7	manual therap*.tw.	1513
8	manual medic*.tw.	194
9	chiropract*.tw.	4817
10	physiotherap*.tw.	17644
11	physical therap*.tw.	15693
12	manipulat* therap*.tw.	864
13	OMT*.tw.	1048
14	Pediatrics/	45050
15	Child, Preschool/ or Infant/ or Infant, Newborn/	1367091
16	Infant, Premature/	44779
17	(pediatric* or paediatric*).tw.	247751
18	(baby* or babies or infant* or infancy).tw.	397831
19	(newborn or neonat* or preterm* or premature*).tw.	406003
20	pre-school*.tw.	3997
21	(toddler* or nursery school* or kindergar*).tw.	12720
22	preschool*.tw.	20817
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	66104
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1797322
25	23 and 24	5198
26	limit 25 to (humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)") and humans and (case reports or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or government publications or guideline or journal article or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews or validation studies))	**3788**
	Nb: adding "." to a two word phrase does not reduce the hits.	

Search strategy EMBASE searched 23/3

1	Musculoskeletal Manipulations/	9520
2	physiotherapy/	70,576
3	chiropractic/	4070
4	Manipulative medicine/	30
5	Osteopathic medicine/	69
6	osteopath*.ab.ti	6628
7	osteopathic medicine.ab.ti	551
8	manual therap*.ab.ti	2181
9	chiropract*.ab.ti	4837
10	Physiotherap*.ab.ti	34,098
11	manipulat* therap*.ab.ti	1012
12	Physical therapy:ab,ti	19,848
13	OMT.ti.ab	1729
14	Child/	1,518,179
15	Prematurity/	87,967
16	Newborn/	513,711
17	Preschool child/	332829
18	Pediatric*.ab.ti OR paediatric*.ab.ti	378,867
19	Baby*.ab.ti OR babies.ab.ti OR infant*:ab.ti OR infancy:ab.ti	543,298
20	Newborn*:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti	546,221
21	Toddler*:ab,ti OR nursery school:ab,ti or kindergar*:ab,ti	8760
22	Pre-school*:ab,ti	5996
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	108,853
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2,604,523
25	23 AND 24	11443
26	25 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim)	**1642**

Search strategy WOS searched 28/3

# 1	TS="manipulative therap*"	670
#2	TS="manual therap*"	1518
#3	TS="manual medic*"	158
#4	TS= (osteopath*)	2539
#5	TS="osteopathic medicine*"	274
#6	TS="musculoskeletal manipulat*"	117
#7	TS= (chiropract*)	3763
#8	TS= (physiotherap*)	15,228
#9	TS= ("physical therap*")	14,452
#10	TS=OMT	1006
#11	TS=(pediatric* OR paediatric*)	258,801
#12	TS=(baby* or babies or infant* or infancy)	389,506
#13	TS=(newborn* or neonat* or preterm* or premature*)	404,386
#14	TS=pre-school*	3780
#15	TS=preschool*	39,891
#16	TS=(toddler* OR "nursery school*" OR kindergar*)	20,504
#17	TS=child*	1,260,094
#18	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	35,258
#19	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11	1,867,978
#20	#18 AND #19 Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	3890
#21	(#20) *AND* DOCUMENT TYPES: (Article OR Abstract of Published Item OR Discussion OR Proceedings Paper OR Review) Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	**3603**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes P5-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes P1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes P6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes P7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes Supp file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes P7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes P8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes P8 Tables 1&2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes P8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes P8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	Yes P8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes P8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes P10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes T1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes T1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes P20-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Yes P20-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes P20-21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes T2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes P25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes P26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes P1

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	4
Hypothesis statement	Yes	5
Description of Study Outcome(s)	Yes	7
Type of exposure or intervention used	Yes	7
Type of study design used	Yes	6
Study population	Yes	6
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	8
Search strategy, including time period included in the synthesis and keywords	Yes	7
Effort to include all available studies, including contact with authors	Yes	7
Databases and registries searched	Yes	7
Search software used, name and version, including special features used (eg, explosion)	Yes	8
Use of hand searching (eg, reference lists of obtained articles)	No	
List of citations located and those excluded, including justification	Yes	9
Method for addressing articles published in languages other than English	Yes	6
Method of handling abstracts and unpublished studies	Yes	7
Description of any contact with authors	No	
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8-9
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	8-9
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	8

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	9
Assessment of heterogeneity	Yes	21 &22
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	8-9
Provision of appropriate tables and graphics	Yes	11, 13-14, 16-2
Reporting of Results		
Table giving descriptive information for each study included	Yes	13-14
Results of sensitivity testing (eg, subgroup analysis)	No	
Indication of statistical uncertainty of findings	Yes	23
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	23
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	24
Assessment of quality of included studies	Yes	24
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	25
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	26
Guidelines for future research	Yes	26
Disclosure of funding source	Yes	1

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

BMJ Open

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019040.R2
Article Type:	Research
Date Submitted by the Author:	13-Nov-2017
Complete List of Authors:	Carnes, Dawn; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Plunkett, Austin ; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health Ellwood, Julie; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, National Council for Osteoapthic Research, Centre for Primary Care and Public Health Miles, Clare; Blizard Inst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Primary Care and Public Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Complementary medicine
Keywords:	manual therapy, PAEDIATRICS, 'colic', excessive crying, infants

Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses.

Dawn Carnes[a,c], Austin Plunkett[a], Julie Ellwood[b], Clare Miles[a]

Affiliations:

[a] Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Centre for Primary Care and Public Health, London, UK

[b] National Council for Osteoapthic Research, London, UK

[c] Universtiy of Applied Sciences, Western Switzerland, Faculty of Health, Fribourg, Switzerland

Address correspondence to:

Dawn Carnes

Email: d.carnes@qmul.ac.uk,

Author contribution statement

Dawn Carnes conceptualised and designed the study, contributed to the data selection, extraction and analysis, drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript submitted.

Clare Miles managed the data, contributed to the data selection, extraction and did the meta-analyses, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Austin Plunkett contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

Julie Ellwood contributed to the data selection and extraction, reviewed and revised drafts of the manuscript and approved the final manuscript submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

PROSPERO Registration Number: CRD42016037353

Funding: This research received no specific grant from any funding agency in the public, commercial or 'not-for-profit sectors.

This study was Crowd funded from public donations.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors, except Julie Ellwood, had

financial support from the National Council for Osteopathic Research from crowd funded donations for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing: Full datasets, analyses and all full searches are available on request from the corresponding author at d.carnes@qmul.ac.uk. No individual patient level data was used in this study.

Word count: 3984

Tables: 3

Figures: 3

Abstract

Objective: To conduct a systematic review and meta-analyses to assess the effect of manual therapy interventions for healthy but unsettled, distressed and excessively crying infants, to provide information to help clinicians and parents inform decisions about care.

Methods: We reviewed published peer-reviewed primary research articles in the last 26 years from 9 databases (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL). Our inclusion criteria were: manual therapy (by regulated or registered professionals) of unsettled, distressed and excessively crying babies or children who were otherwise healthy and treated in a primary care setting. Outcomes of interest were: crying, feeding, sleep, parent-child relations, parent experience/satisfaction and parent-reported global change.

Results: Nineteen studies were selected for full review: 7 randomised controlled trials, 7 case series, 3 cohort studies, 1 service evaluation study and 1 qualitative study.

We found moderate strength evidence for the effectiveness of manual therapy on: reduction in crying time (favourable: -1.27 hours per day (95% CI -2.19, -0.36)); sleep (inconclusive); parent-child relations (inconclusive); and global improvement (no effect). The risk of reported adverse events was low: 7 non-serious events per 1,000 infants exposed to manual therapy (n= 1308) and 110 per 1,000 in those not exposed.

Conclusions: Some small benefits were found but whether these are meaningful to parents remains unclear as does the mechanisms of action. Manual therapy appears relatively safe.

Word count 235

Strengths and limitations

Meaningful outcomes for parents with distressed, unsettled and excessively crying infants were investigated to help inform their decisions about seeking manual therapy care for their infants.

Compiling evidence for distressed unsettled and excessively crying infants based on multiple 'clinical diagnoses' using varied definitions is difficult.

The mechanism of action of complex interventions was not explained by the pragmatic research investigations used in this review.

Low to moderate quality studies limited the certainty of conclusions, suggesting they are liable to change with further research.

Introduction

Unsettled infant behaviour and colic are terms used to describe a range of behaviours in infants aged up to twelve months which include prolonged episodes of crying, difficulties with sleeping and/or feeding [1]. Reports suggest a prevalence of approximately twenty percent [2] and the incidence is equal between sexes [3]. The problems are found more commonly in first-borns and infants who have siblings who also had this condition [4-6]. High levels of multiple health service use have been found in the post-partum period, including visits to emergency departments [1, 4]. A cost burden analysis found that the annual cost to the UK National Health Service of infant crying and sleeping problems in the first twelve weeks of life was £65 million [5]. There are associations between unsettled infant behaviour and high maternal depression scores [6] and the natural crying peak at 6 weeks coincides with the peak age for severe infant injury or death as a result of child abuse [7].

Many aetiological factors for unsettled infant behaviour have been explored including diet, feeding and digestive issues [8, 9, 10, 11], musculoskeletal strains and disorders [12, 13,], developmental progress [14, 15, 16, 17] and parenting [18, 19, 20, 21, 22]. Despite extensive research, causative factors and effective treatment remain elusive.

Medicalising these symptoms is controversial as they are seen as self-limiting with infants normally settling after twelve weeks. However coping with these infants during this period can be very difficult.

Manual therapists offer a mix of health screening, education, advice, psychological support and touch therapy for these infants. Manual treatment is based upon the premise that infants may have musculoskeletal strains or limitations affecting comfort, feeding and gut motility causing distress. A previous Cochrane review (2012) of manual therapy and colic meta-analysed data from six randomised controlled trial (RCT) and found small positive (statistically significant) changes in crying time outcomes overall. However a sensitivity

analysis of data from only RCT studies where parents were blinded to treatment did not show beneficial effects [23]. Other analyses showed a small beneficial effect for sleep but not for 'recovery'. The studies included in this review were generally small and methodologically prone to bias, so definitive conclusions could not be drawn and effects were downgraded accordingly [23].

There are some concerns around the safety of manual techniques in the treatment of infants but published data of cases of serious adverse events are rare [24]. No reviews to our knowledge have explored qualitative research and non-specific effects such as parental confidence and satisfaction. In this review we aimed to update the Cochrane review [23] of RCTs for crying time and investigate non RCT studies and outcomes that are important to parents, rather than bio-medical markers alone that might be of more interest to primary researchers exploring aetiology, as our selected population was babies that were considered healthy.

METHOD

Types of studies

We included the following types of peer reviewed studies in our search: RCTs, prospective cohort studies, observational studies, case control studies, case series, questionnaire surveys, and qualitative studies. We excluded single case studies and non-peer reviewed literature (editorials, letters, Masters and undergraduate theses). Systematic reviews were identified to inform our research and for citation tracking. There were no language restrictions in our search criteria.

Types of participants

Participants were aged between 0-12 months (infants) when they received manual therapy treatment. They were healthy, thriving and not receiving other medical interventions. Their presenting symptoms were excessive crying, distress, and unsettledness: they might also be decribed as having colic, constipation, breastfeeding/feeding difficulties and, or gastroesophageal reflux/discomfort.

'Colic' was determined using the Wessel 'rule of three' [25] or Rome III [26] criteria. The latter considers infants to have colic if they were thriving and healthy, but had paroxysms of irritability, fussing or crying lasting for a total or more than three hours a day and occurring on more than three days a week for more than one week [26].

We excluded studies that included infants requiring treatment for conditions that needed specialist or hospital based clinical care for conditions such as: respiratory disorders, developmental disorders (learning and motor), cystic fibrosis, cerebral palsy, otitis media, neuralgia, congenital torticolis or musculoskeletal trauma. We also excluded studies about plagiocephaly or brachycephaly.

The intervention

We included studies where the manual therapy intervention was delivered in primary care by statutorily registered or regulated professional(s). This included osteopaths, chiropractors, physiotherapists and any other discipline using manual contact as the primary therapeutic component. The intervention or therapy had to involve physical and/or manual contact with the patient for therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aids/products/procedures. We excluded mixed or multidisciplinary interventions where the response to the manual therapy elements would have been unclear/undeterminable. Studies where the professional trained a non-professional to deliver the therapy or where parents delivered the therapy were excluded also.

Types of outcome measures

Outcomes of interest were unsettled behaviours, experience/satisfaction and global change scores. Unsettled behaviours included, for example, excessive crying, lack of sleep, displays of distress or discomfort (back arching, drawing up of legs) and difficulty feeding. Adverse events data were also collected.

Selection of articles

Nine electronic databases were searched from January 1990 to January 2017: the last 26 years (Medline OVID, EMBASE, WOS, PEDro, OSTMED.DR, Cochrane (all databases), Index of Chiropractic Literature, Open Access Theses and Dissertations (OATD), and CINAHL). We selected this timeframe because our scoping work revealed that most papers prior to January 1990 were theory driven position papers on the manual therapy care of infants and for pragmatic reasons in terms of access to full text original articles.

The main search string (modified for the different engines) is included in the electronic supplementary appendices. It included the key terms: musculoskeletal, manipulation, manual and physical therapy, physiotherapy, osteopathy and chiropratic with infant baby and new borns. We updated the search to end of January 2017 using Medline Ovid and search alerts

from EMBASE, Cochrane and WOS. We also located articles through peer networks. Four reviewers (the authors in two teams of two) reviewed the titles and abstracts, then the full texts independently. Where there was disagreement between the reviewers, a third reviewer from the other team arbitrated the final decision to select reject. Review articles retrieved in the search were citation-tracked to identify additional studies. Covidence software was used to organise and classify the articles [27]. See Figure 1 for a flowchart of the search process.

Quality appraisal of included studies

Two reviewers independently rated the quality of each included study (either CM/JE or DC/AP). We used the appropriate quality appraisal tools for each type of study design [28-30]. An overall quality score for each study was assigned by summing the number of quality criteria which were present. For RCTs: 6 risk of bias criteria were assessed [28] (5-6 quality criteria evaluated as present indicated low risk of bias = high quality, 3-4 = moderate quality and 1-2 = low quality). For cohorts: 11 quality criteria were assessed [29] (8-11 quality criteria evaluated as present = high quality, 4-7 = moderate quality, 0-3 = low quality). For case series: 9 quality criteria were assessed [30] (if 7-9 quality criteria were present = high quality, if 3-6 = moderate quality and 0-3 = low quality). For qualitative studies: 10 criteria were assessed [29] (if 8-10 quality criteria were present = high quality, 4-7 = moderate quality and 0-3 = low quality). All low quality cohort and case series studies were regarded as severely methodologically flawed and were not included in the final analyses.

Data extraction and synthesis

One reviewer extracted the data and another checked the data extractions (all authors).

Analyses

We aimed to meta-analyse data for RCTs and matched or paired cohort studies. For RCTs, we planned to extract final value scores for each group and convert them to standardised mean

differences (SMD) and weighted mean differences for comparison using a random effects model due to the expected differences in treatment protocols and effects between studies. Where there was a majority of either change or final value scores we planned sensitivity analysis to check 'consistency' / meaning of the meta-analyses. We planned to extract Risk Ratios (RR) for comparison of adverse events between treatment and control groups. I^2 was used to calculate heterogeneity. REVMAN software (version 5.3) was used to conduct the meta-analyses.

For non-RCTs studies, analyses proposed were descriptive and narrative but change scores and RRs were extracted where possible. If there were a sufficient number of qualitative studies, we proposed to organise and synthesise findings from the qualitative data, by identifying emergent themes and sub-themes.

Strength of evidence

We rated the strength of evidence across studies for each outcome, as either high, moderate or low, taking note of the quality and overall direction of results (inconclusive, favourable or unfavourable) [31]. Strength of evidence was considered as follows:

High: Consistent results from at least two high quality RCTs, or other well-designed studies, conducted in representative populations where the conclusion is unlikely to be strongly affected by future studies

Moderate: Available evidence from at least one higher quality RCT or two or more lower quality RCTs but constrained by: number, size, quality, inconsistency in findings and limited generalisability to clinical practice. The conclusions are likely to be affected by future studies.

Low: Evidence was insufficient with limitations in data provision, number, power, quality, inconsistency in results and findings not generalisable to clinical practice. All studies that were rated as low quality rated were treated as inconclusive regardless of author findings.

Two reviewers rated the quality and strength of evidence, and a consensus vote was used in cases of disagreement.

RESULTS

Search results

A total of 11,423 studies were retrieved. After duplicate removal, 8,844 remained. There were 8,638 references excluded by title and abstract predominantly because the population was not appropriate, for example, the children were too old and / or treatment settings were not primary care. We acquired full text for 206 references and 19 of these fulfilled our inclusion criteria. Reasons for exclusion are listed in Figure 1.

There were 19 primary studies included: seven RCTs [32-38], seven case series [39-45], three cohort studies [46-48], one service evaluation survey [49], and one qualitative study [50]. One other primary study was excluded due to translation difficulties of technical terms in chinese medicine [51]. All studies were published between January 1990 and January 2017. Countries represented across the studies were the UK [32-34, 41-43, 46, 47, 49], USA [35, 40, 48], Canada [38], Australia [39, 44, 50], Norway [36], Denmark [37, 45]. The following conditions were represented in the studies: colic (11 studies) [32-34, 36, 37, 39, 40, 43, 45-47]; gastroesophageal reflux (2 studies) [35, 40]; breastfeeding difficulties (5 studies) [38, 42, 44, 48, 49], and infant signs of distress (described as headache) (1 Study) [41]. With the exception of four studies, all used chiropractic intervention. The other four studies used massage therapy [35], and osteopathic intervention [33, 38, 49]. Eight studies used control groups [32, 33, 34, 35, 36, 38, 46, 47]. The controls varied across studies, from no physical treatment [33, 34, 36, 46, 47], to a sham treatment [35, 38] or drug [37]. See Table 1 for characteristics of included studies.

In the few cases where there was uncertainty with selection choice these were all resolved after discussion with a third reviewer.

1

Table 1. Characteristics, study design and quality rating of included studies.

Author/ year	Country of study	Participants reported condition	Type of study design and follow up period (FU)	Intervention	Outcomes reported	Quality appraisal
Browning 2008 [32]	UK	Colic	RCT (spinal manual therapy (SMT) vs occipital decompression (OSD) FU: 4 weeks post treatment.	Chiropractic	Sleep Resolution of symptoms	**High**
Hayden 2006 [33]	UK	Colic	RCT Osteopathic treatment vs no treatment FU: 4 weeks	Osteopathy	Parents involvement Sleep Crying	**Mod**
Herzhaft-Le Roy 2017 [38]	Canada	Breastfeeding difficulties	RCT Groups : Osteopathic treatment vs sham FU: over 10 days	Osteopathy + lactation consultant	Feeding Nipple pain Global improvement:	**High**
Miller 2012a [34]	UK	Colic	RCT: Treatment blinded (TB) vs treatment not blinded (TNB) vs no treatment blinded (NTB) FU: 10 days	Chiropractic	Crying Improved Global change	**High**
Neu 2014 [35]	USA	Gastro-oesophageal reflux	PILOT RCT: Massage vs no massage FU: 6 weeks	Massage therapy	Parent-child relations	**High**
Olafsdottir 2001 [36]	Norway	Colic	RCT: Chiropractic vs no treatment FU: over 8-14 days	Chiropractic	Crying hours Improvement of symptoms	**Mod**
Wiberg 1999 [37]	Denmark	Colic	RCT : Chiropractic vs dimethicone FU: between 8-11 days	Chiropractic	Daily hours of infantile colic	**Low**
Miller 2009a [47]	UK	Colic	Controlled Cohort study FU : Behaviour at 2-3 years of age	Chiropractic	Sleep Temper tantrums	**Low**
Miller 2012b [46]	UK	Colic	Prospective cohort study FU: End of treatment (duration, not reported)	Chiropractic	Consolability, Crying Personal stress, Sleep	**Low**
Miller 2016 [49]	UK	Breastfeeding difficulties	Service evaluation (survey) FU: 6-12 weeks after attending clinic	Chiropractic and midwife	Breastfeeding	**Mod**
Vallone 2004 [48]	USA	Breastfeeding difficulties	Cohort study: Infants with breastfeeding difficulties vs infants without difficulties FU: over 6-8 weeks	Chiropractic	Feeding	**Low**
Davies 2007	Australia	Irritable bowel	Case series	Chiropractic	Resolution of symptoms	**Mod**

[39]		syndrome (IBS)	FU: over 30 days			
Elster 2009 [40]	USA	Acid reflux and/or colic	Retrospective case series FU: over 2 weeks – 6 months	Chiropractic	Resolution of symptoms	**Low**
Marchand 2009 [41]	UK	'Headache' behaviours	Retrospective case series FU: none	Chiropractic	Improvement of Symptoms	**Low**
Miller 2008 [43]	UK	Colic	Retrospective case review FU: over 2 year period	Chiropractic	Adverse events	**Mod**
Miller 2009b [42]	UK	Breastfeeding difficulties	Prospective case series FU: within a 2 week period	Chiropractic	Improvement in feeding Number of treatments	**Mod**
Stewart 2012 [44]	Australia	Breastfeeding difficulties	Case review / Before and after study FU: at end of treatment (duration, not reported)	Chiropractic	Improvement feeding behaviour	**Low**
Wiberg 2010 [45]	Denmark	Colic	Retrospective review of clinical records FU: 11 years.	Chiropractic	Crying time	**Mod**
Cornall 2015 [50]	Australia	Breastfeeding difficulties	Qualitative study FU: none	Osteopathy	Observation regarding "the osteopathic therapeutic cycle".	**High**

2

Quality assessment

The methodological quality of the studies varied (Table 2). Five studies were rated as high quality: four RCTs (low risk of bias) [32, 34, 35, 38] and a qualitative study [50]. Seven were of moderate quality [33, 36, 39, 42, 43, 45, 49]. The remaining seven were rated as low quality due to severe methodological flaws (for example: small samples, the treating clinician observed and reported outcomes) [37, 39, 41, 44, 46, 47, 48] (Table 2). The non-RCT studies rated as low quality were excluded from further analyses.

Table 2. Quality appraisal of studies

	Neu 2014	Wiberg 1999	Hayden 2006	Miller 2012a	Olafsdottir 2001	Browning 2008	Herzalft-Le Roy 2017
RCTs*							
1. Sequence generation	L	L	L	L	U	L	L
2. Allocation concealment	L	U	U	L	L	U	L
3. Blinding of parents	L	H	H	L	L	L	L
4. Blinding of outcome assessors	L	L	H	L	L	L	L
5. Incomplete outcome data	L	H	L	H	U	L	L
6. Selective outcome reporting	L	U	L	L	U	L	H
Quality assessment	**High**	**Low**	**Mod**	**High**	**Mod**	**High**	**High**
Cohort Studies**	Vallone 2004	Miller 2009a	Miller 2012b	Miller 2016+			
1. Clear focused issue?	YES	YES	NO	YES			
2. Cohort recruitment acceptable?	CD	YES	CD	NO			
3. Exposure accurately measured?	NO	CD	NO	CD			
4. Outcome accurately measured?	NO	NO	NO	NO			
5a. Confounders identified?	NO	NO	CD	YES			
5b. Confounders considered appropriately?	NO	NO	NO	YES			
6a. Follow up complete enough?	CD	NO	CD	CD			
6b. Follow up long enough?	CD	YES	YES	CD			
9. Results believable?	NO	NO	CD	YES			
10. Results applicable?	NO	NO	CD	NO			
11. Results consistent with others?	CD	N/A	CD	YES			
Quality assessment	**Low**	**Low**	**Low**	**Mod**			
Case series***	Elster 2009	Miller 2009b	Stewart 2012	Miller & Benfield 2008	Wiberg 2010	Davies 2007	Marchand 2009
1. Question clearly stated?	YES	YES	NO	YES	YES	YES	YES
2. Population clearly described?	NO	YES	NO	YES	YES	YES	CD
3. Were cases consecutive?	CD	YES	CD	YES	YES	YES	CD
4. Were subjects comparable?	CD	YES	CD	YES	YES	YES	CD
5. Intervention clearly described?	NO	NO	NO	NO	NO	YES	NO
6. Outcomes consistent and appropriate across all participants?	NO	NO	NO	NO	NO	NO	NO
7. Follow-up adequate?	CD	CD	NO	CD	NO	CD	CD
8. Statistics described and appropriate?	NO	N/A	YES	YES	CD	N/A	N/A
9. Results clear?	NO	YES	NO	YES	NO	NO	NO
Quality assessment	**Low**	**Mod**	**Low**	**Mod**	**Mod**	**Mod**	**Low**
Qualitative studies**	Cornall 2015						
1. Clear research question?	YES						
2. Qual. Method appropriate?	YES						
3. Research design appropriate	YES						
4. Recruitment strategy appropriate?	YES						
5. Data collection appropriate?	YES						
6. Relationship between researchers and participants considered?	YES						

7. Ethics considered?	YES
8. Data analysis rigorous?	YES
9. Findings clear?	YES
10. Research valuable?	YES
Quality assessment	**High**

CD = can not determine * Cochrane Risk of bias tool (28) ** CASP checklist for cohort studies and qualitative studies (29) *** NIH Quality assessment tool for case series (30)

Review findings

Table 3 shows the results from studies reporting similar outcomes. Six studies reported outcomes related to improvement in feeding [38, 42, 44, 48-50], seven reported a reduction in crying time [32-34, 36, 37, 45, 46], five reported global improvement in symptoms [32, 34, 36, 39, 40], four reported sleep outcomes [32, 33, 38, 46] and three reported outcomes about parent – child relations [33,35,46]. The remaining outcomes were from one study only.

Table 3: Findings from included studies by similar outcomes

Author/year/ (Quality rating)	Participants, n and age	Outcomes and Findings /results (parent reported outcomes unless otherwise stated)	Magnitude or direction of effect: Moderate to high quality studies only
Reduction in crying : Overall strength of evidence MODERATE			
Miller 2012a [34] * (High)	N = 104 Age: < 8 weeks	Mean crying times all groups decreased by day 10, mean decrease was: Treatment blinded (TB) 44.4% (P < .001), Treatment not blinded (TNB) 51.2% (P < .001), and No treatment blinded (NTB) 18.6% (P < .05) 1) TB vs. NTB: using cut-off of 2 or less hours of crying per day and more than 30% change, respectively. Day 10: 12.0 (95% CI: 2.1-68) and 3 (95% CI: 0.8-9). 2) TB vs. NTB: Reduction -1.4 hours of mean crying time (95% CI: -2.5 to -0.3) at day 10 3) TB vs. TNB: No significant difference between blinded treatment groups Adjusted ORs, 0.7 [95% CI, 0.2-2.0] and 0.5 [95% CI, 0.1-1.6] at days 8 and 10, respectively).	Significant favourable effect in treatment group of -1.4 hours less hours of crying
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms (inc crying) in 18/22 infants in the spinal manual therapy (SMT) group and in 14/21 in the occipital decompression group (OSD) as perceived by the parent, (rate ratio of 1.23 (95% CI:0.86—1.76). Infants treated with SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	No difference between groups, both treatment groups improved. Head to head trial.
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a statistically significant difference between the 2 groups in the mean reduction in crying time of 1.0 (95% CI: 0.14, 2.19) hours/24 hr. Overall reduction in crying time from weeks 1-4 was 63% in the treatment compared to 23% in the control group.	Significant favourable effect in treatment group of 1 less hour of crying
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	There was no difference between those treated and not treated (student's t-test, p=0.982). A reduction in crying hours per day in both groups was seen during the study, from a mean of 5.1 to 3.1 hours per day in the treatment group and 5.4 to 3.1 hours in the control group.	No difference between groups, both treatment groups improved
Wiberg 2010 [45] (Moderate)	N = 276 Age: 0-3 months	No apparent link between the clinical effect of chiropractic treatment and a natural decline in crying was found.	No clinical difference between treatment and natural decline.
Wiberg 1999[37]* (Low)	N=45 Age: mean 5.4 weeks	There was a significantly larger reduction in colic symptoms from pre-treatment to days 8-11 in the manipulation group (-1.0 hr/day, +/- 0.4 SE) compared to the dimethicone group (-2.7 hr/day, +/-0.3 SE).	Inconclusive (low quality)

Sleeping time: Overall strength of evidence MODERATE			
Herzhaft-Le Roy 2017 [38]* (High)	N = 97 Age: mean 15 days	16.5% of mothers in the osteopathic treatment group, reported that their infants slept better, appeared soothed, or better enjoyed lying on their back, in the days that followed treatment.	Inconclusive: Favourable outcome but only reported in the treatment group
Browning 2008 [32] * (High)	N = 43 Age: <8 weeks	At day 14, the mean hours of sleep per day were significantly increased in both groups (SMT, by 1.66 hr/day, p<0.01; OSD, by 1.03 hr day, p<0.01).	No difference between groups, both treatment groups improved
Hayden 2006 [33] * (Moderate)	N = 28 Age: 10-83 days	There was a significant difference between treated and control groups: mean increase in sleeping time of 1.17 hrs/24hr more (95% CI: 0.29- 2.27) (p<0.05). Overall improvement in sleeping time by wk 4 was 11% for the treated group and less than 2% in the control group (mean % change).	Significant favourable effect in treatment group of 1 .17 hours of more sleeping
Parent-child relations : Overall strength of evidence MODERATE			
Neu 2014 * [35] (High)	N = 43 Age: 4-12 weeks	Effect Size (ES) massage group relative to the non-massage group for Sensitivity to Cues, Social-Emotional Growth Fostering, Cognitive Growth and Fostering (0.24 to 0.56 - small to moderate. Not significant) Response to Distress (ES -0.18) in unintended direction (not significant)	Inconclusive: Non-significant favourable effects in the treatment group
Hayden 2006 [33]* (Moderate)	N = 28 Age: 10-83 days	The mean difference in contact time between week 1 and 4 for the treated group was 1.3hr (p<0.015) and 2 hrs for the control group.	Significant favourable effects with less contact time required for the treated group, compared to control.
Global improvement / resolution of symptoms: Overall strength of evidence MODERATE			
Miller 2012a [34]* (High)	N = 104 Age: < 8 weeks	Treatment Group Blinded vs Non-blinded treatment group (Adjusted Odds Ratios [95% CI), 44.3 (7.7-253).	Significant favourable effect in change with treatment
Browning 2008 [32]* (High)	N = 43 Age: <8 weeks	At 4 weeks post-trial there was complete resolution of colic symptoms in 18/22 infants in the SMT group and in 14/21 in the OSD group as perceived by the parent, (rate ratio of 1.23 (95% CI 0.86—1.76). Infants treated with SMT were 20% more likely to resolve compared to infants treated with OSD. Not statistically significant.	No difference between groups, both treatment groups improved
Davies 2007 [39] (Moderate)	N = 52 Age: Median 7 weeks	45 of 52 improved. 1 in 4 infants required only 1 adjustment. (treating chiropractor reported data)	Inconclusive: Favourable descriptive statistics only. No control group.
Olafsdottir 2001 [36] * (Moderate)	N = 100 Age: 3-9 weeks	69.9% of Treatment groups vs 60% Control showed some degree of improvement) (Fisher's exact test, p=0.374).	No difference between groups, both treatment groups improved
Improvement in feeding : Overall Strength of Evidence LOW			

Herzhaft-Le Roy 2017* [38] (High)	N = 97 Age: mean 15 days	Ability to latch improved more in the treatment group (Time 3, mean score = 9.22, SD = 0.92) than in the control group (Time 3, mean score = 8.18, SD = 1.60); p = 0.001.	Significant favourable effect in those having osteopathic treatment
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks	7% (n = 5) reported no difference in feeding after attending the clinic. 86% reported exclusive breastfeeding at follow-up (compared to the 26% at start of the study). Relative RR of exclusive breastfeeding after attending the clinic was 3.6 (95% CI =2.4-5.4).	Significant favourable effect in those attending the clinic
Miller 2009b [42] (Moderate)	N = 114 Age: 2 days-12 weeks	All showed improvement. 78% (n=89) were able to be exclusively breastfed after 2-5 treatments, within a 2-week time period. 20% (n=23) required at least some bottle-feeding.	Inconclusive Descriptive statistics only. No control group. Favourable findings.
Cornall 2015 [50] (High)	N = 13 Mothers/ Osteopath dyads Age: mothers: median =32 years and newborns	Findings support optimal breastfeeding through a progressive, transitional cycle process, which is supported by four inter-related categories: i) connecting; ii) assimilating; iii) rebalancing; and iv) empowering. The findings outline contextual determinants that shaped women's views and experiences, osteopaths' professional identity and health care as a commodity.	Qualitative data affirming the need for a structured, yet creative and individualised approach to infant manual therapy, with the goal of helping the mother to achieve optimal breastfeeding.
Maternal satisfaction: Overall strength of evidence LOW			
Miller 2016 [49] (Moderate)	N = 85. Age: ≤ 4 weeks.	98% (n=83) planned to continue breastfeeding their baby, and would recommend the clinic to friends.	Inconclusive: Favourable descriptive statistics only. No control group.
Nipple pain: Overall strength of evidence LOW			
Herzhaft-Le Roy 2017 [38] * (High)	N = 97 Age: mean 15 days	VAS mean scores over time (p = .713). No statistical difference between groups.	No difference between groups.
Adverse events			
Miller 2008 [43] (Moderate)	N = 697 Age: 75% <12weeks	7/697 of those attending treatment at clinic reported adverse reactions to treatment, 5 of these were treated for colic. Reactions reported were mild, transient and no medical care required.	Adverse events are minimal and transient

*RCT

Meta-analyses

A meta-analysis was only possible for the RCTs with outcomes measuring reduction in crying time and for adverse events.

Meta-analyses for global improvement in symptoms, parent-child relations, sleeping time and feeding were not possible because: several studies did not have a 'no-treatment' control group [32, 39, 40, 42, 44, 48-50], did not present data at their primary endpoints [34, 36], did not collect enough data, or the data and outcomes were too heterogeneous.

Reduction in crying time

Seven studies reported data on crying time: [32-34, 36, 37, 45, 46]. There were sufficient data from four studies in the form of final value scores for the outcome of reduced crying time that could be meta-analysed for comparison of treatment effects. This replicated a previous meta-analysis [23]. Our replicated meta-analysis (Figure 2) gave a slightly different but still significant outcome for reduced crying time of -1.27 (95% CI -2.19, -0.36) hours per day (Figure 2). The difference is due to apportioned weighting given by the different versions of REVMAN. One study [37] used dimethicone as a comparison, the other studies' controls were no treatment or placebo. We classified dimethicone as a placebo control (See Figure 2). Parents were blinded to their child's treatment in only two of the studies included in the meta-analysis [34, 36].

Adverse events

We were able to extract dichotomous data for adverse events and calculate RRs for meta-analysis (Figure 3). Of the eigth studies that reported presence or absence of adverse events [33, 34, 37-39, 42, 43, 45], three studies reported there were no adverse events [38, 42, 45], two reported adverse events after manual therapy [39, 43] and three reported adverse events (worsening symptoms) in the control group [33, 34, 37].

Using data from all the studies reporting adverse events there were 1,308 infants exposed to manual therapy and nine non-serious adverse events recorded, giving an incidence rate of seven non serious events per 1,000 infants. Conversely there were 11 non-serious adverse events in the infants not exposed to manual therapy (n= 97) giving an incidence rate of around 110 per 1,000 infants.

Figure 3 shows the meta-analysis for the RCTs, which was possible for four studies [33, 34, 37, 38]. There was an overall RR of 0.12 (95% CI: 0.12, 0.66), i.e. those who had manual therapy had an 88% reduced risk of having an adverse event compared to those who did not have manual therapy.

Discussion

In this systematic review we searched for both RCT and non-RCT evidence. We found seven RCTs and 12 non-RCTs investigating the effects of manual therapy on healthy but unsettled, distressed and excessively crying infants treated in primary care.

Using Brontfort *et al's* (2010) approach to overall evidence rating we found: moderate strength evidence for a small positive effective of manual therapy on reduction in crying time, inconclusive evidence for sleep and parent-child relations and no effects for global improvement (Table 3).

Previous systematic reviews from 2012 and 2014 [23, 52] concluded there was favourable but inconclusive and weak evidence for manual therapy for infantile colic. Since 2014, two new RCTs have been published: one pilot study RCT (n=18) [35] and one high quality RCT (n=97) [38] but neither presented new data on crying time for the meta-analysis. These two new RCTs blinded the parents to treatment but they reported outcomes on feeding and global

improvement and parent-child relations respectively. This meant we were unable to update the meta-analyses conducted by Dobson *et al* (2012).

We considered all methodological study types narratively and looked at: direction of effect, quality of the study and results presented (Table 3). However, because the low quality studies were so methodologically flawed we did not include their results in the final analyses (this indicates a need for more scientific rigour in this field of research). We were still able to review the effects of manual therapy on multiple outcomes in 12 of our 19 selected studies. With the exception of reduced crying time the findings were inconclusive and the absence of effect shown for global improvements might suggest that the reduction in crying time of just over one hour was not sufficient enough to be meaningful for parents.

We anticipated that there would be more measurement of outcomes related to parent satisfaction and confidence or parent-child relations, but only five studies reported these outcomes [33, 35, 46, 49, 50]. This paucity of information about the reciprocity of parent-infant psychosocial development indicates a gap in the literature considering the importance of the parent-infant dyad in positive bonding [53] and the relationship between parent mood and psychosocial development of infants [54-57].

Results in context with other research

The Cochrane review by Dobson *et al* (2012) [23] included two studies that we excluded because they were not peer-reviewed: one a Masters thesis [58] and one from conference proceedings [59]. We repeated the Dobson *et al* (2012) sensitivity meta-analysis for peer-reviewed studies only, using their imputed standard deviation for one study [36]. The data extracted were the same but the meta-analysis results were slightly different due the different versions of REVMAN assigning different weights (we used REVMAN version 5.3 whilst Dobson *et al* used REVMAN 5.1). Both showed a significant reduction in the weighted mean

difference of just over one hour in daily crying time (-1.01 hours (95% CI -1.78, -0.24) [23] vs -1.27 hours (95% CI -2.19, -0.36). As mentioned above whether this reduction of around one hour of daily crying is meaningful to parents remains to be answered.

The I^2 statistic in our meta-analysis and Dobson et al's (2014) were 69% and 55% respectively, indicating heterogeneity between the studies analysed. This was not unexpected due to the potential variation in treatments (and hence effects), loose diagnostic criteria and the power of the samples for the RCTs. Therefore, the results have to be considered with caution and are likely to change with further research. The meta-analysis helps illustrate and indicate that future research in this field requires well powered studies, flexible but protocolised treatment and parental blinding.

Dobson *et al* (2012) conducted a sensitivity meta-analysis to explore parent blinding to their infant's treatment (Miller *et al* (2012) [34] and Olafsdottir *et al* (2001) [36]) and interestingly their results showed that there was no difference in crying time between groups with blinding.

Our searches also revealed 19 references to other systematic reviews of manual therapy paediatric care for conditions that were not the focus of our review, *e.g.,* otitis media, asthma, cerebral palsy and motor development. Our review draws similar conclusions to these other reviews *i.e.* more high quality RCTs are needed, but methodological problems with research in this field might preclude researchers taking on this challenge. The gold standard to test effectiveness is the RCT, but double-blinding is not possible (one cannot blind the treating therapist) and some parents are reluctant to blinding and being separated from their child. Other issues particular to allied, complementary and alternative therapies include: loose definitions and diagnostic criteria, describing and or protocolising interventions that are bespoke and determining the active elements of these multi-component interventions. These problems are further compounded by the self-limiting nature of many childhood conditions.

These methodological issues may help explain the equivocal findings, small numbers recruited and low quality assessments presented in systematic reviews.

Data about non-specific effects of treatment such as the impact of care on parental confidence, and clinician reassurance was not found, possibly because these are difficult to assess as direct, indirect or independent of the study intervention. In one study we reviewed [36] all infants and parents received the same support, advice and non-manual therapy care. They found no difference in outcomes between the group who had manual therapy in addition, and both groups improved over time. The authors of this study suggested that the counselling, support and natural progression of the condition played a more powerful role than the manual therapy.

It remains unclear what the active components of a manual therapy consultation are but we suggest that it would be valuable to understand why parents seek manual therapy care, despite the presence of other healthcare providers.

Safety

The safety data we extracted regarding adverse events indicated that manual therapy is a relatively low risk intervention, reflecting similar findings in other studies [24]. The definitions of adverse events recorded in the studies reviewed ranged from 'worsening symptoms' to seeking other forms of care: a comprehensive prospective cohort study specifically focused on adverse events in children is necessary to draw better conclusions.

Strengths and limitations

This was a comprehensive and rigorously conducted review that included studies in all languages, including a growing number of articles published from China (titles and abstracts were in English for indexing). There was one Chinese paper that was selected for full paper review. We translated this article but we were unable to fully interpret and understand the

treatment given and the outcomes which related to Chinese Traditional Medicine energy points [51]. In other words, the therapeutic paradigm presented was beyond our knowledge from a Western medicine perspective.

Inclusion criteria were specific to our population of interest *i.e.* thriving infants who were inexplicably unsettled, distressed and excessively crying who were treated in primary care. This symptom-based approach to selection permitted the inclusion of studies relating to various diagnoses, for example breastfeeding, gastric and behavioural problems. However, this latitude could also be interpreted as a weakness, since definitions of unsettledness, distress and excessive crying and otherwise healthy were not always clear. Perhaps a more stringent, universally accepted definition of 'colic' is required. We may have failed to include some studies due to the authors' descriptions of their populations.

Future research

Outcomes for parental satisfaction and confidence were under-researched and we did not find much data about these. Collecting parent outcomes may provide more informative data about the active components of care.

A well-powered RCT with: parental blinding, blinded assessment of reported outcomes, testing both non-specific and manual therapy effects of manual therapist care is needed to supplement research in this area.

Conclusions

We found moderate favourable evidence for the reduction in crying time in infants receiving manual therapy care (around one hour per day), but this may change with further research evidence. We still do not know if this result is meaningful to parents or if the reduction is due to the manual therapy component of care or other aspects of care. For other outcomes the strength of evidence was low and inconclusive.

Figure 1: Flowchart of search process for the review

Figure 2: Reduction in crying: RCTs mean difference

Footnote:

*Like Dobson et al 2012[23] we were unable to determine the standard deviations for the Olafsdottir2001 data [36]. The Dobson review assigned the standard deviation of change scores based on the correlation coefficient of other, similar, studies, because personal correspondence was not successful with the author. We used the data from the Dobson 2012 review.

**Miller 2012a is the same study labelled Miller 2010 in the Dobson review which was a conference report in advance of the 2012 publication

Figure 3: Adverse events meta-analysis: RCTs Relative Risk

References

1. Don N, McMahon C, Rossiter C. Effectiveness of an individualized multidisciplinary programme for managing unsettled infants. *J Paediatr Child Health* 2002; 38(6):563-567.
2. Hiscock H, Jordan B. Problem crying in infancy. *Med J Aust* 2004; 181(9):507-512.
3. Johnson JD, Cocker K, Chang E: Infantile Colic: Recognition and Treatment. *Am Fam Physician* 2015; 92(7):577-582.
4. McCallum SM, Rowe HJ, Gurrin L, Quinlivan JA, Rosenthal DA, Fisher JR. Unsettled infant behaviour and health service use: a cross-sectional community survey in Melbourne, Australia. *J Paediatr Child Health* 2011; 47(11):818-823.
5. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child* 2001; 84(1):15-19.
6. Vik T, Grote V, Escribano J, Socha J, Verduci E, Fritsch M, Carlier C, von Kries R, Koletzko B. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatr* 2009; 98(8):1344-1348.
7. Overpeck MD, Brenner RA, Trumble AC, Trifiletti LB, Berendes HW. Risk factors for infant homicide in the United States. *N Engl J Med* 1998; 339(17):1211-1216.
8. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J. Paediatr. Child health.2012; 48 (2): 128-37.
9. Miller J, Weber S. Is infant colic an allergic reaction to cow's milk: What is the evidence? J. Clin Chiro.Pediatr. 2013; 14(1) 1097-1102.
10. Sung V, CollettS, de Gooyer T et al. Probiotics to prevent or treat excessive infant crying: systematic review and meta-analysis. JAMA. 2013; 167(12):1150-1157
11. Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* 2014; 348:g2107.
12. Ernst E. Chiropractic spinal manipulation for infant colic: a systematic review of RCTs. Int. J. Clin. Prac. 2009; 63(9): 1351-1353
13. Langkau J, Miller J. An investigation of musculoskeletal dysfunction in infants includes a case series of KISS diagnosed children. J. Clin Chiro.Pediatr. 2012; 13(1) 958-967.
14. Rao MR, Brenner RA, Schisterman EF, Vik T, Mills JL. Long term cognitive development in children with prolonged crying. *Arch Dis Child* 2004; 89(11):989-992.
15. St James-Roberts I, Peachey E. Distinguishing infant prolonged crying from sleep-waking problems. Arch. Dis. Child. 2011; 96(4): 340-4.
16. Wolke D, Bilgin A, Samara M. Systematic review and meta-analyses: fussing and crying durations and prevalence of colic in infants. J.Pediatr. 2017; 185: 55-61
17. Barr R. Changing our understanding of infat colic (Editorial). Arch. Pediatr. Adolesc.Med. 2002; 156(12): 1172-1174
18. Douglas PS, Hiscock H. The unsettled baby: crying out for an integrated multidisciplinary primary care approach.
19. Talachian E, Bidari A, Rezaie MH. Incidence and risk factors for infantile colic in Iranian infants. World J. Gastroenterol. 2008; 14 (29): 4662-4666.
20. Kurth E, Spichager E, Cignacco E, Powell Kennedy H et al. Predictors of crying problems in the early postpartum period. JOGNN, 2010, 39: 250-262
21. Dihigo SK. New strategies for the treatment of colic: modifying the parent/infant interaction. *J Pediatr Health Care* 1998; 12(5):256-262.

22. Wolke D, Gray P, Meyer R: Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics* 1994; 94(3):322-332.
23. Dobson D, Lucassen Peter LBJ, Miller Joyce J, Vlieger Arine M, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database of Systematic reviews.2012; 12. Art. No.: CD004796
24. Todd AJ, Carroll MT, Robinson A, Mitchell EK. Adverse Events Due to Chiropractic and Other Manual Therapies for Infants and Children: A Review of the Literature. *J Manipulative Physiol Ther* 2015; 38(9):699-712.
25. Wessel MA, Cobb JC, Jackson EB, Harris GS, Jr., Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954; 14(5):421-435.
26. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006; 130(5):1519-1526.
27. Software. Csr: Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org
28. Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. 2011.
29. CASP: Critical Appraisal Skills Programme (CASP) 2014. CASP Checklists (URL used) Oxford. CASP. 2014.
30. National Institutes of Health (NIH). Quality Assessment Tool for Case Series Studies. 2014. Available online at https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series.
31. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. *Chiropractic & Osteopathy* 2010; 18(3):Epub.
32. Browning M, Miller J. Comparison of the short-term effects of chiropractic spinal manipulation and occipito-sacral decompression in the treatment of infant colic: A single-blinded, randomised, comparison trial. *Clin Chiropr* 2008; 11(3):122-129.
33. Hayden C, Mullinger B. A preliminary assessment of the impact of cranial osteopathy for the relief of infantile colic. Complementary Therapy in Clinical Practice. 2006; (12): 83-90.
34. Miller J, Newell N, Bolton J. Efficacy of manual therapy in infant colic: A pragmatic single-blind randomised controlled trial. J. of Manip. and Physiological Therapeutics 2012a; 35 (8): 600-607
35. Neu M, Schmiege SJ, Pan Z, Fehringer K, Workman R, Marcheggianni-Howard C, Furuta GT. Interactions during feeding with mothers and their infants with symptoms of gastroesophageal reflux. *Journal of Alternative & Complementary Medicine* 2014; 20(6):493-499.
36. Olafsdottir E, Forshei S, Fluge G, Markestad T. Randomised controlled trial of infantile colic treated with chiropractic spinal manipulation. *Archives of Disease in Childhood* 2001; 84(2):138-141.
37. Wiberg JM, Nordsteen J, Nilsson N. The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer. J. of Manip. and Physiological Therapeutics. 1999;22 (8); 1999: 517-522.
38. Herzhaft-Le Roy J, Xhignesse M. Efficacy of an Osteopathic Treatment Coupled With Lactation Consultations for Infants' Biomechanical Sucking Difficulties: A Randomized Controlled Trial. *Journal of Human Lactation* 2017; 33 (1):165-172.
39. Davies NJ, Jamison JR. Chiropractic management of irritable baby syndrome. *Chiropr J Aust* 2007; 37(1):25-29.

40. Elster E. Sixteen infants with acid reflux and colic undergoing upper cervical chiropractic care to correct vertebral subluxation: A retrospective analysis of outcome. *J Pediatr Matern & Fam Health - Chiropr* 2009;(2).
41. Marchand AM, Miller JE, Mitchell C. Diagnosis and chiropractic treatment of infant headache based on behavioral presentation and physical findings: a retrospective series of 13 cases. *J Manipulative Physiol Ther* 2009, 32(8):682-686.
42. Miller JE, Miller L, Sulesund AK, Yevtushenko A. Contribution of Chiropractic Therapy to Resolving Suboptimal Breastfeeding: A Case Series of 114 Infants. *Journal of Manipulative and Physiological Therapeutics* 2009b; 32(8):670-674.
43. Miller JEB, K. Adverse effects of spinal manipulative therapy in children younger than 3 years: a retrospective study in a chiropractic teaching clinic. *Journal of Manipulative & Physiological Therapeutics* 2008; 31(6):419-423.
44. Stewart A. Paediatric chiropractic and infant breastfeeding difficulties: A pilot case series study involving 19 cases. *Chiropr J Aust* 2012; 42(3):98-107.
45. Wiberg KR, Wiberg JM. A Retrospective Study of Chiropractic Treatment of 276 Danish Infants With Infantile Colic. *Journal of Manipulative & Physiological Therapeutics* 2010; 33(7):536-541 536p.
46. Miller J, Newell D: Prognostic significance of subgroup classification for infant patients with crying disorders: A prospective cohort study. *J Can Chiropr Assoc* 2012b, 56(1):Online access only.
47. Miller JE, Phillips HL: Long-Term Effects of Infant Colic: A Survey Comparison of Chiropractic Treatment and Nontreatment Groups. *Journal of Manipulative and Physiological Therapeutics* 2009a; 32(8):635-638.
48. Vallone S. Chiropractic Evaluation and Treatment of Muskuloskeletal Dysfunction in Infants Demonstrating. *J Clin Chiro Pediatrics* 2004; 6(1):349-368.
49. Miller J, Beharie MC, Taylor AM, Simmenes EB, Way S. Parent Reports of Exclusive Breastfeeding After Attending a Combined Midwifery and Chiropractic Feeding Clinic in the United Kingdom: A Cross-Sectional Service Evaluation. *J Evid Based Complementary Altern Med* 2016; 21(2):85-91.
50. Cornall D. Promoting optimal breastfeeding through the osteopathic therapeutic cycle. 2015.PhD thesis. Victoria University, Australia.
51. Hu WQ. [Clinical observation on manipulation without syndrome differentiation in treating infantile diarrhea]. *Zhong Xi Yi Jie He Xue Bao/Journal of Chinese Integrative Medicine* 2004; 2(3):220-221.
52 Clar C, Tsertsvadze A, Court R, Hundt GL, Clarke A, Sutcliffe P: Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: systematic review and update of UK evidence report. *Chiropr Man Therap* 2014; 22(1):12.
53. Costa R, Figueiredo B. Infant's psychophysiological profile and temperament at 3 and 12 months. *Infant Behav Dev* 2011; 34(2):270-279.
54. Barr RG: Colic and crying syndromes in infants. *Pediatrics* 1998; 102(5 Suppl E):1282-1286.
55. Canivet CA, Ostergren PO, Rosen AS, Jakobsson IL, Hagander BM. Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. *Scand J Public Health* 2005; 33(1):26-34.
56. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ* 1993; 307(6904):600-604.
57. Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. *Pediatrics* 2001; 108(4):893-897.

58. Heber A, Senger U. [DIE OSTEOPATHISCHE BEHANDLUNGBEI3–MONATSKOLIK IM VERGLEICHZURKONVENTIONELLENTHERAPIE]. Osteopathic Treatment Of Infantile Colic *Masters thesis* 2003; Germany: Akademie für Osteopathie (AFO).
59. Mercer C. A Study to Determine the Efficacy of Chiropractic Spinal Adjustments as aTreatment Protocol in the Management of Infantile Colic. *Thesis* 1999, Durban, SA: Technikon Natal, Durban University.

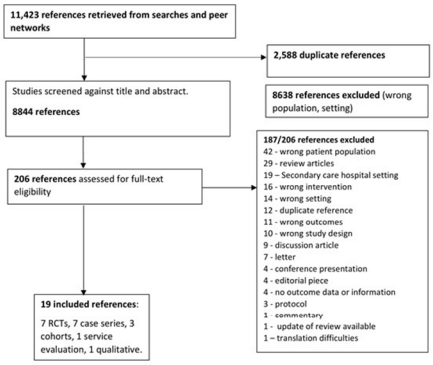


Figure 1: Flowchart of search process for the review

108x60mm (300 x 300 DPI)

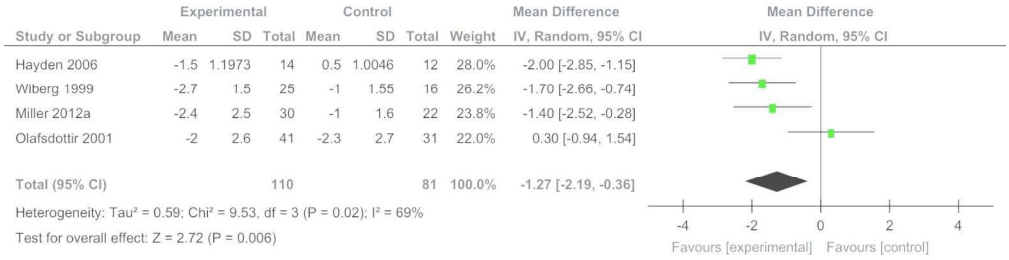


Figure 2: Reduction in crying: RCTs mean difference

184x49mm (300 x 300 DPI)

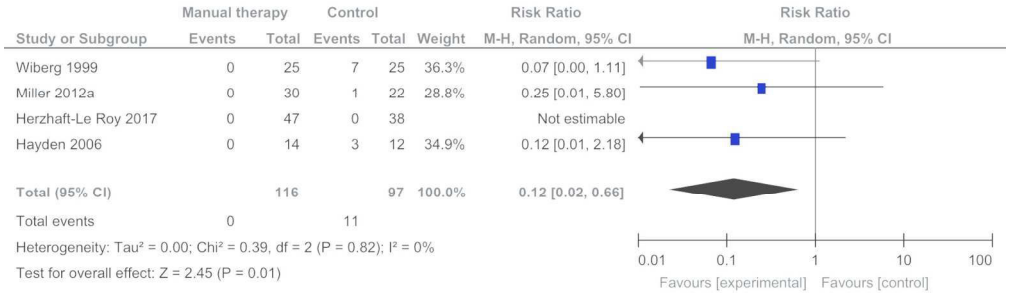


Figure 3: Adverse events meta-analysis: RCTs Relative Risk

184x54mm (300 x 300 DPI)

Supplementary Appendix

Search strategy MEDLINE (Ovid). Searched on 20/3

1	Musculoskeletal Manipulations/	1113
2	Chiropractic/ or Manipulation, Chiropractic/	3748
3	Osteopathic Medicine/ or Manipulation, Osteopathic/	3458
4	Physical Therapy Modalities/ or Physical Therapy Specialty/	33016
5	osteopath*.tw.	4428
6	osteopathic medicine.tw.	447
7	manual therap*.tw.	1513
8	manual medic*.tw.	194
9	chiropract*.tw.	4817
10	physiotherap*.tw.	17644
11	physical therap*.tw.	15693
12	manipulat* therap*.tw.	864
13	OMT*.tw.	1048
14	Pediatrics/	45050
15	Child, Preschool/ or Infant/ or Infant, Newborn/	1367091
16	Infant, Premature/	44779
17	(pediatric* or paediatric*).tw.	247751
18	(baby* or babies or infant* or infancy).tw.	397831
19	(newborn or neonat* or preterm* or premature*).tw.	406003
20	pre-school*.tw.	3997
21	(toddler* or nursery school* or kindergar*).tw.	12720
22	preschool*.tw.	20817
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	66104
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	1797322
25	23 and 24	5198
26	limit 25 to (humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)") and humans and (case reports or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or government publications or guideline or journal article or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews or validation studies))	**3788**
	Nb: adding "." to a two word phrase does not reduce the hits.	

Search strategy EMBASE searched 23/3

1	Musculoskeletal Manipulations/	9520
2	physiotherapy/	70,576
3	chiropractic/	4070
4	Manipulative medicine/	30
5	Osteopathic medicine/	69
6	osteopath*.ab.ti	6628
7	osteopathic medicine.ab.ti	551
8	manual therap*.ab.ti	2181
9	chiropract*.ab.ti	4837
10	Physiotherap*.ab.ti	34,098
11	manipulat* therap*.ab.ti	1012
12	Physical therapy:ab,ti	19,848
13	OMT.ti.ab	1729
14	Child/	1,518,179
15	Prematurity/	87,967
16	Newborn/	513,711
17	Preschool child/	332829
18	Pediatric*.ab.ti OR paediatric*.ab.ti	378,867
19	Baby*.ab.ti OR babies.ab.ti OR infant*:ab.ti OR infancy:ab.ti	543,298
20	Newborn*:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti	546,221
21	Toddler*:ab,ti OR nursery school:ab,ti or kindergar*:ab,ti	8760
22	Pre-school*:ab,ti	5996
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	108,853
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2,604,523
25	23 AND 24	11443
26	25 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim)	**1642**

Search strategy WOS searched 28/3

# 1	TS="manipulative therap*"	670
#2	TS="manual therap*"	1518
#3	TS="manual medic*"	158
#4	TS= (osteopath*)	2539
#5	TS="osteopathic medicine*"	274
#6	TS="musculoskeletal manipulat*"	117
#7	TS= (chiropract*)	3763
#8	TS= (physiotherap*)	15,228
#9	TS= ("physical therap*")	14,452
#10	TS=OMT	1006
#11	TS=(pediatric* OR paediatric*)	258,801
#12	TS=(baby* or babies or infant* or infancy)	389,506
#13	TS=(newborn* or neonat* or preterm* or premature*)	404,386
#14	TS=pre-school*	3780
#15	TS=preschool*	39,891
#16	TS=(toddler* OR "nursery school*" OR kindergar*)	20,504
#17	TS=child*	1,260,094
#18	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	35,258
#19	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11	1,867,978
#20	#18 AND #19 Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	3890
#21	(#20) *AND* DOCUMENT TYPES: (Article OR Abstract of Published Item OR Discussion OR Proceedings Paper OR Review) Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years	**3603**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes P4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes P5-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes P1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes P6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes P7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes Supp file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes P7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes P8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Yes P8 Tables 1&2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes P8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Yes P8

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	Yes P8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Yes P8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes P10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Yes T1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes T1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes P20-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Yes P20-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Yes P20-21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes T2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Yes P25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes P26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Yes P1

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	4
Hypothesis statement	Yes	5
Description of Study Outcome(s)	Yes	7
Type of exposure or intervention used	Yes	7
Type of study design used	Yes	6
Study population	Yes	6
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	8
Search strategy, including time period included in the synthesis and keywords	Yes	7
Effort to include all available studies, including contact with authors	Yes	7
Databases and registries searched	Yes	7
Search software used, name and version, including special features used (eg, explosion)	Yes	8
Use of hand searching (eg, reference lists of obtained articles)	No	
List of citations located and those excluded, including justification	Yes	9
Method for addressing articles published in languages other than English	Yes	6
Method of handling abstracts and unpublished studies	Yes	7
Description of any contact with authors	No	
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8-9
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	8-9
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	8

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	9
Assessment of heterogeneity	Yes	21 &22
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	8-9
Provision of appropriate tables and graphics	Yes	11, 13-14, 16-2
Reporting of Results		
Table giving descriptive information for each study included	Yes	13-14
Results of sensitivity testing (eg, subgroup analysis)	No	
Indication of statistical uncertainty of findings	Yes	23
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	23
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	24
Assessment of quality of included studies	Yes	24
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	25
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	26
Guidelines for future research	Yes	26
Disclosure of funding source	Yes	1

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.