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Pediatric tuina for the treatment of anorexia in children under 14 years: a systematic review and meta-analysis of randomized controlled trials

Shi-Bing Liang[a,b], Bao-Yong Lai[c], Hui-Juan Cao[a], Qiu-Han Cai[d], Xue Bai[a], Jing Li[a], Ya-Peng Zhang[a], Yuan Chi[a], Nicola Robinson[e,a], Jian-Ping Liu[a,f,g,*]

[a] Centre for Evidence-Based Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China
[b] School of Basic Medicine, Shanxi University of Chinese Medicine, Taiyuan, 030000, China
[c] The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, 100029, China
[d] Clinical Trial Center, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, 300193, China
[e] School of Health and Social Care, London South Bank University, London, SE1 0AA, UK
[f] Institute of Integrated Traditional Chinese Medicine and Western Medicine, Guangzhou Medical University, Guangzhou, China
[g] National Research Center in Complementary and Alternative Medicine (NAFKAM), Department of Community Medicine, Faculty of Health Science, UiT, The Arctic University of Norway, 9037 Tromsø, Norway

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ABSTRACT

Background: Pediatric tuina is used to prevent and treat disease by employing various manipulative techniques on specific parts of the body, appropriate to the child's specific physiological and pathological characteristics.
Objective: To evaluate the effects and safety of pediatric tuina as a non-pharmaceutical therapy for anorexia in children under 14 years.
Methods: Randomized controlled trials (RCTs) comparing pediatric tuina with medicine for anorexia were included in this review. Six electronic databases were searched from inception to June 2019. Two authors independently extracted data and assessed the risk of bias. Significant effective rate (defined as appetite improved and food intake returning to 3/4 or more of normal intake) was used as primary outcome. Secondary outcomes included food intake, compliance and adverse events. Trial sequential analysis (TSA) was used to calculate the required information size in a meta-analysis and to detect the robustness of the results. Certainty of the evidence was assessed using the online GRADEpro tool.
Results: Of the included 28 RCTs involving 2650 children, the majority had a high or unclear risk of bias in terms of allocation concealment, blinding, and selective reporting. All trials compared tuina with western medicine or Chinese herbs. For significant effective rate, meta-analysis showed that tuina was superior to western medicine (risk ratio (RR) 1.68, 95 % confidence interval (CI) [1.35, 2.08]) and Chinese herbs (RR 1.36, 95 % CI [1.19, 1.55]). For food intake, 9 trials evaluated it in the form of score (1 points, 2 points, 4 points and 6 points) calculated according to the reduction degree of food intake. Six points represented the most serious. Meta-analysis showed tuina was superior to western medicine (mean difference (MD) -0.88, 95 % CI [-1.27, -0.50]) and Chinese herbs (MD -0.69, 95 % CI [-1.00, -0.38]) on lightening the reduction degree of food intake. Two trials reported compliance and six trials reported no adverse events occurred in pediatric tuina group. TSA for significant effective rate demonstrated that the pooled data had insufficient power regarding both numbers of trials and participants.
Conclusions: Low certainty of evidence suggested pediatric tuina was beneficial and safe for the treatment of anorexia in children under 14 years. Furthermore well-designed RCTs with adequate sample sizes are needed.

Abbreviations: RCT, Randomized controlled trial; RR, risk ratio; CI, confidence interval; TSA, Trial sequential analysis; TCM, Traditional Chinese medicine; MD, mean difference; GRADE, Grading of Recommendations Assessment Development and Evaluation criteria

* Corresponding author at: Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, Chaoyang District, Beijing, 100029, China.

E-mail addresses: zyi20126185@163.com (S.-B. Liang), baoyonglai@bucm.edu.cn (B.-Y. Lai), huijuancao327@hotmail.com (H.-J. Cao), happyqiuhan@126.com (Q.-H. Cai), 20170931127@bucm.edu.cn (X. Bai), lj@bucm.edu.cn (J. Li), zhangyapeng@bucm.edu.cn (Y.-P. Zhang), chiyuan0717@163.com (Y. Chi), nicky.robinson@lsbu.ac.uk (N. Robinson), Liujp@bucm.edu.cn (J.-P. Liu).

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1. Introduction

Pediatric anorexia is an eating disorder of childhood, characterized by long-term decrease or disappearance of appetite, reduction or even refusal to eat.[1] Children of all ages may suffer from this disease, especially children aged 1–6, and can affect up to 45 % of children.[2,3] Anorexia in children may lead to malnutrition, conditions such as rickets and scurvy, and may delay growth, effect cognitive ability and immunity, if it cannot be resolved it can last for a long time.[4,5] Western medicine for anorexia mainly focuses on treatment with gastric motility drugs, trace elements (*e.g.* zinc) and vitamin preparations.[6] However, western medicine may cause side effects, and vitamins may lead to imbalances for example too much zinc may lead to anemia and neutropenia.[7,8] Traditional Chinese medicine (TCM) treatments include, Chinese herbal therapy and non-pharmaceutical treatment such as acupuncture, cupping and tuina (Chinese massage).[9]

Parents are often aware of the possible harmful nature of drugs on their children,[10] and in China, both parents and doctors try to explore non-pharmaceutical treatment options such as pediatric tuina. Pediatric tuina is guided by the basic theory of TCM, according to the physiological and pathological characteristics of the child. Various manipulative techniques such as spine pinching are used on specific parts of the child's body, in order to prevent and treat pediatric diseases.[11,12] Tuina has benefits in the treatment of many children's diseases, such as diarrhea, anorexia, torticollis, cerebral palsy, enuresis, *etc.*[13]

Many clinical studies on pediatric tuina for anorexia in children under 14 years have been conducted. This review aimed to systematically review the results of randomized controlled trials (RCTs) with pediatric tuina *versus* medicine or no treatment for anorexia in children under 14 years, and to evaluate the effects and safety of pediatric tuina for anorexia.

2. Methods

Protocol of this review was registered in PROSPERO (CRD42018105819) on August 15th 2018 and is available from: http://www.crd.york.ac.uk/PROSPERO/.

2.1. Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) randomized controlled trial (RCT); 2) participants younger than or equal to 14 years old, but there were no gender or race restrictions, and they had to be diagnosed as anorexia for at least two weeks[14]; 3) studies compared pediatric tuina alone to medicine or no treatment. The types of pediatric tuina mainly include acupoint massage, abdominal massage, spinal pinching, *etc.*

Exclusion criteria were as follows: 1) Anorexia caused by drugs, iatrogenic factors, and/or other diseases; 2) Children with moderate to severe malnutrition, organic disease, mental illness or serious complications were also excluded; 3) the full text of the literature could not be obtained; (4) the literature was suspected of plagiarism; 5) any duplicated literature.

2.2. Search strategy

PubMed, the Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang Database and VIP Database were searched from inception to June 2019. Language was limited to English and Chinese. The terms tuina or massage or rubbing abdomen or chiropractic or technique or spinal manipulation combined with anorexia were used for the search, and the search strategies were adjusted for use in the different databases. Details of the six databases are shown in Appendix 1.

2.3. Study selection and data extraction

One author (SBL) imported the retrieved bibliography citations into NoteExpress V3.0.4.6732, and duplicates were deleted. Two authors (SBL and JL) selected the potential eligible articles based on the reading of titles and abstracts. Full texts screening and data extraction was conducted afterwards by two authors (SBL and QHC) independently. If there was any uncertainty or discrepancy, a third author (JPL) was consulted.

2.4. Outcomes

Significant effective rate was used as the primary outcome. Significant effective was defined as the appetite improving and food intake returning to three quarters or more of the normal intake. Significant effective rate = (the number of significant effective participants / total number of participants) × 100 %.

Secondary outcomes included food intake, adverse events and compliance with interventions. Food intake was evaluated in the form of score according to the efficacy evaluation criteria in guidance principle of clinical study on new drug of traditional Chinese medicine[15]. The score was calculated according to the reduction degree of food intake: 1) 0 points: the reduction of food intake < 1/4 of normal food intake; 2) 2 points: 1/4 of normal ≤ the reduction < 1/3 of normal; 3) 4 points: 1/3 of normal ≤ the reduction < 1/2 of normal; 4) 6 points: the reduction ≥ 1/2 of normal. The higher the score, the more serious the reduction degree of food intake. Six points represented the most serious.

2.5. Risk of bias assessment

The risk of bias of the included trials was assessed independently by two authors (BYL and YPZ) using the risk of bias tool recommended by the Cochrane Collaboration.[16] The items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (assessed according to comparability of baseline data). We judged each item and categorized them into three levels: low risk of bias, high risk of bias and unclear risk of bias.

2.6. Data synthesis

All statistical analyses were performed using Review Manager (RevMan) Version 5.3 [17]. We presented binary data as a risk ratio (RR) with 95 % confidence interval (CI), and continuous data as a mean difference (MD) with 95 % CI. Meta-analysis was conducted if the trials had acceptable statistical heterogeneity and similar clinical characteristics. The clinical heterogeneity was assessed by evaluating similarities of the participants and interventions, as well as the outcomes measured in the included studies and the methodological heterogeneity was assessed by evaluating variability in study design and risk of bias. Considering potential sources of clinical heterogeneity, the random-effect model (REM) was used for meta-analysis. Furthermore, statistical heterogeneity among the included trials was evaluated using the Chi^2 test and I-square(I^2) statistic.[18] If $P < 0.10$, there is heterogeneity among the included studies. when $I^2 > 50$ %, it may represent a considerable/high heterogeneity among the studies,[18,19] then subgroup analysis or sensitivity analysis (based on patients' population, interventions and control, outcomes, and methodological difference) were conducted if data available. We planned to merge the data for all children with anorexia in a single meta-analysis for the same outcome from the same comparison. We planned to conduct the following subgroup analyses if appropriate: 1) subgroup analysis based on different treatment courses, such as short courses of treatment (≤15 days), medium courses of treatment (16 − 30 days), and long courses of treatment (< 30 days), to detect whether patients can benefit more from long-term treatment; 2)

subgroup analysis was conducted by gender to detect whether gender affected the efficacy of tuina, such as whether male children with anorexia were better treated than female children with anorexia.

Besides, a funnel plot was performed to explore the possibility of publication bias, if ten or more trials were included in a meta-analysis for primary outcomes.[20,21] Certainty of evidence for each key outcome was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation criteria) approach to conduct management recommendations[22] by the GRADEpro guideline development tool (GDT) online (https://gradepro.org/). If there were more than 8 trials in a meta-analysis for primary outcomes, the trial sequential analysis (TSA) were used to calculate the required information size (based on two-sided tests with a type I error of 5%, a power of 80 %) in the meta-analysis and to test the robustness of the results.[23,24]

3. Results

3.1. Study selection

A total of 2076 records were identified of which 2048 were excluded for various reasons by screening the titles, abstracts and full-texts. Finally, 28 trials [25–52] involving 2650 participants were included in this review. A flow diagram of the study selection process is shown in Fig.1.

3.2. Study characteristics

Table 1 shows the characteristics of the included 28 trials.

The trials were all conducted in China and published between 2007 and 2019. Only three trials[26,39,44] reported sources of funding. Of all the trials, 25 trials[25–37,40–41,43–52] were two-armed, 2 trials[38,42] had three-arms and the remaining one[39] was a four-armed trial. In total, 2619 participants were included in the data analysis and of these 1248 were in the tuina group. Ratio of male to female was about 1.13 : 1 based on 25 trials[26–39,41–50,52] reporting this information. The average age of participants was 4 months to 14 years according to 17 trials.[26–27,29–32,34,36,38,41,44,46–48,50–52] The duration of anorexia was 2 weeks to 4 years based on 13 trials.[29–31,34–35,38–39,44,46–47,50–52] Only one trial[41] reported the severity of the disease. The treatment duration of tuina for majority included trials mainly varied from 7 days to 15 days, and the frequency for all included trials was once a day.

In summary, there were two categories of comparisons among all the included trials. One was tuina compared with western medicine (mainly included vitamin preparations and trace elements, *e.g.* zinc), and the other was tuina compared with Chinese herbs (Chinese patent medicine or Chinese medicine decoction for enhance stomach digestive function, *e.g.* Jianwei Xiaoshi Oral Solution, Sijunzi Decoction and Yigong San Granules, et al).

3.3. Assessment of risk of bias

In terms of the random sequence generation methods of the

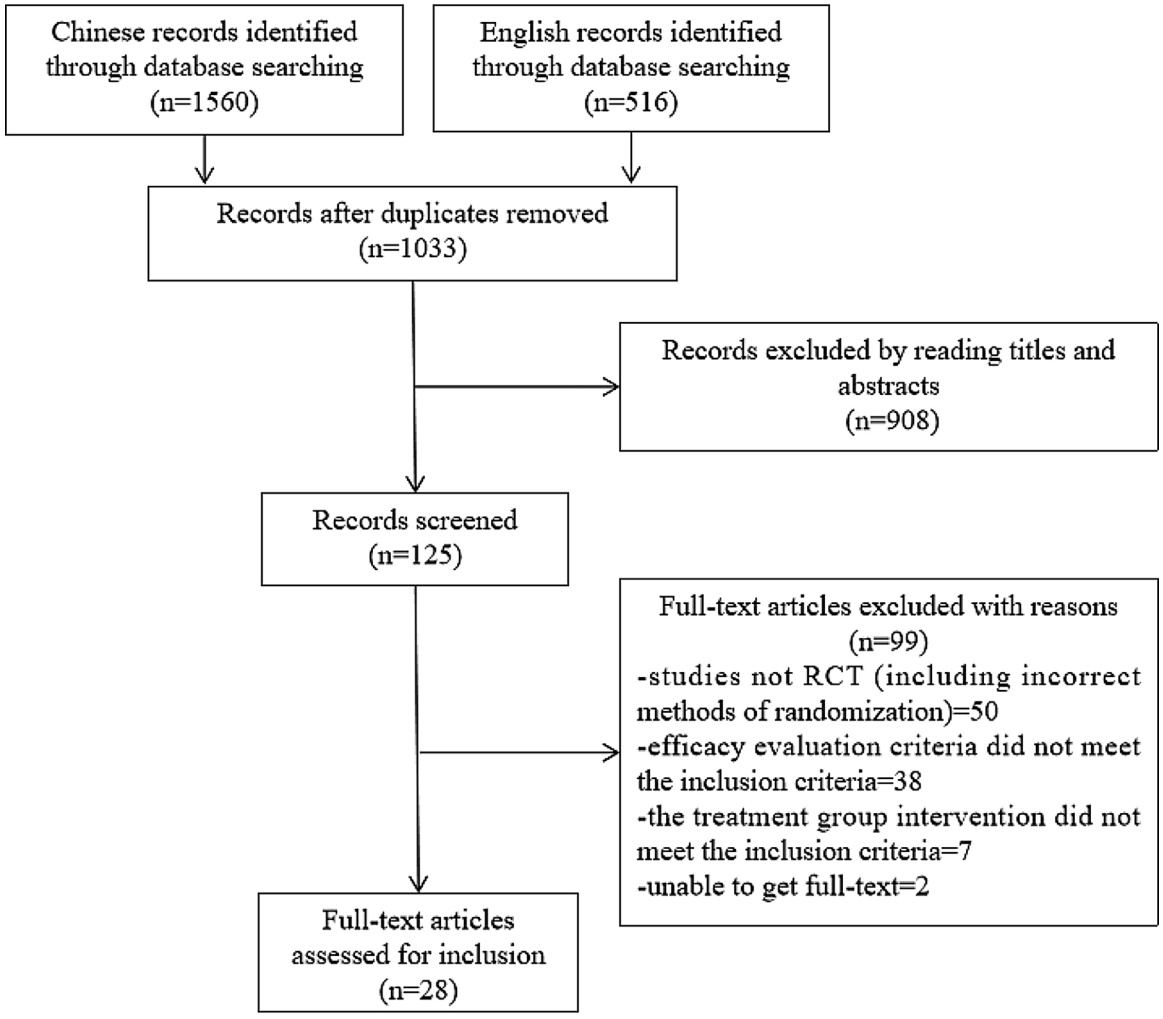

Fig. 1. Flow diagram of searches and study selection.

Table 1
The characteristics of included 28 trials.

Study ID	Sample size (M/F)		Age		Duration of anorexia		Control group		Course of treatment	Outcoms
	T	C	T	C	T	C	Intervention	Type		
Cai KY2016[25]	60		2.51 ± 0.97 y	2.67 ± 1.19y	1.15 ± 0.93y	1.05 ± 1.03 y	*Xiao'er Xiaoshi* Tablets (oral)	CH	28d	①②③
Cui X2008[26]	44/19	32/14	3.85 ± 2.46y (0.5 − 12y)	3.46 ± 2.10y (0.5 − 12y)	NR	NR	Licorzinc Granules (oral)	CH	14d	①②
Cui X2012[27]	27/20	19/13	2.89 ± 1.71y (1 − 8y)	3.38 ± 1.45y (1 − 8y)	19.43 ± 2.71 m	17.30 ± 2.60 m	*Jianwei Xiaoshi* Oral Solution (oral)	CH	6d	①
Dai LH2014[28]	17/13	18/12	3.47 ± 1.76y	3.87 ± 1.65y	13.37 ± 14.04 m	13.63 ± 9.78 m	*Sijunzi* Decoction (oral) + *Pingwei San* (oral)	CH	12d	①
Du HM2019[29]	28/32	25/35	3.91 ± 0.80y (1 − 6y)	4.12 ± 0.90y (1 − 6y)	7.22 ± 1.48 m (3 − 12 m)	6.91 ± 1.51 m (3 − 12 m)	*Xiao'er Chanwei Kang* Granules (oral)	CH	10d	①
He Y2016[30]	20/12	18/14	4.70 ± 1.40y (2 − 7y)	4.80 ± 1.50y (1 − 8y)	14.7 ± 1.3 m (13 − 17 m)	14.5 ± 1.5 m (12 − 18 m)	*Huashi Xiaoji* Oral Solution (oral)	CH	7d	①
Ji LY2015[31]	20/25	23/22	23.29 ± 16.01 m (1 − 6y)	20.59 ± 14.38 m (1 − 6y)	1 − 19m		*Yanshi* Granules (oral)	CH	NR	①
Jiang YL2010[32]	16/14	15/15	1 − 6y	1 − 6y	NR	NR	*Bailing Jianpi* Granules (oral)	CH	10d	①②
Li HM2011[33]	13/17	14/16	3.10 ± 1.03y	3.26 ± 1.00y	NR	NR	*Xiao'er Xiaoshi* Tablets (oral)	CH	28d	①②
Li JY2019[34]	19/24	21/22	8.24 ± 3.04y (3 − 12y)	9.01 ± 3.51y (4 − 13y)	14.57 ± 5.57 m (1.3 − 20.5 m)	15.24 ± 6.12 m (1.5 − 2.8 m)	Self-made Xiaoshi Jianpi Decoction (oral)	CH	28d	①③
Liang FY2015[35]	18/12	16/14	3.63 ± 1.75y	3.37 ± 1.87 y	2w-3 m	2w-3 m	*Yigong San* Granules (oral)	CH	10d	①③
Lv J2007[36]	21/9	15/15	1 − 6y	1 − 6y	2.20 ± 0.52y	1.89 ± 0.99y	*Xiao'er Huashi Xiaoji* Oral Solution (oral)	CH	7d	①②
Tang LZ2017[37]	16/14	17/13	40.47 ± 16.22 m	40.80 ± 17.29 m	10.57 ± .68 m	9.67 ± 5.31 m	*Shanmai Jianpi* Oral Solution (oral)	CH	30d	①②③
Wang GJ2013-1[38]	12/8	7/13	1 − 14y		3 w		*Jian'er Su* Granules (oral)	CH	14d	①
Wang GJ2013-2[38]	12/8	11/9	1 − 14y		3 w		Zinc Gluconate Granules (oral)	WM	14d	①
Wu Q2016-1[39]	64/61	51/74	3.50 ± 2.30y	3.30 ± 2.20y	2m-4y		*Sijunzi* Decoction (oral)	CH	10d	①③
Wu Q2016-2[39]	64/61	56/69	3.50 ± 2.30y	3.70 ± 2.30y	2m-4y		2‰ Zinc Sulfate Oral Solution (oral) + Yeast Tablets (oral)	WM	10d	①③
Xiao YB2010[40]	248		NR		NR		*Jianwei Xiaoshi* Tablets (oral)	CH	15d	①
Zhang JJ2016[41]	9/21	12/18	1 − 6y	1 − 5y	NR	NR	*Jian'er Xiaoshi* Oral Solution (oral)	CH	30d	①
Zhang Q2013-1[42]	16/14	18/12	5.52 ± 1.34y	4.98 ± 2.11y	NR	NR	*Jian'er Su* Granules (oral)	CH	14d	①②
Zhang Q2013-2[42]	16/14	17/13	5.52 ± 1.34y	5.43 ± 1.42y	NR	NR	Zinc Gluconate Granules (oral)	WM	14d	①②
Zhou H2017[43]	19/17	17/19	32.77 ± 17.46 m	26.37 ± 15.46 m	301.00 ± 254.37d	267.83 ± 210.21d	*Xiao'er Jianwei Xiaoshi* Tablets (oral)	CH	12d	①②④
Deng LJ2018[44]	33/35	38/30	2.51 ± 1.48y (4m-6y)	2.35 ± 1.50y (0.5 − 6y)	5.04 ± 5.42 m (1m-2y)	5.28 ± 4.95 m (1m-2y)	Lysine Inosite and Vitamin B_{12} Oral Solution (oral)	WM	12d	①②
Huang ZQ2014[45]	18/17	19/16	2.78 ± 1.69y	2.89 ± 1.51y	NR	NR	Lysine Inosite and Vitamin B_{12} Oral Solution (oral)	WM	14d	①②③
Jian YM2007[46]	28/17	25/20	2 − 12y	2 − 12y	6 m-3y	6 m-3y	Multivitamin Tablets (oral) + Multienzyme Tablets (oral)	WM	90d	①
Sun FY2019[47]	18/14	18/14	4.50 ± 1.77y (1 − 9y)	4.80 ± 1.60y (1 − 8y)	13.9 ± 1.6 m (11 − 18 m)	14.3 ± 1.5 m (10 − 18 m)	Multivitamin Tablets (oral) + Multienzyme Tablets (oral)	WM	10d	①
Wang C2018[48]	24/16	27/13	5.00 ± 1.20y (2 − 12y)	5.10 ± 1.30y (2 − 12y)	NR	NR	Calcium and Zinc Gluconate Oral Solution (oral)	WM	7 − 21d	①
Wang KT2017[49]	13/15	14/14	3.45 ± 0.89y	3.21 ± 1.02y	NR	NR	Domperidone Suspension (oral)	WM	14d	①④
Xu H2016[50]	18/18	20/16	6.58 ± 0.56y (1 − 12y)	6.85 ± 0.88y (1 − 12y)	2.45 ± 0.11 w (2 − 3 w)	2.48 ± 0.18 w (2 − 3 w)	Zinc Gluconate Granules (oral)	WM	14d	①
Zeng YE2015[51]	75		0.5 − 3y		3 w		Multivitamin Tablets (oral) + Multienzyme Tablets (oral)	WM	30d	①
Zhang LQ2019[52]	80/54		1 − 7y		8 − 15 m		Multivitamin Tablets (oral) + Multienzyme Tablets (oral)	WM	10d	①

T: Treatment group; C: Control group; CH: Chinese herbs; WM: Western medicine; y: years; m: months; w:weeks; d: days; NR: Not reported. ①Significant effective rate; ②Food intake; ③Adverse events; ④Compliance.

included 28 trials, 11 trials[27–28,33,34,37,39,43–44,48,52] used random number tables, two trials[47,50] used lot-drawing, one trial[42] used Excel software and the remaining 14 trials[25–26,29–32,34,36,38,40–41,46,49,51] only mentioned random or randomization without describing the specific randomization methods. In terms of allocation concealment, only one trial [37] performed this by using a sealed, opaque envelope. Therefore, the risk of selection bias was unclear for the majority of the included trials due to insufficient information being available on random sequence generation and allocation concealment. The risk of performance bias was high for all included trials due to absence of blinding to participants and personnel. Only three trials [37,39,43] performed blinding regarding the outcome assessment and the remaining 25 trials[25–36,38,40–42,44–52] did not report relevant information, thus the risk of detection bias for majority of the included trials was unclear. In terms of attrition bias, 24 trials[26–30,32–35,37–44,46–52] were assessed as low risk due to complete outcome data or incomplete outcome data being adequately addressed, and the remaining four trials[25,31,36,45] were assessed as high risk due to incomplete outcome data that were not adequately addressed. Since all protocols or registration information of the included trials were not available, the reporting bias for all trials was assessed as unclear. All 28 trials reported the comparability of baseline data, so they were assessed as having low risk of other bias. Fig.2 demonstrates the risk of bias of included 28 trials.

3.4. Effects of interventions

All the included trials reported the primary outcome of significant effective rate, 9 trials[25–26,32–33,36–37,42–43,45] reported food intake, six trials[25,34–35,36,38,45] reported adverse events information and two trials[43,49] reported compliance with interventions. We conducted a subgroup analysis according to different courses of treatment. We were unable to perform a subgroup analysis based on gender because a mixed population of male and female children with anorexia in all included trials.

3.4.1. Primary outcome of significant effective rate

3.4.1.1. Comparison 1: tuina compared with western medicine. A pooled results showed that tuina was superior to western medicine (RR 1.68, 95 % CI [1.35, 2.08], 12 RCTs[38–39,42,44–52] involving 1116 participants). As P = 0.0002 < 0.10, I^2 = 69 % < 50 %, subgroup analysis was conducted according to the treatment duration: for short courses of treatment, nine trials[38–39,42,44–45,47,49–50,52] showed that tuina was also more beneficial compared with western medicine (RR 1.77, 95 % CI [1.34, 2.34]); for medium courses of treatment, one trial[51] showed that there was no statistically difference (RR 1.26, 95 % CI [0.70, 2.30]) between tuina and western medicine; for long courses of treatment, one trial[46] showed that tuina had a better effect than western medicine (RR 1.76, 95 % CI [1.15, 2.71]). One trial[48] reported seven to twenty-one days of treatment (both short and medium courses of treatment) and showed that there was no statistically difference (RR 1.33, 95 % CI [0.87, 2.04]) between tuina and western medicine. Fig.3 illustrates the details of these results.

3.4.1.2. Comparison 2: tuina compared with Chinese herbs. A pooled results showed that tuina was superior to Chinese herbs (RR 1.36, 95 % CI [1.19, 1.55], 19 RCTs[25–43] involving 1676 participants). As P = 0.0005 < 0.10, I^2 = 60 % < 50 %, subgroup analysis was conducted according to the treatment duration: for short courses of treatment, a meta-analysis of data from 13 trials[26–30,32,35–36,38–40,42–43] showed that tuina was more beneficial than Chinese herbs (RR 1.25, 95 % CI [1.09, 1.44]); for medium courses of treatment, a meta-analysis of data from 5 trials[25,33–34,37,41] showed that tuina was more effective than Chinese herbs (RR 1.66, 95 % [CI 1.20, 2.28]); for long courses of treatment, no trial reported this outcome; one trial[31] did not report the treatment course and showed that tuina was more beneficial than Chinese herbs (RR 1.47, 95 % CI [1.09, 1.99]). Fig.4 illustrates details of these results.

3.4.2. Secondary outcomes

3.4.2.1. Food intake

3.4.2.1.1. Comparison 1: tuina compared with western medicine. Only 2 trials reported this outcome, and both were short courses of treatment. A pooled data of the two trials[42,45] showed that tuina was superior to western medicine (MD -0.88, 95 % CI [-1.27, -0.50]) on lightening the reduction degree of food intake. Fig.5 illustrates details of the result.

3.4.2.1.2. Comparison 2: tuina compared with Chinese herbs. A pooled date of 8 trials[25–26,32–33,36–37,42–43] showed that tuina was better than Chinese herbs (MD -0.69, 95 % CI [-1.00, -0.38]) on lightening the reduction degree of food intake. As P = 0.02 < 0.10, I^2 = 58 % < 50 %, subgroup analysis was conducted according to the treatment duration: for short courses of treatment, a meta-analysis of 5 trials[26,32,36,42–43] showed that tuina was more beneficial than Chinese herbs (MD -0.61, 95 % CI [-1.06, -0.16]); for medium courses of treatment, a meta-analysis of data from 3 trials[25,33,37] showed that tuina was better than Chinese herbs (MD -0.81, 95 % CI [-1.21, -0.41]); for long courses of treatment, no trial reported this outcome. Fig.6 illustrates details of these results.

3.4.2.2. Adverse events. In total, six trials[25,34–35,37,39,45] reported adverse event information. Of these, 5 trials[25,34,37,39,45] reported no adverse events occurring in either the tuina or the medicine group. One trial[34] reported 5 cases with adverse events (two bloating, one nausea and two vomiting) occurred in Chinese herbs group and no adverse events occurred in tuina group.

3.4.2.3. Compliance with interventions. Two trials[43,49] reported this outcome. One trial[49] reported that all patients included had cooperated in completing the trial. Another trial[43] reported that some patients had poor compliance and could not complete half of the treatment course and dropped out of the trial.

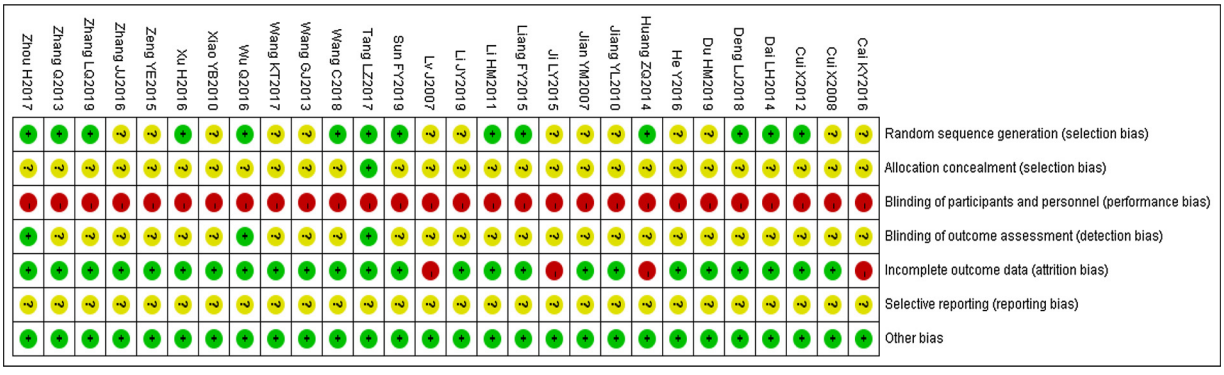

Fig. 2. Risk of bias of all the included studies.

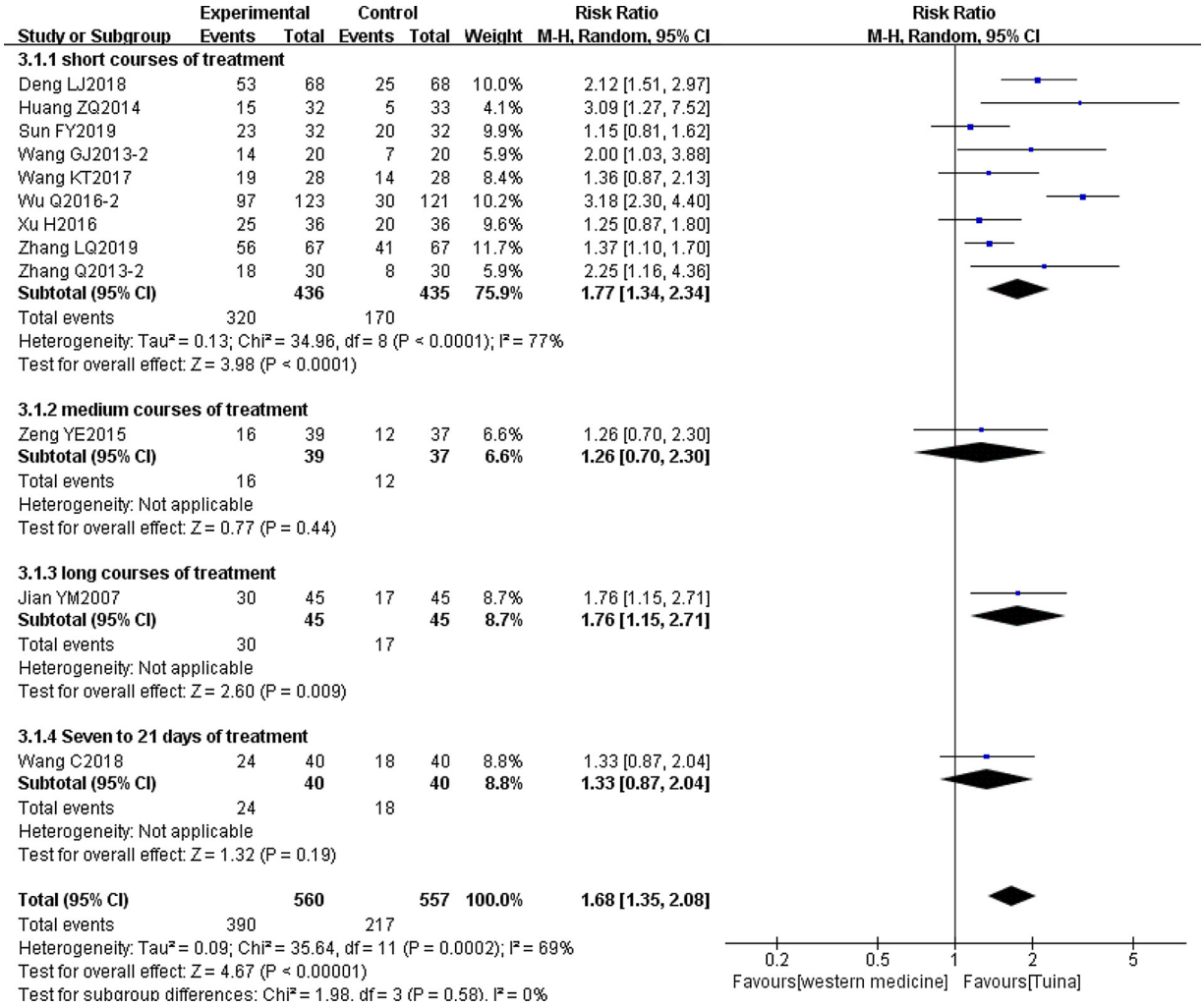

Fig. 3. Forest plot comparison between pediatric Tuina *versus* western medicine on significant effective rate.

3.5. Certainty of evidence by GRADE

Certainty of evidence for key outcomes were all evaluated as low or very low. Table 2 showed the details of the certainty of available evidence. The certainty of evidence was downgraded mainly due to the following three reasons: high risk of bias (such as no trial achieved blinding to participants and personnel); inevitable clinical heterogeneity between studies, such as variable level of specialist expertise and intensity of tuina in comparator conditions; only one trial with small sample size was included.

3.6. Trial sequential analysis

TSA of 19 trials comparing tuina with Chinese herbs for significant effective rate showed that the Z-curve (blue dashed line) crossed the lower 1.96 (black solid line) and the trial sequential monitoring boundary for benefit (lower red solid line), but not the TSA required information size (= 3041, vertical red line), as shown in Fig.7-A. This indicates that tuina for children with anorexia may be encouraging, but we did not have sufficient power to confirm the conclusion before acquired information size of 3041 participants (that mean the sample size was not large enough for confirm the conclusion).

TSA of 12 trials comparing tuina with western medicine for significant effective rate also showed that the Z-curve (blue dashed line) crossed the lower 1.96 (black solid line) and the trial sequential monitoring boundary for benefit (lower red solid line), but not the TSA required information size (= 3248, vertical red line), as shown in Fig.7-B. This indicates that tuina for children with anorexia may be a potentially useful treatment, but we did not have enough power to confirm the conclusion before acquired information size of 3248 participants.

3.7. Funnel plot analysis

Funnel plot analysis (see Fig.8) was conducted for two comparisons (tuina *versus* western medicine or Chinese herbs) separately, due to the number of RCTs included in each meta-analysis was more than ten. As can be seen from the figure, both funnel plots (Fig.8-A and Fig.8-B) are asymmetrical, and the degree of asymmetry of Fig.8-A is more obvious. This demonstrates that publication bias probably existed in the included literature.

4. Discussion

4.1. Summary of the main findings

Twenty-eight RCTs involving 2650 participants (complete data sets were available for 2619 participants for use in the data analysis) were included in this review. The results of this review showed that tuina was better than western medicine or Chinese herbs on increasing significant effective rate and food intake for anorexia in children under 14 years. Subgroup analysis according to different courses of treatment showed

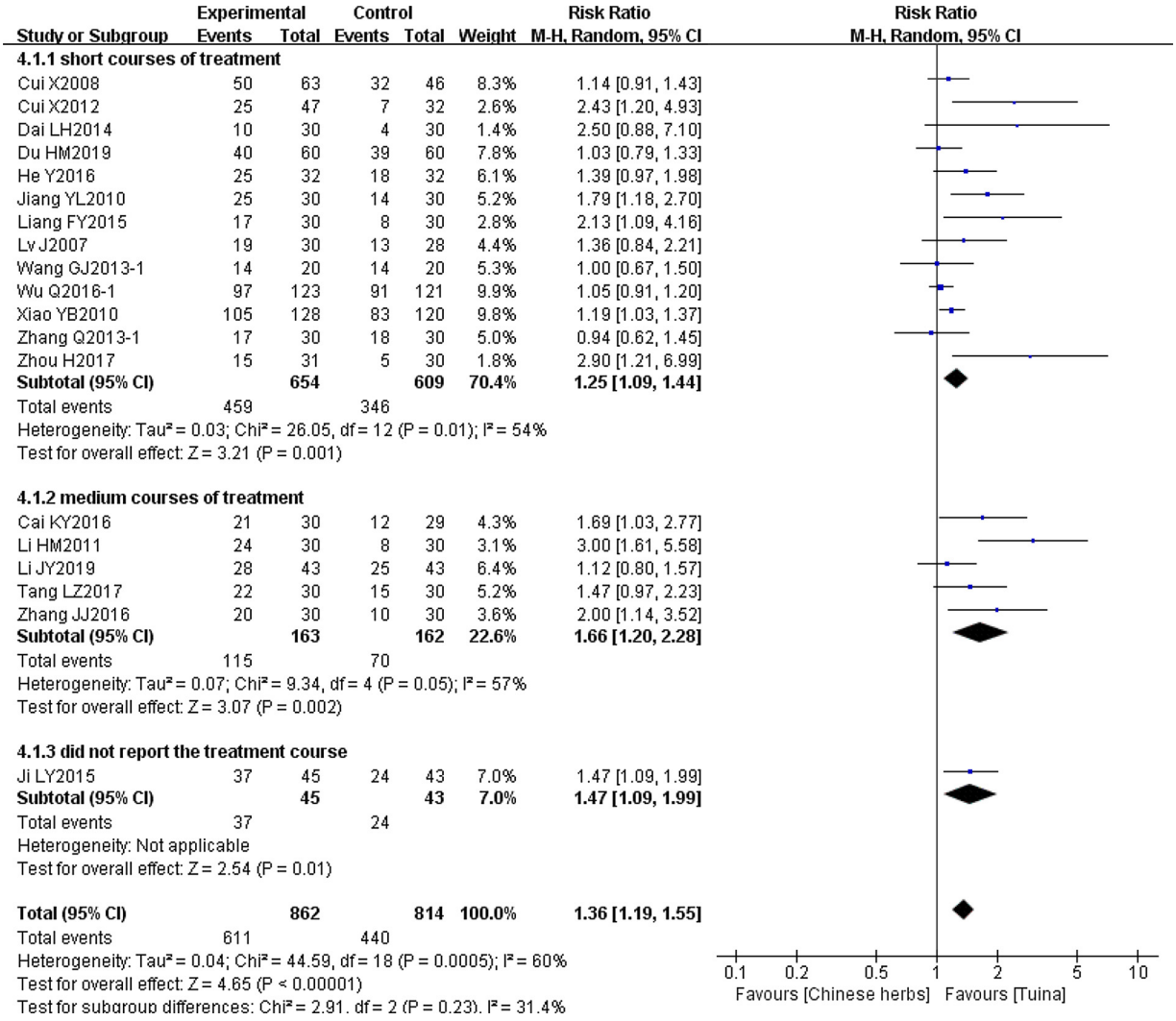

Fig. 4. Forest plot comparison between pediatric Tuina *versus* Chinese herbs on significant effective rate.

that the longer the course of treatment, the greater possible benefits of tuina and that, tuina was safe for children with anorexia. However, sufficient evidence to confirm the conclusion on safety is still required.

4.2. Comparison with previous studies

A previous review[53] showed that the total clinical effective rate of tuina group was higher than that of control group. Our review analyzed the significant effective rate, and the result showed that tuina group was better than that of control group. In addition, our review analyzed improvement of main symptom (food intake), safety outcomes (adverse reactions/events) and compliance. Furthermore, our review conducted subgroup analyses based on different treatment courses. The search date for the previous systematic review was up to December 2016, and our review was up to June 2019.

4.3. Limitations

This review not only draws conclusions about the total clinical effective, but also on the main symptom (food intake), safety outcomes (adverse reactions/events) and compliance. In addition, the subgroup analysis was performed based on treatment duration in this review. These are more comprehensive and conducive to guiding the clinical application of tuina in the treatment of anorexia.

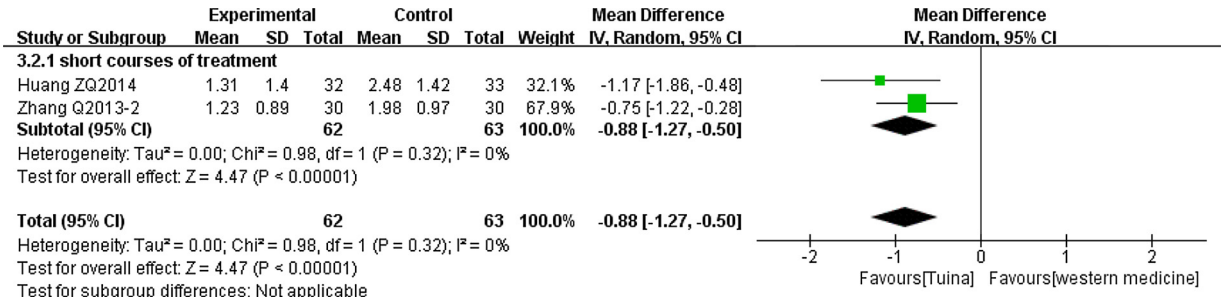

Fig. 5. Forest plot comparison between pediatric Tuina *versus* western medicine on food intake.

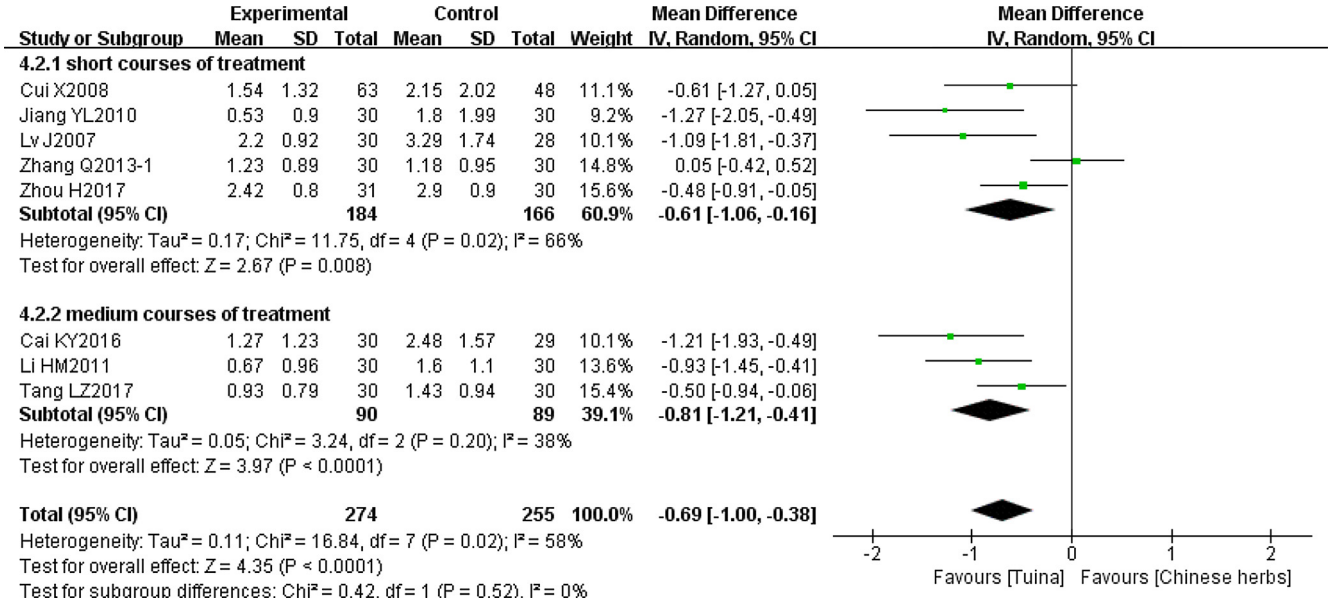

Fig. 6. Forest plot comparison between pediatric Tuina *versus* Chinese herbs on food intake.

There are also some limitations. First, although the included studies used pediatric tuina, there may be some differences in the choice of the massage site or technique for each study. Another potential limitation of this review was the language restriction for literature searching. Due to resource constraints, other language publications such as Japanese or Korean were not retrieved, which may have missed some relevant trials.

4.4. Implications for clinical practice

For children with anorexia, oral medication is difficult. Tuina, as a non-pharmaceutical therapy, can help children with anorexia to overcome this problem. Moreover, this review found that tuina was more beneficial in treating anorexia in those under 14 years than western medicine and Chinese herbs. Also, tuina was safe. Therefore, tuina may be a good choice for anorexia in children under 14 years, especially for children with poor medication compliance. According to the course of treatment of the included trials, it is recommended that children with anorexia should be treated with tuina for at least 2 weeks. The frequency of treatment is once a day or 6 days a week. However, current evidence is insufficient to directly guide the clinical use of tuina due to potential bias and the poor quality of included trials. Also, all the included studies were conducted in China, and different countries have different definition and diagnostic criteria for pediatric anorexia. Therefore, whether this evidence is equally applicable to other countries outside China requires further studies in other countries.

4.5. Implications for future research

One of the main reasons for the decline in evidence grade is the high risk of bias caused by the poor methodological quality of the included studies. Future studies should pay more attention to research methodology, such as randomization (including the correct generation of random sequences and the effective implementation of random allocation concealment), blinding, estimation of sample size, missing data management and so on. One of big challenge for the trial of tuina is blinding. It is very difficult to blind the patients to avoid performance bias is because of the particularity of tuina. But in our systematic review, the participants were all children under 14 years, so clinically, the influence of lack of blinding could be less than that on adult participants. But we still have the problem that the influence of their parents is unavoidable in terms of efficacy evaluation, such as the efficacy evaluation of food intake, parents who tend to give their children medication but are assigned to the tuina group may deliberately underestimate the effect of tuina. However, the blinding of outcome assessment would be possible in such trials and it could help to avoid detection bias during the assessment of significant effective rate and food intake, so to avoid overestimate of the results. Small sample size is also one of the main reasons for the decline of evidence grade. Furthermore, the results of TSA indicated that a firm conclusion of the effectiveness of tuina cannot be reached before acquired information size. Therefore, large sample, multi-center RCTs should be conducted in the future.

In addition, most studies only treated participants for short-term or medium-term treatment, but not for long-term treatment. Moreover, most studies did not follow up the participants after treatment to observe the recurrence rate. Therefore, it is suggested that future studies should be longer (in addition to long-term treatment of subjects, long-term follow-up after treatment should be conducted to identify recurrence). Safety is also important for application of tuina, but most of included RCTs did not report this outcome. So, future studies should aware of this and report the safety outcome.

5. Conclusion

Low or very low certainty of evidence suggested pediatric tuina was beneficial and safe for the treatment of anorexia in children under 14 years. Furthermore well-designed RCTs with adequate sample sizes are needed.

Author's contribution

JPL and SBL conceived and designed the review. SBL, QHC and JL were responsible for the searching, screening and selecting studies. SBL and QHC participated in data extraction. BYL and YPZ assessed the risk of bias of the included trials. SBL performed the statistical analysis. BYL, HJC and XB helped to perform the statistical analysis. SBL drafted the manuscript. JPL, HJC, YC and NR were all involved in critically revising the manuscript. All authors have read and approved the final manuscript. All authors approved the final version of the article, including the authorship list.

Table 2
GRADE evaluation form of evidence certainty.

Patient or population:children with anorexia					
Setting: outpatients and wards					
Intervention: pediatric Tuina comparison: medicine therapy					
Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Anticipated absolute effects[a] (95% CI)		Relative effect (95 % CI)
			Risk with Tuina	Risk with control group	
Significant effective rate					
● Tuina *versus* western medicine	1117 (12 RCTs)	⨁⨁◯◯[1,2] (Low)	655 per 1000 (526–810)	390 per 1000	RR 1.68 (1.35–2.08)
- *-Short courses of treatment (≦15 days)*	871 (9 RCTs)	⨁⨁◯◯[1,2] (Low)	692 per 1000 (524–914)	391 per 1000	RR 1.77 (1.34–2.34)
- *-Medium course of treatment (16－30 days)*	76 (1 RCTs)	⨁⨁◯◯[1,3] (Low)	409 per 1000 (227–746)	324 per 1000	RR 1.26 (0.70–2.30)
- *-Long course of treatment (> 30 days)*	90 (1 RCTs)	⨁⨁◯◯[1,3] (Low)	665 per 1000 (434 to 1000)	378 per 1000	RR 1.76 (1.15–2.71)
- *-Seven to twenty-one days of treatment*	80 (1 RCTs)	⨁⨁◯◯[1,3] (Low)	599 per 1000 (392–918)	450 per 1000	RR 1.33 (0.87–2.04)
● Tuina *versus* Chinese herbs	1676 (19 RCTs)	⨁⨁◯◯[1,2] (Low)	735 per 1000 (643–838)	541 per 1000	RR 1.36 (1.19–1.55)
- *-Short courses of treatment (≦15 days)*	1263 (13 RCTs)	⨁⨁◯◯[1,2] (Low)	710 per 1000 (619–818)	568 per 1000	RR 1.25 (1.09–1.44)
- *-Medium course of treatment (16－30 days)*	325 (5 RCTs)	⨁⨁◯◯[1,3] (Low)	704 per 1000 (575–864)	432 per 1000	RR 1.63 (1.33–2.00)
- *-Long course of treatment (> 30 days)*	None				
- *-Did not report the treatment course*	88 (1 RCTs)	⨁⨁◯◯[1,3] (Low)	820 per 1000 (608 to 1000)	558 per 1000	RR 1.47 (1.09–1.99)
Food intake					
● Tuina *versus* western medicine	125 (2 RCTs)	⨁◯◯◯[1,2,3] (Very low)	MD 0.88 lower (1.27 lower to 0.5 lower)		
- *Short courses of treatment (≦15 days)*	125 (2 RCTs)	⨁⨁◯◯[1,3] (Low)	MD 0.88 lower (1.27 lower to 0.5 lower)		
- *Medium course of treatment (16－30 days)*	None				
- *Long course of treatment (> 30 days)*	None				
● Tuina *versus* Chinese herbs	529 (8 RCTs)	⨁⨁◯◯[1,2] (Low)	MD 0.69 lower (1 lower to 0.38 lower)		
- *Short courses of treatment (≦15 days)*	350 (5 RCTs)	⨁⨁◯◯[1,2] (Low)	MD 0.61 lower (1.06 lower to 0.16 lower)		
- *Mediun course of treatment (16－30 days)*	179 (3 RCTs)	⨁◯◯◯[1,2,3] (Very low)	MD 0.77 lower (1.08 lower to 0.47 lower)		
- *Long course of treatment (> 30 days)*	None				

GRADE Working Group grades of evidence.
Low certainty (⨁⨁◯◯): Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect;
Very low certainty (⨁◯◯◯): We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Reason for the downgrade of evidence: 1. high risk of performance bias (no trial achieved blinding to participants and personnel); 2. Inevitable clinical heterogeneity between studies, such as variable level of specialist expertise and intensity of Tuina in comparator conditions; 3. only one trial with small sample size was included.
No.: number; CI: Confidence interval; RR: Risk ratio; MD: Mean difference; RCT: randomized controlled trial.
[a] The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI).

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Conflicts of interest

All authors declare that they have no conflicts of interest concerning this article.

Statement

All data included in this review were supported by six open electronic databases for published studies. Details of the six databases were showed in Appendix 1.

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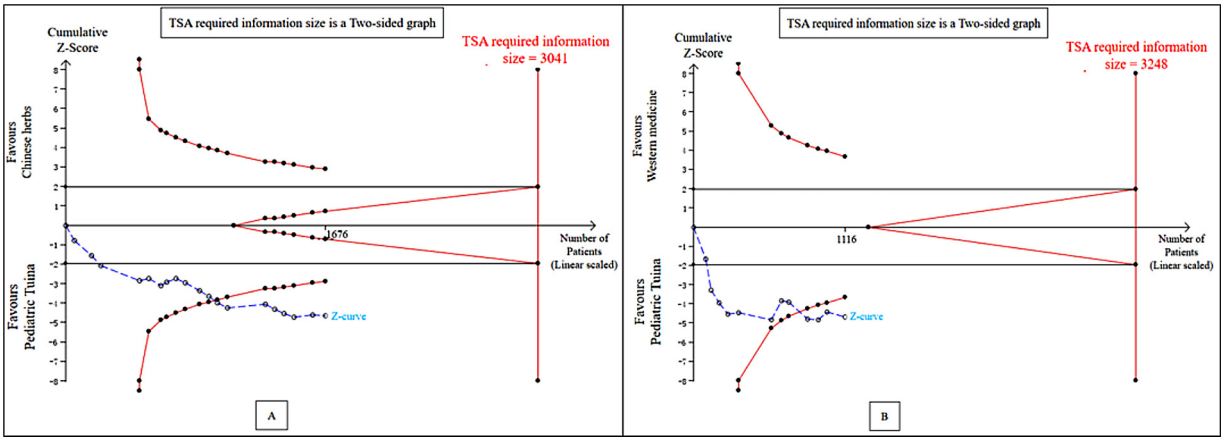

Fig. 7. Trial sequential analysis (TSA) for significant effective rate.

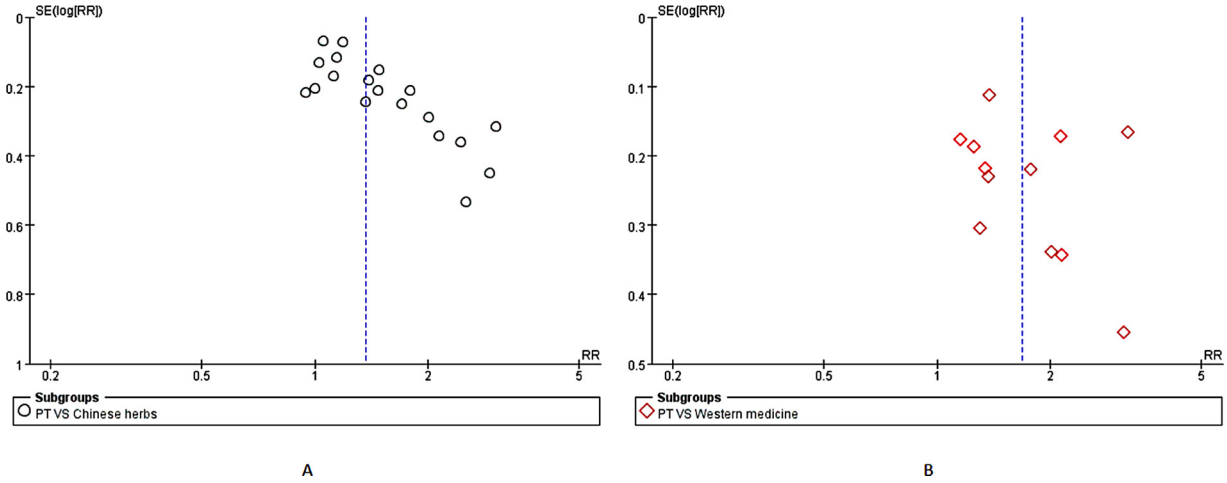

Fig. 8. Funnel plot of comparison between pediatric Tuina *versus* Chinese herbs (Fig.8-A) or western medicine (Fig.8-B) on significant effective rate.

Appendix 1 Search strategy for six open electronic databases

Databases	Search strategy
CNKI	#1: SU = 'Tuina(推拿)' + 'Anmo(按摩)' + 'Shoufa(手法)' + 'Nieji(捏脊)' + 'Mofu(摩腹)' #2: SU = 'Yanshi(厌食)' + 'Xiaoeryanshi(小儿厌食)' + 'Ertongyanshi(儿童厌食)' #3: #1 AND #2
Wanfang	#1: Major Topic:"Tuina(推拿)" + Major Topic:"Anmo(按摩)" + Major Topic:"Shoufa(手法)" + Major Topic:"Nieji(捏脊)" + Major Topic:"Mofu(摩腹)" #2: Major Topic:"Yanshi(厌食)" + Major Topic:"Xiaoeryanshi(小儿厌食)" + Major Topic:"Ertongyanshi(儿童厌食)" #3: #1 AND #2
VIP	#1: M = Tuina(推拿) OR M = Anmo(按摩) OR M = Shoufa(手法) OR M = Nieji(捏脊) OR M = Mofu(摩腹) #2: M = Yanshi(厌食) OR Xiaoeryanshi(小儿厌食) OR Ertongyanshi(儿童厌食) #3: #1 AND #2
PubMed	#1: (Tuina OR massage OR rubbing abdomen OR technique OR chiropractic OR spinal manipulation[MeSH Major Topic]) #2: (anorexia OR childhood anorexia OR infantile anorexia[MeSH Major Topic]) #3: #1 AND #2
Embase	#1: ('tuina':ti OR 'massage':ti OR 'rubbing abdomen':ti OR 'chiropractic':ti OR 'technique':ti OR 'spinal manipulation':ti) #2: ('anorexia':ti OR 'childhood anorexia':ti OR 'infantile anorexia':ti) #3: #1 AND #2
The cochrane library	#1: (Tuina OR massage OR rubbing abdomen OR chiropractic OR technique OR spinal manipulation):ti,ab,kw #2: (anorexia OR childhood anorexia OR infantile anorexia):ti,ab,kw #3: #1 AND #2

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