

# Chuna manual therapy for the treatment of anorexia in children

## A PRISMA-compliant systematic review and meta-analysis

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### Abstract

**Background:** Anorexia in children can cause malnutrition, low immunity, growth retardation, and various secondary infections, resulting in a huge burden on society. In East Asia, Chuna manual therapy has been widely used for the treatment of childhood anorexia. We aimed to comprehensively evaluate the effects of Chuna manual therapy for treating childhood anorexia.

**Methods:** Twelve databases were comprehensively searched from their inception to September 13, 2022. Only randomized controlled trials assessing Chuna manual therapy for the treatment of childhood anorexia were included. The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool. The quality of evidence for each main outcome was evaluated using the grading of recommendations assessment, development, and evaluation approach. A meta-analysis was performed, and the pooled data were presented as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

**Results:** Twenty-five RCTs involving 2230 participants were included. The meta-analysis showed that Chuna manual therapy had a higher total effective rate (TER) based on anorexia symptoms than that of lysine inositol and vitamin B12 (RR: 1.53, 95% CI: 1.28–1.84), multi-enzyme and multi-vitamin (RR: 1.21, 95% CI: 1.11–1.33), and zinc calcium gluconate (RR: 1.22, 95% CI: 1.06–1.39). There was no significant difference in total effective rate between Chuna manual therapy and zinc gluconate plus lysine. No adverse events associated with Chuna manual therapy were reported. Overall, the included studies had an unclear risk of bias, and the quality of evidence was generally moderate to low.

**Conclusion:** Current evidence showed that Chuna manual therapy may be effective and safe for improving anorexia symptoms, especially compared with lysine inositol and vitamin B12, multi-enzyme plus multi-vitamin, and zinc calcium gluconate. However, owing to the low methodological quality of the included studies, more rigorous, high-quality RCTs are required on this topic.

**Abbreviations:** CI = confidence interval, GRADE = grading of recommendations, assessment, development, and evaluation, MD = mean difference, RR = risk ratio, TCM = traditional Chinese medicine, TER = total effective rate.

**Keywords:** anorexia, children, Chuna manual therapy, meta-analysis, systematic review

## 1. Introduction

Anorexia is the most common eating disorder and frequently occurs in children with symptoms of decreased food intake or food refusal. It is a chronic disease associated with prolonged loss of appetite.<sup>[1,2]</sup> According to epidemiological surveys, the prevalence of anorexia in infants and preschool children ranges between 12–34%,<sup>[3]</sup> and according to reports, its prevalence increases annually.<sup>[4]</sup> Anorexia occurs mainly due to poor diet or

psychological problems. It arises mostly between 9 to 18 months when children become more autonomous and make the transition to spoon- and self-feeding. Children with anorexia exhibit extreme food refusal and frequently fail to consume sufficient calories to sustain their growth.<sup>[5]</sup> Delayed treatment results in acute and/or chronic malnutrition, weight loss, low immunity, growth retardation, and various secondary infections in children. Additionally, it affects children's mental health, causing a huge burden on society.<sup>[6,7]</sup>

HL, and BL contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Most of the treatments for anorexia without organic disease are through conventional medications, including gastrointestinal motility drugs and probiotics, and dietary supplements, including vitamins and iron-containing supplements.<sup>[8]</sup> However, they have insufficient evidence of efficacy and many side effects, including those resulting from either excess vitamin intake or deficiency. Excessive zinc intake can cause copper deficiency, leading to anemia and neutropenia.<sup>[9,10]</sup> Therefore, there is increasing interest in developing a relatively safe and effective treatment for anorexia in children.<sup>[8]</sup>

Chuna manual therapy, a complementary and integrative medical therapy based on the meridian-collateral theory, is an ancient and practical chiropractic therapy that has been used for treating children with anorexia for thousands of years in East Asia.<sup>[11]</sup> In this therapy, physicians use their fingers and hands to promote the flow of blood and Qi to improve digestive function in children. Many clinical studies have reported the beneficial effects of Chuna manual therapy, such as enhancing immune function, unblocking meridians and collaterals, and activating Qi and blood.<sup>[12]</sup> Therefore, as a noninvasive and non-pharmacological therapy, Chuna manual therapy has the potential to treat anorexia in children by regulating the flow of Qi and blood throughout the body without drug-related adverse reactions. Accordingly, a number of clinical trials have been conducted to evaluate the effects of Chuna manual therapy on anorexia in children, and systematic reviews have been conducted to summarize the clinical effects.<sup>[13,14]</sup> However, the search year for 1 of these reviews was 2015<sup>[14]</sup> and for another, 2017.<sup>[13]</sup> Moreover, the add-on effect of Chuna manual therapy has not been summarized. Therefore, we conducted a systematic review and meta-analysis of the updated effects and safety of Chuna manual therapy as a monotherapy or as an add-on to conventional treatment for the management of anorexia in children. The findings in this study could contribute to the decision-making by clinicians, researchers, and policymakers.

## 2. Methods

The study protocol was registered with PROSPERO prior to the start of the study (record ID: CRD42021274373) and the study was conducted according to the preferred reporting items for systematic reviews and meta-analyses 2020 guidelines.<sup>[15]</sup> Ethics approval was not required because this study was based exclusively on published literature.

### 2.1. Search sources and search strategies

We searched 12 electronic databases: 4 English (Medline, EMBASE, Cochrane Central Register of Controlled Trials, and Allied and Complementary Medicine Database), 4 Korean (Oriental Medicine Advanced Searching Integrated System, Korean studies Information Service System, Korean Medical Database, and Science ON), 3 Chinese (China National Knowledge Infrastructure, Wanfang Data, and Chongqing VIP), and 1 Japanese (CiNii). The initial search date was June 3, 2021, and an updated search was performed on September 13, 2022, to provide the most updated and comprehensive evidence in the review process. One researcher searched each database, while another reviewed the results.

The reference lists of the included studies and trial registries, such as clinicaltrials.gov, were also reviewed to include as much relevant literature as possible. Gray literature such as degree dissertations, conference proceedings, and papers published in journals was also included. We established the final search strategy after discussion with a systematic review and pediatric expert. The detailed search strategy for each database is described in Supplementary 1, Supplemental Digital Content, <http://links.lww.com/MD/H909>.

## 2.2. Eligibility criteria

**2.2.1. Study design.** We included only randomized controlled trials. Papers that mentioned randomization but did not describe a specific random sequence generation method were excluded, as they were regarded as not being real RCTs. The potential risk of bias was minimized by including only parallel-group studies. There were no restrictions on the written language or the setting in which the clinical trial was conducted.

**2.2.2. Population.** Studies involving children (< 18 years old) with anorexia without organic causes were included. There were no restrictions on the sex, race, and nationality of the population, as well as the diagnostic criteria for anorexia.

**2.2.3. Intervention and comparator.** Regarding treatment interventions, we included studies that used Chuna manual therapy as either monotherapy or add-on therapy for the control group. We excluded studies in which the details of the Chuna manual therapy were not specified. For the control interventions, no treatment or conventional treatment was allowed. In our study, conventional treatments included dietary supplements (e.g., vitamins, minerals, and amino acids) and conventional medications used for gastrointestinal tract system disorders (e.g., domperidone, digestive enzymes, and probiotics), based on the classification system of the Korea Pharmaceutical Information Center<sup>[16]</sup> and drug classification codes of the Ministry of Food and Drug Safety.<sup>[17]</sup> However, studies using other East Asian traditional medicine therapies, such as herbal medicine and acupuncture, in the treatment and control groups were excluded. Additionally, studies that compared different Chuna manual therapies were excluded.

**2.2.4. Outcomes.** The primary outcome was an improvement in the post-treatment clinical symptoms of anorexia, measured by the total effective rate (TER) or appetite recovery time. For the assessment of TER, populations were classified after treatment according to the degree of improvement in anorexia symptoms as “cured” (N1), “markedly improved” (N2), “improved” (N3), or “non-responder.” The TER was calculated using the following formula:  $TER = (N1 + N2 + N3) / total\ sample\ size$ .

The secondary outcomes included: body measurements, such as body weight and height; gastric emptying time; levels of biomarkers related to gastrointestinal function, such as serum levels of leptin and ghrelin; nutrition indices, such as levels of serum trace elements; recurrence rate; and incidence of adverse events during the trial period.

### 2.3. Study selection and data extraction

We imported all studies identified through individual database searches and other sources into EndNote 20 (Clarivate Analytics, Philadelphia), a reference management software. Next, we removed duplicate papers and screened the titles and abstracts of the individual papers. Subsequently, we tried to secure the full text of the included papers and finally included papers that met the eligibility criteria through a full-text review.

We extracted the following information from the included studies using a standardized pilot test Excel 2019 form: basic study characteristics (including the first author’s name and country, publication year, study setting, or funding sources), details of participants (including sample size, mean age, anorexia disease period, anorexia diagnostic criteria, and pattern identification), treatment and control interventions, details of the Chuna manual therapy used, outcomes of interest, results, and information on the risk of bias assessment. In cases of ambiguity or insufficient data, the corresponding authors of the included studies were contacted via e-mail, if possible. Study selection and data extraction were conducted independently by 2 researchers (HL and BL), and any

disagreement was resolved through discussion with a third researcher (SHL).

#### 2.4. Risk of bias assessment

We evaluated the risk of bias in the included studies using the Cochrane Collaboration's risk of bias tool.<sup>[18]</sup> Two researchers (HL and BL) independently assessed the risk of bias in each study, and any discrepancies between the 2 authors were resolved through discussion with 2 other researchers (SHL and GTC). In each study, domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases were assessed as "low risk," "unclear risk," or "high risk." We evaluated other bias domains based on the statistical homogeneity of the baseline clinical characteristics between the treatment and control groups.

#### 2.5. Data analysis and synthesis

Descriptive analyses of the details of the population, intervention, comparators, and outcomes were conducted for each included study. Meta-analysis was conducted when 2 or more studies used the same type of intervention and comparator with the same outcome measures using Review Manager Software (version 5.4; Cochrane, London, UK). Continuous and binary outcomes were presented using the mean difference (MD) and risk ratio (RR) with 95% confidence intervals (CIs).

Heterogeneity between the studies was assessed using both the  $\chi^2$  test and  $I^2$  statistic.  $I^2$  values  $\geq 50\%$  and  $\geq 75\%$  were considered indicative of substantial heterogeneity. We used a random-effects model if the included studies had significant heterogeneity ( $I^2$  value  $\geq 50\%$ ), while we used a fixed-effects model if the heterogeneity was not significant or if the number of studies included in the meta-analysis was  $< 5$ .<sup>[19]</sup>

To identify the robustness of the meta-analysis results, sensitivity analysis was performed by excluding: studies with a high risk of bias; and outliers that were numerically distant from the rest of the data. Publication bias was tested through funnel plot symmetry and Egger's test using STATA/MP software version 16.1 (StataCorp LLC, Texas) if 10 or more studies were included in the meta-analysis.

#### 2.6. Quality of evidence assessment

The quality of evidence for each finding of the meta-analysis was evaluated using the grading of recommendations, assessment, development and evaluation (GRADE) tool.<sup>[20]</sup> The risk of bias, inconsistency, indirectness, imprecision, and publication bias of meta-analyzed results were assessed as "very low," "low," "moderate," or "high." One researcher (BL) conducted the GRADE assessment, while another researcher (SHL) reviewed the results. Any discrepancies were resolved through discussion with the corresponding author.

### 3. Results

#### 3.1. Study selection

We identified 6994 records through the database search and no additional records were identified from searching of registries and citations. After removing duplicates, there were 5643 records. We excluded 5517 irrelevant articles after reviewing titles and abstracts. After assessing their full texts, we excluded 101 articles from the remaining 126 articles, including the following: non-randomized controlled trial ( $n = 14$ ), no description of the randomization method ( $n = 17$ ), not only children ( $n = 1$ ), using traditional Chinese medicine (TCM) as a control

( $n = 30$ ), not for anorexia without the organic disease ( $n = 6$ ), only study protocol ( $n = 1$ ), not assessing Chuna manual therapy alone ( $n = 31$ ), and abstract without raw data ( $n = 1$ ) (Supplementary 2, Supplemental Digital Content, <http://links.lww.com/MD/H910>). Finally, 25 articles<sup>[21-45]</sup> were included in this systematic review and meta-analysis (Fig. 1).

#### 3.2. Study characteristics

Table 1 presents the characteristics of the included studies. All included studies were published in China from 2013 to 2022. In particular, 16 studies published between 2019 and 2022 accounted for more than half of the included studies. There were 23 2-arm and 2 3-arm studies.<sup>[31,42]</sup> Overall, the participants' mean age in each study ranged from 2.35 to 9.75 years, except for 1 study that only reported the participants' median age.<sup>[41]</sup> The participants' mean anorexia disease duration ranged from 6.17 days to 2.57 years.

The most common anorexia diagnostic criteria were "Guiding principle of clinical research on new drugs of TCM," used in 8 studies<sup>[21,23,24,30-32,37,42]</sup> and "Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes" used in 8 studies.<sup>[23,24,26,30,32,34,38,41]</sup> Two studies<sup>[37,42]</sup> used "Zhu Futang Practical Pediatrics," 4<sup>[23,24,27,30]</sup> used "Practical Pediatrics" diagnostic criteria, and 3<sup>[25,27,42]</sup> used "Guidelines for Diagnosis and Treatment of Common Diseases in Pediatrics of TCM." An explanation of the diagnostic criteria is presented in Supplementary 3, Supplemental Digital Content, <http://links.lww.com/MD/H911>.

Sixteen studies<sup>[21,22,24,27,30,31,34-37,39-43,45]</sup> recruited patients with specific pattern identification.<sup>[21,22,24,27,30,31,34-37,39-43,45]</sup> The most common pattern identified was "spleen-stomach Qi deficiency," which was used in 9 articles.<sup>[21,22,27,30,34,37,39,42,45]</sup> In addition, "spleen failing in transportation" was used in 1 article,<sup>[22]</sup> "hyperactivity of liver and spleen deficiency" in 1,<sup>[24]</sup> "spleen-stomach disharmony" in 3,<sup>[24,30,31]</sup> "fever in the spleen and stomach" in 1,<sup>[35]</sup> "spleen deficiency with accumulated heat" in 1,<sup>[36]</sup> "spleen-stomach accumulated heat" in 3,<sup>[40,41,43]</sup> and "food damage" in 5.<sup>[35,36,40,41,43]</sup>

Ten studies<sup>[21,25-29,32,37,38,45]</sup> compared the add-on effects of Chuna manual therapy combined with conventional treatment to that of conventional treatment alone, while 13<sup>[22-24,30,33-36,39-42,44]</sup> compared Chuna manual therapy with conventional treatment. One study<sup>[31]</sup> compared Chuna manual therapy combined with conventional treatment to Chuna manual therapy alone and conventional treatment alone. The remaining study<sup>[43]</sup> compared Chuna manual therapy to no treatment. To date, no placebo-controlled trials have been conducted. Conventional treatments used as control interventions consisted of domperidone, digestive enzymes, minerals, zinc plus probiotics, or a combination of these.

The mean number of Chuna manual therapy sessions was calculated as 20.5 (range: 6-90). The most common treatment period was 14 days recorded in 7 studies.<sup>[21-24,27,37,42]</sup> Four studies recorded 10 treatment days<sup>[25,30,33,41]</sup> and 3 studies recorded 28 treatment days.<sup>[28,31,45]</sup> Li et. al<sup>[27]</sup> wrote response sought (De qi) as "slight sweat on both sides of the spine, flushing of the skin," and Ma et. al<sup>[31]</sup> wrote response sought as "pain" which was not reported in other articles. Four studies<sup>[26,29,32,37]</sup> reported the qualifications or experience of the medical staff or doctors conducting Chuna manual therapy. The follow-up period was reported as 2 weeks in 2 articles.<sup>[22,24]</sup> The characteristics of the included studies are presented in Table 1, and a detailed explanation of the Chuna manual therapy method is presented in Supplementary 4, Supplemental Digital Content, <http://links.lww.com/MD/H912>.

#### 3.3. Risk of bias assessment

In terms of random sequence generation, all studies used appropriate random sequences, such as random number

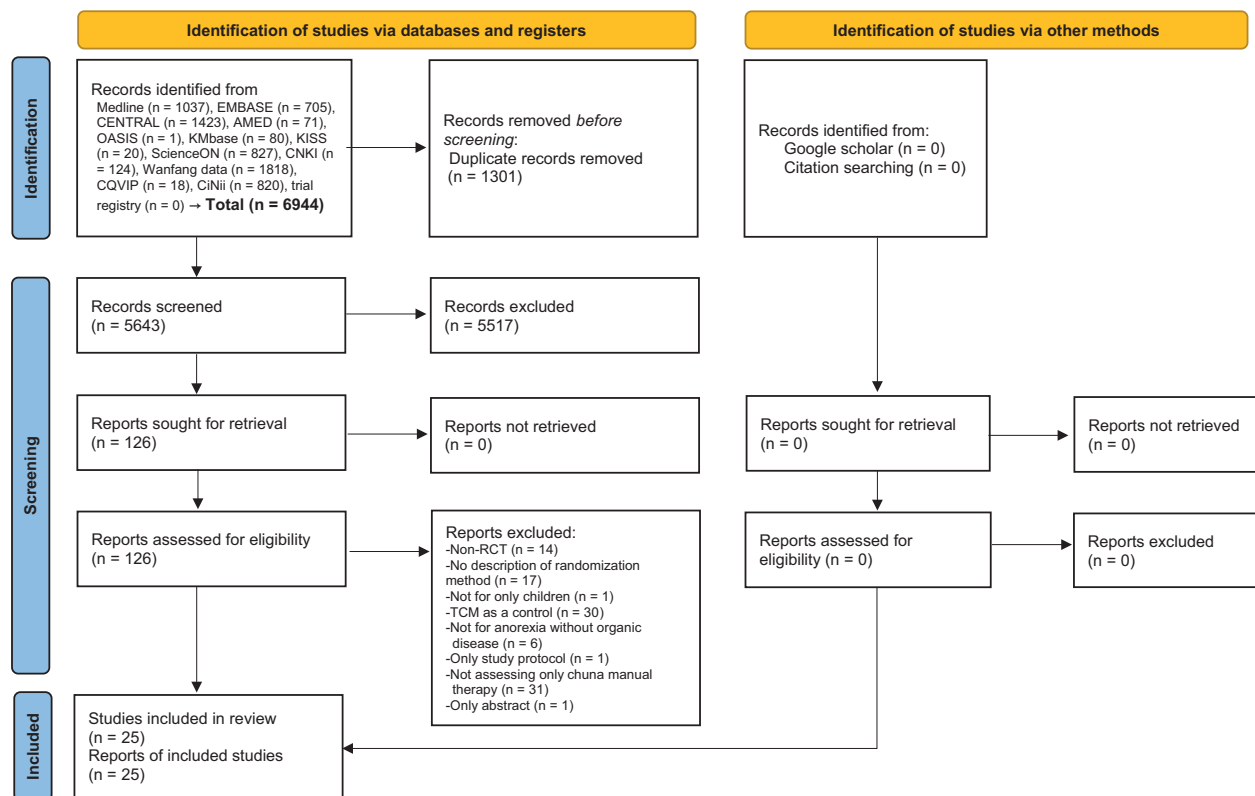


Figure 1. PRISMA flow chart of the literature screening and selection process.

tables, and were classified as “low-risk.” One study<sup>[30]</sup> used sealed opaque envelopes and was rated as having a “low risk” of bias in allocation concealment, while the remaining 24 studies were categorized as “unclear” due to lack of information. All studies were classified as “high risk” in the performance bias category because it is difficult to blind participants and therapists to Chuna manipulation procedures. None of the studies reported blinding of outcome assessment; therefore, all the studies were categorized as “unclear” due to a lack of information. All studies had a “low risk” of attrition bias because they used statistical methods to deal with missing values. One study<sup>[31]</sup> was rated as having a “high risk” of reporting bias because it reported only TER without presenting the raw data. The remaining 24 studies were assessed as having a “low risk” of reporting bias. All the studies were evaluated as “low risk” in the other bias domain except for 1 study<sup>[23]</sup> which lacked information regarding baseline characteristics. The methodological assessments for each included study are presented in Figure 2.

### 3.4. Effect of chuna manual therapy

**3.4.1. Chuna manual therapy versus conventional treatment.** Two studies<sup>[22,24]</sup> compared Chuna manual therapy with lysine inositol and vitamin B12 in terms of TER using anorexia symptoms and anorexia recurrence rate. According to the meta-analysis results, the Chuna manual therapy group had a higher TER than did the lysine inositol and vitamin B12 group (RR 1.53, 95% CI 1.28–1.84;  $I^2=41\%$ ) (Fig. 3). There was no significant difference in anorexia recurrence rate between the 2 groups (RR 0.75, 95% CI 0.43–1.30;  $I^2=80\%$ ).

Compared with zinc gluconate and lysine, Chuna manual therapy had no significant effects on TER (RR 1.09, 95% CI 0.94–1.27;  $I^2=3\%$ )<sup>[23,30,31]</sup> (Fig. 4). In addition, serum zinc

levels were significantly lower after treatment in the Chuna manual therapy group (MD -1.89  $\mu\text{mol/L}$ , 95% CI -3.04–0.74;  $I^2=33\%$ )<sup>[30,31]</sup>. However, hemoglobin levels significantly increased in the Chuna manual therapy group (MD 5.95 g/L, 95% CI 3.04–8.86;  $I^2=64\%$ )<sup>[23,31]</sup>.

Chuna manual therapy had a higher TER than that of multi-enzyme and multi-vitamin group (RR 1.21, 95% CI 1.11–1.33;  $I^2=0\%$ )<sup>[35,39,41]</sup> (Fig. 5) and zinc calcium gluconate (RR 1.22, 95% CI 1.06–1.39;  $I^2=0\%$ )<sup>[36,40]</sup> (Fig. 6).

Chuna manual therapy significantly improved TER compared to that with zinc gluconate plus Bifidobacterium tetralogy,<sup>[33]</sup> domperidone,<sup>[34]</sup> zinc gluconate,<sup>[42]</sup> and conventional medications<sup>[44]</sup> ( $P < .05$ , all), although meta-analysis could not be performed because only 1 study was included in each comparison. In particular, compared to those with zinc gluconate plus Bifidobacterium tetralogy,<sup>[33]</sup> serum zinc and hemoglobin levels were significantly improved in the Chuna manual therapy group ( $P < .01$ , all). Interestingly, compared to that with domperidone,<sup>[34]</sup> gastric emptying half-life significantly decreased, and salivary amylase and serum zinc levels significantly increased in the Chuna manual therapy group ( $P < .05$ , all).

**3.4.2. Chuna manual therapy versus no treatment.** One study<sup>[43]</sup> compared Chuna manual therapy with no treatment group. TER based on the improvement of anorexia symptoms was significantly higher in the Chuna manual therapy group than in the no treatment group ( $P < .05$ ).

**3.4.3. Chuna manual therapy plus conventional treatment versus conventional treatment alone.** In the included studies, various conventional treatments were used as controls, and no study used the same conventional treatment. Due to the clinical heterogeneity, a meta-analysis was not performed, and only qualitative analysis was performed.

When Chuna manual therapy was performed in addition to conventional treatment, the TERs were all significantly higher

**Table 1**

**The characteristics of the included studies.**

Author year	Sample size (A):(B)	Age Mean ± SD	Anorexia disease period Mean ± SD	Anorexia diagnostic criteria	Pattern identification (n)	(A) Treatment group	(B) Control group
Cui 2020	70(35:35)	(A) 3.29 ± 1.25 yr (2–5 yr) (B) 3.51 ± 1.43 yr (1–6 yr)	(A) 4.26 ± 1.24 mo (2–7) (B) 4.58 ± 1.33 mo (1–8)	-Guiding principle of clinical research on new drugs of TCM	Spleen-stomach qi deficiency	Chuna + (B)	Compound pepsin granules (14 d)
Deng 2018	136(68:68)	(A) 2.51 ± 1.48 yr (4 mo–6 yr) (B) 2.35 ± 1.50 yr (6 mo–6 yr)	(A) 5.04 ± 5.42 mo (1 mo–2 yr) (B) 5.28 ± 4.95 mo (1 mo–2 yr)	-Diagnosis and treatment of feeding disorders in infants, toddlers, and young children (Chatoor) -Pediatrics of TCM	(A) Spleen-stomach qi deficiency (19), Spleen failing in transportation (49) (B) Spleen-stomach qi deficiency (23), Spleen failing in transportation (45)	Chuna (The 3-character meridian school Tuina program)	Lysine inositol vitamin B12 oral liquid (14 d)
Guo 2020	30(15:15)	(A) 4.79 ± 0.86 yr (B) 4.81 ± 0.83 yr	(A) 7.67 ± 2.33 mo (B) 7.70 ± 2.26 mo	-Practical Pediatrics. -Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes -Guiding principle of clinical research on new drugs of TCM	None	Chuna	Zinc gluconate oral liquid + 5-dimensional lysine granules. (14 d)
Huang 2014	65(32:33)	(A) 2.78 ± 1.69 yr (B) 2.89 ± 1.51 yr	(A) ≥ 1 mo, <6 mo (14 cases), ≥6 mo, ≤12 mo (10 cases), >12 mo (8 cases) (B) ≥ 1 mo, <6 mo (13 cases), ≥6 mo, ≤12 mo (14 cases), >12 mo (6 cases)	-Guiding principle of clinical research on new drugs of TCM. -Practical Pediatrics. -Standards of the Chinese Medicine Industry of the People's Republic of China. -Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes. -Criteria for Diagnosis and Efficacy of TCM Pediatric Diseases	(A) Spleen-stomach disharmony (22), Hyperactivity of liver and spleen deficiency (10) (B) Spleen-stomach disharmony (21), Hyperactivity of liver and spleen deficiency (12)	Chuna(3-character classics genre Pediatric Tuina)	Lysine inositol vitamin B12 oral liquid (14 d)
Li 2019	85(43:42)	(A) 4.58 ± 1.21 yr (B) 4.47 ± 1.32 yr	(A) 2.43 ± 0.59 yr (B) 2.52 ± 0.48 yr	-Research progress of anorexia in children -Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	None	Chuna + (B)	Zinc-selenium tablets (60 d)
Li 2020	86(43:43)	(A) 4.7 ± 1.1 yr (2–9 yr) (B) 4.6 ± 1.2 yr (2–9 yr)	(A) 21.1 ± 3.2 wk (10–36 wk) (B) 21.2 ± 3.4 wk (9–36 wk)	-Practical Pediatrics. -Guidelines for Diagnosis and Treatment of Common Diseases in Pediatrics of TCM	Spleen-stomach qi deficiency	Chuna + (B)	Multi-enzyme tablets (14 d)
Li 2022	82(41:41)	(A) 4.52 ± 1.48 yr (3–6 yr) (B) 4.11 ± 1.89 yr (2–6 yr)	NR	-Pediatric Internal Medicine. - Guidelines for Diagnosis and Treatment of Common Diseases in Pediatrics of TCM	None	Chuna + (B)	Zinc gluconate oral liquid (10 d)
Liu 2018	72(36:36)	(A) 3.21 ± 0.42 yr (2–6 yr) (B) 3.05 ± 0.47 yr (2–5 yr)	NR	NR	None	Chuna + (B)	Zinc gluconate oral liquid + multi-enzyme tablets (28 d)
Liu 2020	60(30:30)	(A) 4.31 ± 1.16 yr (2–6 yr) (B) 4.52 ± 1.17 yr (3–6 yr)	NR	NR	None	Chuna + (B)	Conventional medication treatment (NR)

(Continued)

**Table 1**  
**(Continued)**

Author year	Sample size (A):(B)	Anorexia disease period		Anorexia diagnostic criteria	Pattern identification (n)	(A) Treatment group	(B) Control group
		Age Mean ± SD	Mean ± SD				
Luo 2019	60(30:30)	(A) 5.06 ± 0.28 yr (B) 5.08 ± 0.26 yr	(A) 7.61 ± 0.66 mo (B) 7.55 ± 0.75 mo	-Practical Pediatrics. -Guiding principle of clinical research on new drugs of TCM. -Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	Spleen-stomach disharmony, Spleen-stomach qi deficiency	Chuna	Zinc gluconate oral liquid + 5-dimensional lysine granules (10 d)
Ma 2017	123(41:41:41)	(A1) 5.92 ± 1.42 yr (A2) 6.34 ± 1.61 yr	(A1) 2.12 ± 0.72 yr (A2) 2.57 ± 0.88 yr	-Guiding principle of clinical research on new drugs of TCM (Trial)	Spleen-stomach disharmony	(A1) Zhiyang bazhen acupoint massage + (B) (A2) Ordinary chuna	Zinc gluconate and lysine granules (28 d)
Miao 2019	130(65:65)	(B) 6.12 ± 1.50 yr (A) 4.63 ± 1.21 yr (2-7 yr) (B) 4.58 ± 1.27 yr (2-7 yr)	(B) 2.32 ± 0.80 yr (A) 7.52 ± 1.05 wk (3 wk-3 mo) (B) 7.49 ± 1.10 wk (3 wk-3 mo)	-Guiding principle of clinical research on new drugs of TCM-Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	None	Chuna + (B)	Conventional western medicine treatment (12 d)
Mou 2020	70(35:35)	(A) 3.1 ± 0.5 yr (2-10 yr) (B) 3.2 ± 0.7 yr (2-10 yr)	(A) 5.2 ± 1.4 mo (2-10 mo) (B) 5.3 ± 1.6 mo (2-12 mo)	NR	None	Chuna	Zinc gluconate oral liquid + bifidobacterium tetralogy (10 d)
Sun 2018	105(54:51)	(A) 3.06 ± 0.84 yr (B) 2.85 ± 0.70 yr	NR	-Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	Spleen-stomach qi deficiency	Chuna	Domperidone suspension (7 d)
Sun 2019	64(32:32)	(A) 4.5 ± 1.77 yr (1-9 yr) (B) 4.8 ± 1.6 yr (1-8 yr)	(A) 13.9 ± 1.6 mo (11-18 mo) (B) 14.3 ± 1.5 mo (10-18 mo)	NR	Fever in the spleen and stomachFood damage	Chuna	Multi-enzyme tablets + multi-vitamin tablets (10 d)
Wang 2018	80(40:40)	(A) 5.0 ± 1.2 yr (2-12 yr) (B) 5.1 ± 1.3 yr (2-12 yr)	NR	NR	Spleen deficiency with accumulated heatFood damage	Chuna	Zinc calcium gluconate oral liquid (7-21 d)
Wang 2019	104(52:52)	(A) 3.67 ± 1.14 yr (1.5-6 yr) (B) 3.64 ± 1.12 yr (1-6 yr)	(A) 6.25 ± 1.81 mo (4-9 mo) (B) 6.27 ± 1.83 mo (3-10 mo)	-Zhu Futang Practical Pediatrics-Guiding principle of clinical research on new drugs of TCM (Trial)	Spleen-stomach qi deficiency	Chuna + (B)	Saccharomyces boulardii powder + conventional treatments including zinc sulfate syrup, iron-containing preparations, vitamin B, vitamin A, and other drugs (14 d)
Xu 2022	90(45:45)	(A) 9.75 ± 1.62 yr (B) 9.23 ± 1.35 yr	(A) 4.52 ± 0.73 mo (B) 4.23 ± 0.97 mo	-Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	None	Chuna + (B)	Bifidobacterium quadruple viable bacteria (1 mo)
Yan 2021	88(44:44)	(A) 3.02 ± 1.33 yr (1-6 yr) (B) 3.05 ± 1.06 yr (2-6 yr)	(A) 12.34 ± 1.23 mo (6-18 mo) (B) 12.85 ± 1.54 mo (6-20 mo)	NR	Spleen-stomach qi deficiency	Chuna	Multi-enzyme tablets + multi-vitamin B tablets (10 d)
Yang 2020	76(38:38)	(A) 5.53 ± 1.43 yr (2-8 yr) (B) 5.64 ± 1.24 yr (2-9 yr)	NR	NR	Spleen-stomach accumulated heat. Food damage	Chuna	Zinc calcium gluconate oral liquid (7 d)

(Continued)

**Table 1**  
(Continued)

Author year	Sample size (A):(B)	Age Mean ± SD	Anorexia disease period Mean ± SD	Anorexia diagnostic criteria	Pattern identification (n)	(A) Treatment group	(B) Control group
Zhang 2013	90(30:30:30)	(A) 5.52 ± 1.34 yr (B1) 4.98 ± 2.11 yr (B2) 5.43 ± 1.42 yr	NR	-Zhu Futang Practical Pediatrics-Guidelines for Diagnosis and Treatment of Common Diseases in Pediatrics of TCM. -Guiding principle of clinical research on new drugs of TCM -Chinese Standards for Effectively Diagnosing of Pediatric Diseases	Spleen-stomach qi deficiency	Chuna	(B1) Herbal medicine (Jianersu granules) (14 d) (B2) Zinc gluconate granules (14 d)
Zhang 2017	200(100:100)	(A) 3.91 ± 1.35 yr (2-6 yr) (B) 3.89 ± 1.47 yr (2-6 yr)	NR		Spleen-stomach accumulated heat. Food damage	Chuna	No treatment
Zhang 2019	134(67:67)	median 5 yr (1-7 yr)	median 12 mo (8-15 mo)	-Criteria for Diagnosis and Efficacy of TCM Diseases and Syndromes	Spleen-stomach accumulated heat. Food damage	Chuna	Multi-enzyme tablets + multi-vitamin tablet (10 d)
Zhang 2021	50(25:25)	(A) 2.85 ± 0.46 yr (0.5-6 yr) (B) 2.91 ± 0.51 yr (0.42-5 yr)	(A) 6.20 ± 1.11 d (B) 6.17 ± 1.08 d		None	Chuna	Conventional medication treatment (NR)
Zhuo 2017	80(40:40)	(A) 3.34 ± 1.21 yr (1-7 yr) (B) 3.31 ± 1.24 yr (1-8 yr)	NR		Spleen-stomach qi deficiency	Chuna + (B)	Zinc gluconate oral liquid + bifidobacterium quadruple viable bacteria tablets (28 d)

NR = not reported, SD = standard deviation, TCM = traditional Chinese medicine.

than those of conventional treatment alone, including compound pepsin granules,<sup>[21]</sup> zinc-selenium,<sup>[26]</sup> multi-enzyme,<sup>[27]</sup> zinc gluconate,<sup>[25]</sup> zinc gluconate and multi-enzyme,<sup>[28]</sup> conventional medication,<sup>[29]</sup> lysine zinc gluconate,<sup>[31]</sup> conventional western medicine treatment,<sup>[32]</sup> *Saccharomyces boulardii*, and conventional treatments including zinc sulfate syrup, iron-containing preparations, vitamins A and B,<sup>[37]</sup> Bifidobacterium quadruple viable bacteria,<sup>[38]</sup> and zinc gluconate plus Bifidobacterium quadruple viable bacteria<sup>[45]</sup> ( $P < .05$ , all).

Compared to that of the zinc gluconate plus Bifidobacterium quadruple viable bacteria group,<sup>[45]</sup> the Chuna combination group showed significant improvement in appetite recovery time ( $P < .01$ ), body weight, and serum levels of zinc, calcium, and hemoglobin ( $P < .05$ , all). Compared to those following treatment with compound pepsin granules<sup>[21]</sup> and Bifidobacterium quadruple viable bacteria,<sup>[38]</sup> serum levels of motilin, gastrin, and zinc significantly increased when Chuna manual therapy was added ( $P < .05$ , all). Compared to that of the zinc-selenium group,<sup>[26]</sup> body weight significantly increased in the Chuna combination group ( $P < .05$ ), and gastric emptying half-life significantly decreased in the Chuna combination group compared to that in the multi-enzyme group ( $P < .05$ ).<sup>[27]</sup> In addition, compared with *S. boulardii* plus conventional treatments including zinc sulfate syrup, iron-containing preparations, and vitamins A and B,<sup>[37]</sup> body weight and serum levels of iron, calcium, and zinc significantly increased in the Chuna combination group ( $P < .05$ , all).

### 3.5. Safety of chuna manual therapy

One study that compared Chuna manual therapy with lysine inositol and vitamin B12 therapy<sup>[24]</sup> and another that compared Chuna manual therapy with zinc gluconate<sup>[42]</sup> reported that there were no adverse events during the treatment period. Other studies did not report any adverse events. No adverse events associated with Chuna manual therapy were reported among the studies included in this review.

### 3.6. Quality of evidence

Regarding the main findings of the meta-analysis, the quality of evidence for TER outcomes evaluated by the GRADE tool was “Moderate” when Chuna manual therapy was compared with lysine inositol and vitamin B12, multi-enzyme and multi-vitamin, and zinc calcium gluconate therapies, respectively. When Chuna manual therapy was compared with zinc gluconate and lysine, the quality of evidence for TER was “Low.” In particular, the high risk of performance bias and imprecision of the meta-analyzed results due to the small sample size and wide CIs were major factors that downgraded the quality of the evidence (Table 2).

## 4. Discussion

Numerous RCTs reporting the effects and safety of Chuna manual therapy as monotherapy or add-on therapy to conventional treatment for childhood anorexia have been published. However, previous systematic reviews only compared Chuna manual therapy with Western/Chinese medicine or other therapies,<sup>[14]</sup> pharmacotherapy, or no treatment.<sup>[13]</sup> Therefore, the effects of Chuna manual therapy as an add-on treatment to conventional treatments have not been reported. In addition, 1 review only analyzed TER,<sup>[14]</sup> and another conducted a subgroup analysis using only TER.<sup>[13]</sup> Therefore, we conducted an updated systematic review and meta-analysis with TER and objective outcomes related to anorexia, including body measurements, gastric emptying time, levels of biomarkers related to gastrointestinal function, nutrition indices, recurrence rate, and incidence of adverse events during the trial period. We further

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cui 2020	+	?	-	?	+	+	+
Deng 2018	+	?	-	?	+	+	+
Guo 2020	+	?	-	?	+	+	?
Huang 2014	+	?	-	?	+	+	+
Li 2019	+	?	-	?	+	+	+
Li 2020	+	?	-	?	+	+	+
Li 2022	+	?	-	?	+	+	+
Liu 2018	+	?	-	?	+	+	+
Liu 2020	+	?	-	?	+	+	+
Luo 2019	+	+	-	?	+	+	+
Ma 2017	+	?	-	?	+	-	+
Miao 2019	+	?	-	?	+	+	+
Mou 2020	+	?	-	?	+	+	+
Sun 2018	+	?	-	?	+	+	+
Sun 2019	+	?	-	?	+	+	+
Wang 2018	+	?	-	?	+	+	+
Wang 2019	+	?	-	?	+	+	+
Xu 2022	+	?	-	?	+	+	+
Yan 2021	+	?	-	?	+	+	+
Yang 2020	+	?	-	?	+	+	+
Zhang 2013	+	?	-	?	+	+	+
Zhang 2017	+	?	-	?	+	+	+
Zhang 2019	+	?	-	?	+	+	+
Zhang 2021	+	?	-	?	+	+	+
Zhuo 2017	+	?	-	?	+	+	+

Figure 2. Summary of risk of bias in all included studies; “+” low risk; “?” unclear risk; “-” high risk.

evaluated the quality of evidence for the main findings to help with clinical decision-making.

A total of 25 RCTs comprising 2230 children were included in this review. Due to the heterogeneity of the interventions used in the control group, only a meta-analysis comparing Chuna manual therapy with lysine inositol and vitamin B12, zinc

gluconate plus lysine, multi-enzyme plus multi-vitamin, and zinc calcium gluconate therapies was performed, while a descriptive analysis was performed for other comparisons. According to the meta-analysis, Chuna manual therapy was more effective in terms of TER based on improvement of anorexia symptoms than lysine inositol and vitamin B12, multi-enzyme plus multi-vitamin, and zinc calcium gluconate therapy. However, there was no difference in TER between Chuna manual therapy and zinc gluconate plus lysine. In the descriptive analysis of the individual studies, Chuna manual therapy significantly improved serum levels of zinc, hemoglobin, and salivary amylase, and lowered gastric emptying half time compared with the conventional treatment. Chuna manual therapy as monotherapy compared with no treatment or add-on to conventional treatment showed significantly higher TER than that of all conventional treatments used in the included studies. Additionally, Chuna manual therapy as an add-on to conventional treatment significantly improved appetite recovery time, body weight, gastric emptying half-time, and serum levels of motilin, gastrin, zinc, calcium, iron, and hemoglobin compared to those of conventional treatment alone.

Chuna manual therapy is performed with fingers in a certain way to knead, hold, and twist the back skin to prevent and treat diseases. Its advantage is that it is simple, noninvasive, has no side effects, as well as is inexpensive; therefore, it is easily accepted by children and their parents.<sup>[46]</sup> According to the results of our study, Chuna manual therapy as monotherapy or add-on to conventional treatment significantly improved anorexia symptoms, body measurements, biomarker levels, and nutritional indices without adverse events. Therefore, based on the results of this systematic review and meta-analysis, Chuna manual therapy may be considered a noninvasive, effective, and safe treatment option for childhood anorexia.

Although there are no studies on the modern medical interpretation of the mechanism of Chuna manual therapy in the treatment of anorexia in children, a recent study has attempted to interpret the mechanism of Chuna manual therapy in children with anorexia from the perspective of intestinal flora and the regulation of host metabolism.<sup>[47]</sup> In addition, several clinical studies have reported significant increases in hemoglobin, serum zinc, and neuropeptide levels, urine D-xylose excretion rate, and a significant decrease in gastric emptying half-time after Chuna manual therapy.<sup>[27,48]</sup> According to the TCM theory, spine pinching, 1 of the most frequently used Chuna manual therapies, usually massages the governor vessel and bladder meridian to control yin and yang, communicate meridians, and promote the functions of the intestines and the movement of Qi and blood. Therefore, it improves gastrointestinal function, aids digestion, increases appetite, and prevents and treats mild malnutrition.<sup>[49]</sup> Furthermore, studies have shown that it promotes gastric juice secretion and gastric fluid movement, and improves the digestive capacity of the stomach for carbohydrates and proteins.<sup>[50]</sup> Future studies on the modern medical interpretation of the mechanism of Chuna manual therapy should be actively conducted.

Our review had several limitations. First, all the studies were conducted in China, which might have caused cultural bias, limiting the generalizability of the findings. Second, the risk of bias in the included studies is not optimal. In particular, the risks of performance bias and detection bias were generally high because blinding of participants, personnel, and outcome assessors was not reported. Accordingly, we were unable to perform a planned sensitivity analysis by excluding studies with a high risk of bias. In addition, there were no outliers that were numerically distant from the rest of the data; thus, a sensitivity analysis excluding outliers could not be performed. In addition, because the number of studies included in the meta-analysis was small, it was not possible to evaluate publication bias using funnel plot symmetry or Egger’s test. Third, there was clinical heterogeneity in the included studies, such



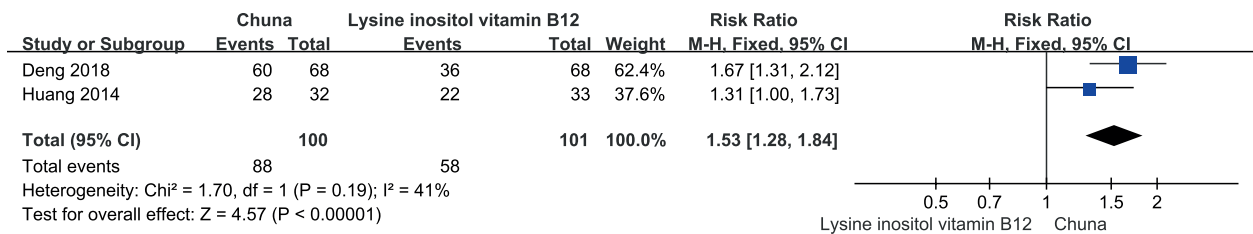


Figure 3. Forest plot for comparison of Chuna manual therapy versus lysine inositol and vitamin B12: Total effective rate.

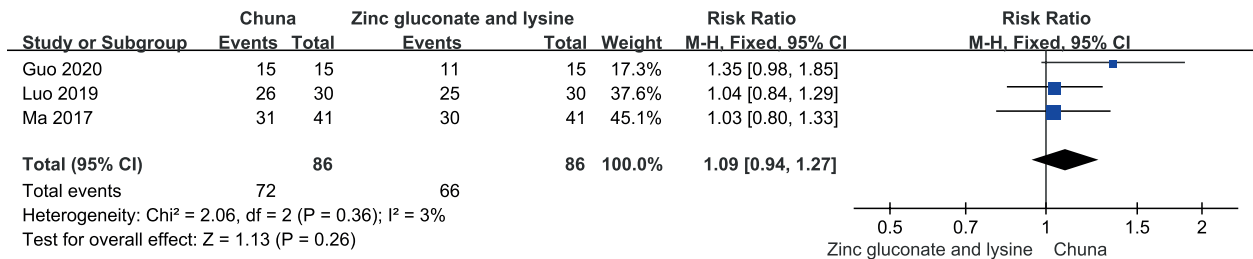


Figure 4. Forest plot for comparison of Chuna manual therapy versus zinc gluconate and lysine: Total effective rate.

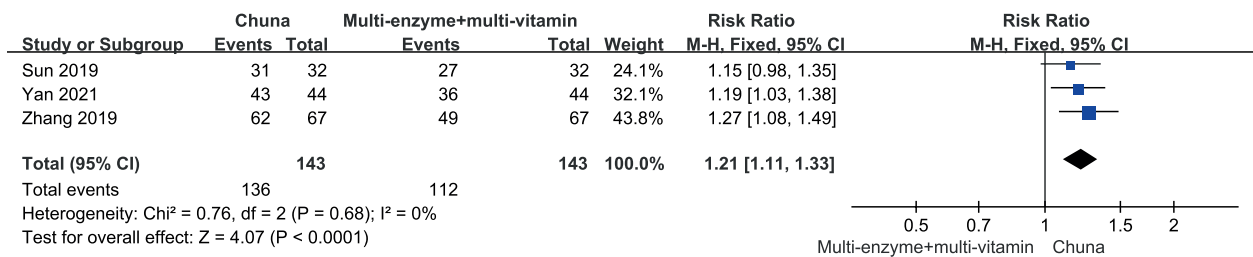


Figure 5. Forest plot for comparison of Chuna manual therapy versus multi-enzyme and multi-vitamin: Total effective rate.

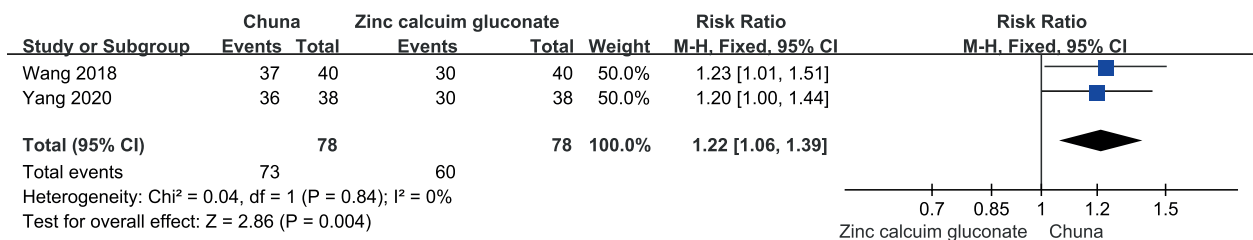


Figure 6. Forest plot for comparison of Chuna manual therapy versus zinc calcium gluconate: Total effective rate.

as different anorexia diagnostic criteria, pattern identification approaches, and the method of Chuna manual therapy, including the number and frequency of treatment sessions. Therefore, caution should be exercised when interpreting the results of this meta-analysis. In particular, the included studies did not use uniform criteria for the diagnosis of anorexia because there are still no standardized diagnostic criteria for anorexia in children. Therefore, in the future, it is necessary to establish standardized diagnostic criteria based on expert consensus and observational studies to develop treatment and evaluation tools based on understanding this disease.

Nevertheless, in the current situation in which safe and effective treatments are needed for childhood anorexia, we comprehensively updated and synthesized the evidence for the effect and safety of Chuna manual therapy for childhood anorexia. We attempted to minimize the related clinical heterogeneity by performing meta-analyses according to the type of conventional treatment used in the control group. In addition, it is significant that the quality of evidence for the main findings was evaluated using the GRADE tool for the 1<sup>st</sup> time to help clinicians make decisions.

### 5. Conclusion

The results of our study suggest that Chuna manual therapy may be effective in improving anorexia symptoms. In particular, it is not associated with serious adverse events compared to those with lysine inositol and vitamin B12, multi-enzyme plus multi-vitamin, and zinc calcium gluconate. However, due to the low methodological quality of the included studies, more rigorous, high-quality RCTs are needed to confirm the effects of Chuna manual therapy and provide high-quality evidence.

### Author contributions

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**Table 2**  
**Summary of findings.**

Outcomes	No. RCTs	No. participants	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I <sup>2</sup> value	Quality of evidence (GRADE)	Comments
			Risk with control group	Risk with chuna group				
Chuna versus Lysine inositol and vitamin B12								
TER	2	201	574 per 1000	879 per 1000 (735 to 1000)	RR 1.53 (1.28 to 1.84)	41	Moderate	Risk of bias (-1)
Recurrence rate	2	146	310 per 1000	233 per 1000 (133 to 403)	RR 0.75 (0.43 to 1.30)	80	Very Low	Risk of bias (-1) Inconsistency (-1) Imprecision (-1)
Chuna versus Zinc gluconate and lysine								
TER	3	172	767 per 1000	837 per 1000 (721 to 975)	RR 1.09 (0.94 to 1.27)	3	Low	Risk of bias (-1) Imprecision (-1)
Serum zinc (umol/L)	2	142	-	MD 1.89 lower (3.04 to 0.74 lower)	-	33	Moderate	Risk of bias (-1)
Hemoglobin (g/L)	2	112	-	MD 5.95 higher (3.04 to 8.86 higher)	-	64	Moderate	Risk of bias (-1)
Chuna versus Multi-enzyme and multi-vitamin								
TER	3	286	783 per 1000	948 per 1000 (869 to 1000)	RR 1.21 (1.11 to 1.33)	0	Moderate	Risk of bias (-1)
Chuna versus Zinc calcium gluconate								
TER	2	156	769 per 1000	938 per 1000 (815 to 1000)	RR 1.22 (1.06 to 1.39)	0	Moderate	Risk of bias (-1)

CI = confidence interval, GRADE = grading of recommendations assessment, development, and evaluation, MD = mean difference, RCT = randomized controlled trial, RR = risk ratio, TER = total effective rate.

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