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E-mail: cjim_en@cjim.cn

Evidence-Based Integrative Medicine

Evaluation on Effectiveness and Safety of Chinese Herbs in Treatment of Sub-health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

ZHAO Jun[1,2], LIAO Xing[3], ZHAO Hui[1], LI Zhi-geng[4], WANG Nan-yue[5], and WANG Li-min[2]

ABSTRACT **Objective**: To evaluate the effectiveness and safety of Chinese herbs in the treatment of sub-health systematically. **Methods**: Nine databases were systematically and extensively searched to collect randomized controlled trials (RCTs) about Chinese herbs in the treatment of sub-health. The outcomes included overall effective rate, main symptoms, quality of life, etc. Literature screening, data extraction and quality assessment were conducted according to Cochrane Handbook 5.1. Meta-analysis was conducted to the included literature with Review Manager Software. **Results**: Seventy-two studies involving 9,296 patients with sub-health were included with 4,908 patients in experimental groups and 4,387 patients in control groups. The overall quality of included clinical research was not high. In the aspect of improving overall effective rate, relieving main symptoms, Pittsburgh sleep quality index (PSQI) score, Athens Insomnia Scale (AIS) score, Fatigue Scale-14 (FS-14), Cornell Medical Index (CMI) score and discontinuation rate, the effects of experimental groups were better than that of control groups. According to available research reports, adverse reactions in Chinese herb groups were mainly mild gastrointestinal symptoms, which did not affect the treatment. **Conclusion**: Chinese herbs have a curative effect in the treatment of sub-health. However, there are no clear criteria for diagnosis and curative effectiveness judgment globally, which would affect the accuracy of curative effect evaluation.

KEYWORDS sub-health, randomized controlled trials, Chinese medicine, systematic review

Sub-health is defined as "a state between health and illness", with signs of decline in vitality, body functions and adaptive capacity for a certain period of time.[1-6] Epidemiological surveies showed that there were 55% to 75% sub-health sufferers in China, with higher rates in the developed regions than the less developed.[7,8] The occurrence of sub-health has been on the increase,[9] reducing people's quality of life and work efficiency, and it is prone to develop into illness without prompt medical interferences. The pathogenesis of sub-health remains unclear, but some researchers believe it is related to society, environment, psychology, living habits, daily diet, inheritance etc.[10,11] mainly caused by mal-function of the neural system, immune system and endocrine system, and overall functional disorders. Currently there is no specific treatment for sub-health, merely symptomatic treatments,[11] applied to relieve the symptoms; but there could be hardly significant improvement.

There are some terms in Chinese medicine (CM) depicting the corresponding signs and symptoms or having similar meaning of sub-health, such as "zhi wei bing" (preventive treatment of disease), "wei bing" (slight ailment), "yu bing" (upcoming illness), etc. These CM terms refer to the precursor or inception of diseases, similar to the concept of sub-health in contemporary medicine. CM doctors hold that healthy condition results from the dynamic balance between human and nature, human and society, and the balance of yin and yang within human body. Once some pathogenic factors intervene in or even break this dynamic balance, the sub-health status or even illness occurs.[12] The diagnosis of sub-health mostly relies on patients' self-reported symptoms and tends to be very subjective, and CM has its unique advantage in the prevention, diagnosis and treatment of

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1. China Academy of Chinese Medical Science, Beijing (100700), China; 2. Beijing University of Chinese Medicine, Beijing (100029), China; 3. Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Science, Beijing (100700), China; 4. Institute of Basic Theory for Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing (100700), China; 5. Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing (100700), China
Correspondence to: Dr. ZHAO Hui, Tel: 86-10-64089838, Fax: 86-10-64013948, E-mail: huizh_519@126.com

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sub-health with its peculiar strategies of comprehensive analysis of the four examinations and treatment according to pattern differentiation. It is shown that CM was effective in treating sub-health.[13-15] This report mainly focuses on systematic review and meta-analysis of the outcomes of CM medicine treating sub-health.

METHODS

Database and Search Strategy

Several databases were searched from the foundation of the database until February 29, 2016, including China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Science and Technology Periodical Database (VIP), Wanfang Database, EMbase, MEDLINE, Clinical Trials, Web of Science, and Cochrane Library. The Chinese search terms are "ya jiankang" (sub-health), "ci jian kang" (also means sub-health), "zhongyi" (CM), and "zhongyao" (Chinese material medica). The English search terms are "subhealth", "sub-health", and "sub health". After searching both titles and full texts, 9,141 articles were got in the preliminary search. In accordance with Cochrane Handbook 5.1, two researchers independently screened the literature, extracted data and evaluated the quality, and ultimately there were 72[17,18,20-89] articles of randomized controlled trials (RCTs) of CM treating sub-health included.

Inclusion and Exlusion Criteria

Inclusion criteria included (1) study types: RCTs of Chinese herbs for treating sub-health, and no restriction on language or published form; (2) participants: research report for the sub-health patients, and no restriction on age, gender and race; (3) interventions: the control group treatment including Western medicine, CM, placebo control, blank control and other therapies, the experimental group treatment including Chinese herbs, Chinese herbs combined the other Chinese herbs, Chinese herbs combined with other therapies, and only adding Chinese herbs on the basis of the medicines used in the control group. Chinese herbs include Chinese herbal medicine compound based on syndrome differentiation, Chinese patent drug, extract of active ingredients of Chinese herbs and other kinds of CM formulations, unlimited usage; (4) outcomes: the main outcomes were the total effective rate and the symptom scores, the secondary outcomes include the quality of life, discontinuation rate, safety evaluation, compliance, and the other related indexes related to the therapeutic effects. Exclusion criteria included diagnosis of sub-health, but sub-health symptoms are not outstanding; wrong data; unable to get the full text; repetitive publication or repetitive data (keep the latest and most comprehensive, eliminate duplicate); other uncorrelated literature.

Statistical Methods

Meta-analysis was carried out using Review Manager Software (version 5.3), provided by the Cochrane Collaboration. Dichotomous data were presented as relative risk (RR) and continuous data as mean difference (MD) or standardized mean difference (SMD). For different studies with same variants, MD was used as the analysis quantity if using the same measuring tools, and SMD was used if using the different measuring tools,[16] 95% confidence interval (CI) were calculated in all the above analyses. The analyses of the therapeutic effect evaluation indicators conformed to the principle of intentional analysis. If there was no mention of intentional analysis data in the primary research, the systematic review would only include data that conform to our research plan.

Based on Cochrane Handbook5.0.2, heterogeneity were assessed using the I-squared (I^2), to find more about the source of heterogeneity, subgroup analysis were carried out, based on the difference in interventions, CM formula, outcome indicator, course of treatment, and some observation indicators in certain outcome indicator. For the studies with good clinical and methodological homogeneity, the fixed effect model were used to analyze; for those with statistical heterogeneity, if there was no significant clinical or methodological heterogeneity, random effect model were used. As for some indicators or subgroups that contain more than one study that cannot be combined, descriptive analysis was carried out using the effect sizes, 95% CI and forest plot. When research objects of a certain outcome indicator amounted to 10 or even more, funnel plot analysis was used to decide whether there was publication bias.

Based on the results of systematic, the GRADE profiler software recommended by Cochrane Collaboration was used to evaluate the quality of the evidence and determine the strength of recommendation with rating methods.

RESULTS

Analysis of Risk Bias

A total of 72 RCTs carried out in China were included, enrolling 9,295 cases of sub-health, with the

sample size varying from 26 to 1,356, totally 4,908 (52.80%) in the treatment group and 4,387 cases (47.20%) in the control group. Among the included 72 trials, 67 (93.05%) described the comparability of baseline data between groups, 39 (54.17%) reported same diagnostic criteria, 28 (38.89%) reported same treatment effect evaluation criteria. Nineteen included trials (26.38%) explained their randomization methods, 6 (8.33%) used random allocation concealment, 15 (20.83%) used blinding methods; 19 (26.38%) reported the number of patients who dropped out, withdrew, or lost to follow-up, 2 trials used intention-to-treat (ITT) analysis; 10 (13.89%) reported the follow-up results, 22 (30.56%) reported adverse effect, 4 (5.56%) reported adverse events. The adverse effects (AEs) in CM treatment groups were mainly minor gastrointestinal symptoms, not diminishing the treatment effect; 4 trials (5.56%) evaluate treatment compliance. No trial reported any record of trial registration or trial schemes, thus selective reporting bias was not clear.

Meta-Analysis

One study[17] included 4 intervene groups, another[18] included 6 intervene groups, but the interventions were independent of each other and there was no unit bias, and thus these studies as multi-arm trials were processed as follows: these studies[17,18] were transformed into 2- or 3-arm trials, and analyzed using random effect model.[19]

CM *vs.* Blank Control

Four studies[17,20-22] were included to evaluate overall effective rate, main symptoms, quality of life (QOL), and quality of sleep between CM and blank control groups. As for overall effective rate analysis, 3 studies[17,20,22] were included. There was no significant heterogeneity among the studies (P=0.26, I^2=25%). As one study[17] included 4 intervention groups, random effect model was used. The overall effective rate in CM groups was higher than that in blank control groups (RR=1.82, 95% CI: 1.39, 2.40; P<0.0001, Figure 1).

Four studies[17,20-22] were included for main symptom scores using descriptive analysis. A study[21] showed that the main symptoms scores in experimental groups were lower than that in the blank control groups after treatment, but the difference was not statistically significant (SMD=–0.22, 95% CI: –0.59, 0.15). The other 3 studies[17,20,22] showed that the main symptoms scores in experimental groups were higher than that in the blank control groups (SMD_{17a}=–2.28, 95% CI: –3.13, –1.43; SMD_{17b}=–1.95, 95% CI: –2.70, –1.20; SMD_{20}=–2.06, 95% CI: –2.51, –1.61; SMD_{22}=–0.94, 95% CI: –1.32, –0.55).

Two studies[21,22] were included for QOL, both used Abbreviated World Health Organization Quality of Life Questionaire (WHOQOL-BREF) to evaluate the patients' life quality, giving scores from the 4 aspects of physiology, psychology, environment and social relationships. As the 2 studies used different CM (Appendix 1, the difference in scores of 4 aspects between experimental and blank control groups was statistically significant, and the QOL of experimental groups was higher than that of the blank control groups. In 1 study[22] the score in the environmental aspect of the experimental groups was lower than that of the blank control groups, but the scores in the other 3 aspects of the experimental groups were all higher than that of the blank control groups.

One study[21] was included for quality of sleep, and showed that sleep improvement in the experimental group was higher than that of the control group (MD=–5.42, 95% CI: –7.57, –3.27; P<0.00001).

CM *vs.* Placebo Control

Six studies[23,24,26-29] were included in the analysis of overall effective rate by using descriptive analysis. The results showed that the overall effective rate in experimental groups was significantly higher than that in

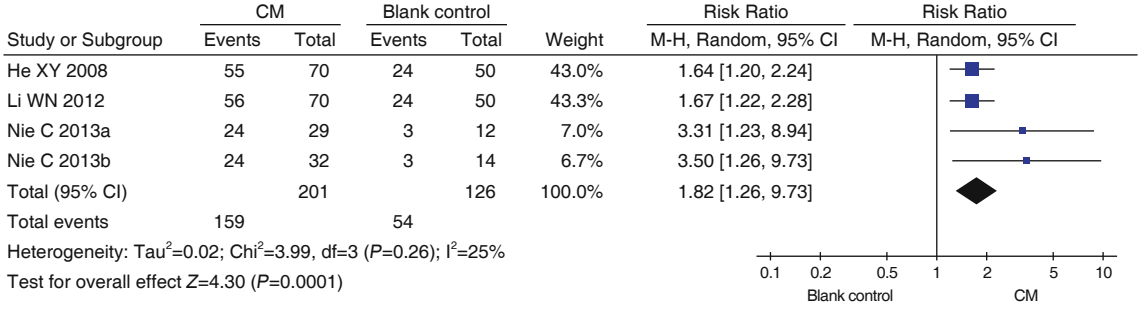

Figure 1. Comparison of Overall Effective Rate between CM and Blank Control Groups

the placebo groups (Appendix 2.1). Three studies[23,25,28] have reported that the treatment effect of the experimental groups was better than that of the placebo control groups in terms of FS-14 effect, leukocyte counts increase, chronic fatigue treatment [RR=1.44, 95% CI (1.14, 1.81), *P*=0.002; RR=3.75, 95% CI (1.97, 7.15), *P*<0.0001; RR=2.67, 95% CI (1.32, 5.39), *P*=0.006].

Four studies[25,26,28,29] were included for main symptom scores and descriptive analysis was carried out with SMD [95% CI] values as follows: –1.09 [–1.56, –0.62], –2.52 [–3.18, –1.85], –1.22 [–1.90, –0.54], –1.06 [–1.30, –0.81]. The scores of main symptoms alleviation of the experimental groups are better than that of placebo control groups.

One study[27] was included for analysis of QOL, which used WHOQOL-BREF of Taiwan version. The differences of scores of overall QOL both in 14 and 28 day were not statistically significant (Appendix 2.2).

One study[23] was included for fatigue status, which used FS-14 to report the fatigue scores in the follow-up surveys on day 42, 84, and 126. The MD [95% CI] were –1.22 [–1.96, –0.48] (*P*=0.001), –1.59 [–2.37, –0.81] (*P*<0.0001), and –1.77 [–2.54, –1.01] (*P*<0.00001). It is shown that relief of fatigue in experimental groups was greater than that in the placebo control groups in the monitoring point of time, and the patients continue to report significant improvement in the follow-ups (on day 84 and 126) after treatment.

CM *vs*. WM

Fifteen studies[30-40,42-44] were included in the analysis of overall effective rate. Since there was significant heterogeneity among them (*P*=0.0003, I^2=66%), random effect model analysis was conducted. One study[43] was removed due to high heterogeneity; the remaining studies showing medium heterogeneity (*P*=0.06, I^2=41%, Figure 2). CM groups had better therapeutic effect than WM groups [RR=1.18, 95% CI: 1.12, 1.25; *P*<0.00001]. Among these, 1 study[40] reported the overall effective rate in the follow-ups at 10 days after the treatment; 1 study[35] reported Pittsburgh Sleep Quality Index (PSQI) normal rate, showing that the difference between the two groups after treatment was statistically significant and the RR (95% CI) were 2.11 (1.52,2.92; *P*<0.00001), 1.29 (1.02,1.62; *P*=0.03), respectively.

Five studies[30,34,38,42,43] were included for main symptoms evaluation using fixed effect model. The therapeutic effect in CM groups was better than that in WM groups (SMD=–1.92, 95% CI: –2.14, –1.70; *P*<0.00001, Appendix 3.1).

Six studies[30,35,38-41] were included for quality of sleep and among them 3 studies[35,39,41] used PSQI, the results of which showing no difference through heterogeneity tests (*P*=0.43, I^2=0%), and thus fixed effect model was used to analyze the data. Scores of quality of sleep in CM groups were better than those of WM groups (MD=–2.11, 95% CI: –2.75, –1.46; *P*<0.00001, Appendix 3.2). The other 3 studies[30,38,41] used AIS showing no difference through heterogeneity tests (*P*=0.25, I^2=28%), and hence fixed effect model was used. The scores of quality of sleep in CM groups was better than those in WM groups (MD=–3.21, 95% CI: –3.74, –2.68; *P*<0.00001, Appendix 3.2).

One Particular CM *vs*. Other CMs

Fourteen studies[18,45-57] in total were included to evaluate overall effective rate, main symptom scores, QOL, sleep quality, fatigue status, Clinical Global Impression (CGI) scores, and discontinuation rate. One study[55] only reported the average score of "sleep improvement scale" and "fatigue measurement scale", not mentioning the standard deviation, and thus cannot be included in meta-analysis. One study[57] gave scores with its own sub-health screening and diagnosis scale (Appendix 4).

As for overall effective rate, 10 studies[18,45-53] were included, and there was significant heterogeneity among the studies (*P*<0.0001, I^2=71%). The studies were divided into 2 subgroups into Shen (Kidney) replenishing group and non-Shen replenishing groups. There were 2 studies[45,52] in the Shen replenishing groups with no heterogeneity (*P*=0.97, I^2=0%), and therefore fixed effect model was used. The overall effective rate in the particular CM groups was higher than that in other CM groups (RR=2.10, 95% CI: 1.69, 2.62; *P*<0.00001). Eight studies[18,46-51,53] was included in the non-Shen replenishing subgroups, the heterogeneity among them was small (*P*=0.06, I^2=45%) and 1 study[18] was a multi-arm test, and thus random effect model were used. The overall effective rate in the particular CM groups was higher than that in other CM groups (RR=1.30, 95% CI: 1.20, 1.42; *P*<0.00001, Appendix 4.1).

Two studies,[52,54] both using FS-14 to grade the

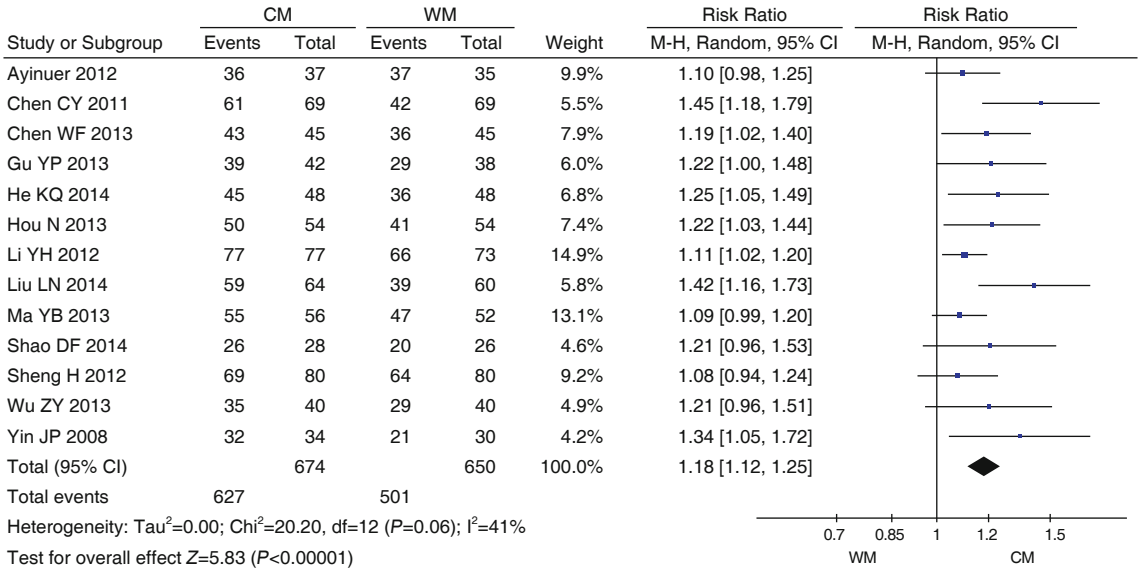

Figure 2. Comparison of Overall Effective Rate between CM and WM Groups

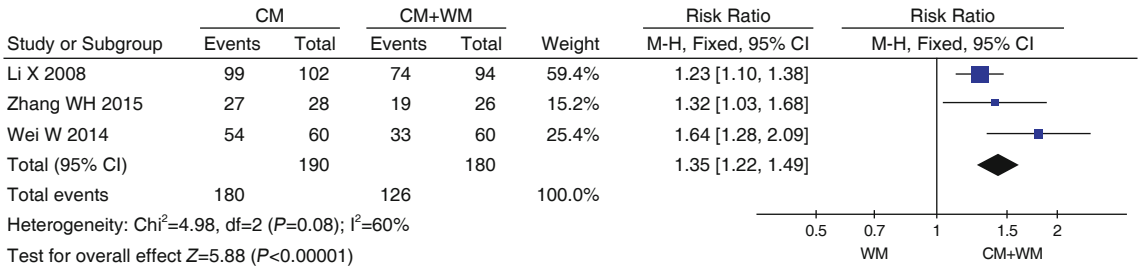

Figure 3. Comparison of Overall Effective Rate between CM Plus WM and WM Groups

performance, were included for fatigue status. One study[54] reported scores of mental fatigue, physical fatigue, and the total scores, and the other[52] only reported mental fatigue scores. They were divided into subgroups meta-analysis. The results of experimental groups were better than the control groups ($MD_{total\ scores}$=–2.24, 95% CI: –3.14, –1.34, *P*<0.00001; $MD_{mental\ fatigue}$=–0.90, 95% CI: –1.19, –0.60, *P*<0.00001; $MD_{physical\ fatigue}$=–1.22, 95% CI: –1.89, –0.55, *P*=0.0004, Appendix 4.2). One study[18] was included for CGI scores and showed that clinical general impression in the experimental groups was better than that in the control groups on day 28 (MD: –0.49, 95% CI: –0.75, –0.23; *P*=0.0002) and day 42 (MD: –0.62, 95% CI: –0.89, –0.35; *P*<0.00001).

CM Plus WM *vs.* WM

Three studies[58-60] were included to evaluate overall effective rate. Since there were medium heterogeneity (*P*=0.08, I^2=60%), random effect model was used, and overall effective rate in experimental groups was higher than that in control groups (RR=1.35, 95% CI: 1.22, 1.49, *P*<0.00001, Figure 3). As for quality of sleep, 2 studies[58,60] were included, both of which used PSQI to evaluate quality of sleep, the course of treatment were 28 and 40 days respectively. The results showed that quality of sleep in the experimental groups was higher than that in the control groups (RR_{28d}=-3.84, 95% CI: –4.77, –2.92; RR_{40d}=–1.37, 95% CI: –1.68, –1.06).

CM Plus Non-Medicine Intervention (NMI) *vs.* NMI

As for overall effective rate, 11 studies[61-71] were included in total. As there as high heterogeneity among the groups due to their difference in overall effective rate evaluation and course of treatment, only descriptive analysis could be carried out. The difference between experimental groups and control groups in 8 studies[61,63,64,66,67,69-71] was statistically significant, and the overall effective rate in the experimental groups was higher than that in the control groups; another 3 studies[62,65,71] reported higher effective rates in the experimental groups than the control groups, but there was no statistical significance in the difference; 1 study[68] reported FS-14 and the overall effective rate of main symptom scores, and it showed that these

were higher in the experimental groups than the control groups (RR_{FS-14}=1.19, 95% CI: 1.02, 1.39, *P*=0.03; $RR_{main\ symptoms}$=1.25, 95% CI : 1.05, 1.48, *P*=0.01). Other results of main symptom scores, QOL, and fatigue status were shown in Appendix 5.

CM Plus CM-Featured Sleep Guidance *vs*. CM

Three studies[72-74] were included for overall effective rate, which compared overall effective rate of groups using CM and CM combined with CM-featured sleep guidance, there was homogeneity (*P*=0.34, I^2=8%), and therefore fixed effect model was used and found that the overall effective rate between the two groups was quite similar (RR=0.99, 95% CI: 0.82, 1.49; *P*=0.85, Figure 4). One study[72] evaluated the overall rate of PSQI normally scored trials, the result in experimental group was better than that in the control groups (RR=1.36, 95% CI: 1.00, 1.84; *P*=0.85). Other analysis results of CGI main symptom scores, QOL, quality of sleep between groups were shown in Appendix 6.

A Particular CM Plus NMI *vs*. Other CM Plus NMI

As for overall effective rate, 2 studies[75,76] were included, both of which used the decrease rate of CMI and CM syndrome scores after treatment as their therapeutic effect evaluation indicators. One study[76] used the decrease rate of PSQI scores as its therapeutic effect evaluation indicators, and reported the overall effect in the follow-ups on day 14, 28 and 90 (Appendix 7.1). Taking decrease rate of CMI scores after treatment as the evaluation indicator, both studies[75,76] showed higher overall effective rate in experimental groups than control groups on every monitoring point of time, and the overall effective rate increased with the extension of course of treatment. Results in 1 study[76] were statistically significant, but results in another study[75] were not. Taking the decrease rate of CM syndrome scores as the evaluation indicator, 1 study[76] reported higher rate in experimental groups than in control groups with statistic significance. The another study[75] reported higher overall effective rate in experimental groups than control groups in the follow-ups on day 14, 28, 90 and it increased with the extension of course of treatment. The results of day 14 and 28 were statistically significant, but those of day 90 were not. Taking the decrease rate of PSQI scores after treatment as an indicator, 1 study[76] reported better performance in the experimental groups than the control groups at every monitoring point of time, which was statistically significant. The analysis results of CMI between groups were shown in Appendix 7.2.

CM Plus NMI *vs*. WM Plus NMI

For overall effective rate, 8 studies[77-83,85] were included, which showed homogeneity through heterogeneity text (*P*=0.40, I^2=4%), so fixed effect model was used. The overall effective rate of the experimental group was higher than that in the control group (RR=1.14, 95% CI: 1.07, 1.23; *P*=0.0002, Figure 5). The analysis results of quality of sleep between groups were shown in Appendix 8.

Others

There was only 1 study included in the intervention group comparisons, and some contained too many observation indicator scales to reveal the therapeutic effect of the interventions, thus we did not make any detailed analysis of them. The intervention group comparisons included: comparison between group of CM combined with kinesitherapy and group of kinesitherapy only,[86] comparison between group of CM combined CM doctors' advice on health preservation and group of CM health preservation guidance only,[87] comparison between group of oral administration CM combined with foot bath and group of ear acupuncture combined with sleep guidance,[88] and comparison between group of foot bath with CM and group of foot bath in hot water.[89] The outcome indicators include recurrence rate,[71] scale of observing fatigue,[69] self-rating scale of fatigue symptoms,[69] multi-dimensional

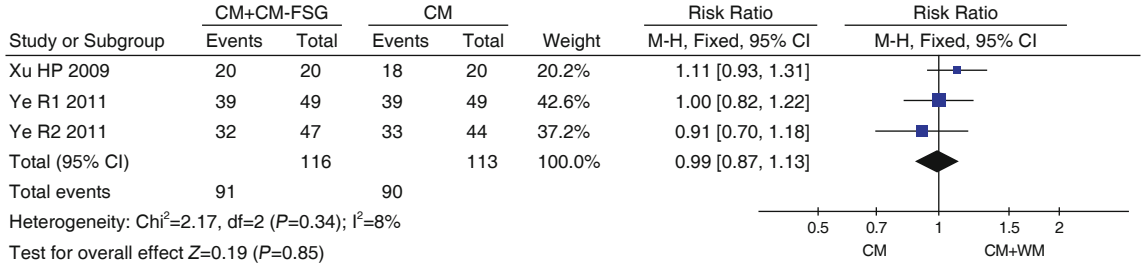

Figure 4. Comparison of Overall Effective Rate between CM and CM Plus CM-Featured Sleep Guidance Groups

Notes: FSG: teatured sleep guidance

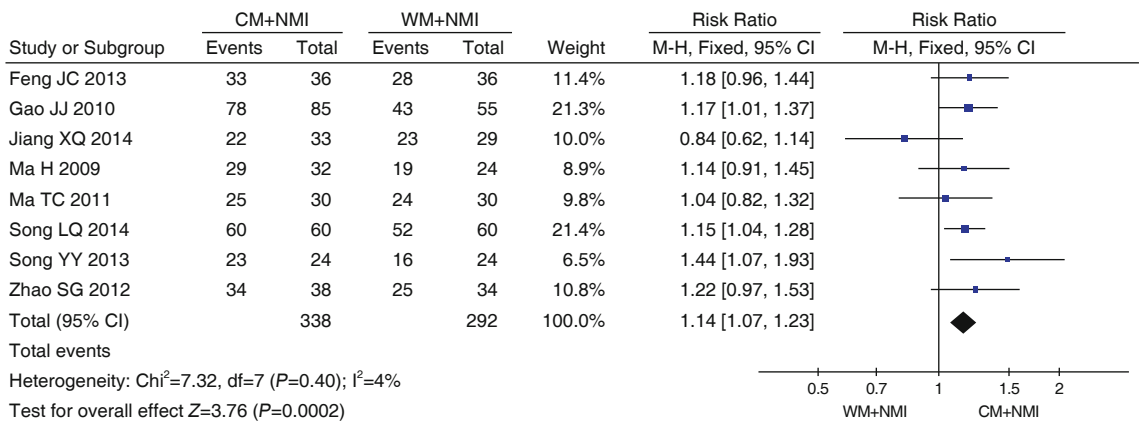

Figure 5. Comparison of Overall Effective Rate between Groups of CM Plus NMI and WM Plus NMI
Note: NMI: non-medicine intervention

scale of fatigue,[61] scale of sub-health,[63] scale of CM examination,[36] scale of response to psychological and social stresses,[23] Multifunctional Microscope Diagnostic Instrument (MDI) scoring,[52] PSQI with 6 sleeping factors,[72] self-rating scale of fatigue,[58] etc.

Funnel Plot Analysis

In this study, 14 studies were included for the comparison between groups using CM and groups using WM, 10 for the comparison between groups using one particular CM and groups using other CM, and 11 for the comparison between groups of CM+NMI and NMI only, with the overall effective rate as their outcomes. The funnel plot of the comparison between groups using CM and WM was shown in Appendix 9. It is not symmetrical, indicating that the included studies have varied qualities and publication bias existed.

Evidence Quality and Strength of Recommendation of GRADE System

As a large number of interventions and therapeutic effect evaluation indicators were included in this systematic review, here only evidence quality for the overall effective rate of main outcome indicators were evaluated. It showed that the evidence quality was low in the comparison between groups using CM and blank control, the comparison between CM and WM groups, the comparison between groups of CM combined with CM-featured sleep guidance and CM only, and the comparison between groups of CM combined with non-medicine intervention and WM combined with non-medicine intervention; evidence quality was rated as "extremely low" in the other comparison groups. With results from the 7 aspects of the "bias risk evaluation" tool mentioned above, we think the main reasons for the result of "low quality" or "extremely low quality" of the comparison evaluation are: (1) low quality of research plan design; (2) high heterogeneity among the studies; (3) existence of publication bias; (4) lack of evidence that can be updated; small effect size of combing the studies; no included studies studying the relationship between doses and therapeutic effects, etc.

DISCUSSION

Through qualitative, descriptive analysis and meta-analysis in this systematic review, it was found that treatment of CM alone, or combined with WM or other interventions had certain effect on improving overall effective rate and reliving main symptoms, especially when it comes to improving sleep and resisting fatigue. This conclusion is consistent with some results of the earlier systematic reviews. The evidence we have currently are not sufficient to draw an affirmative conclusion of CM's effectiveness in treating sub-health, and more proof are still needed before recommending that CM could be widely used to treat sub-health clinically. The trials included in our review were all conducted in China and published in Chinese, and thus there was a lack of grey literature. Chances are that we might have left out studies of negative results, and get false positive clinical results out of it, which might result in publication bias. Besides, all the participants in the included trials are Mongoloid, which put a limit to the application of the research results. Moreover, the included studies were quite different from each other in diagnostic criteria, interventions and outcome evaluation indicators, and most of them were of low quality in methodology, and deficient in terms of outcome data, follow-ups, and safety insurance. Since these studies did not have much in common, it was found difficult to interpret the results and thus resorted to explain the overall

tendency of treatment effect instead of drawing any definite conclusion. This might have diminished the strength of evidence of our systematic review.[15,90-93]

The research results have shown that using CM to treat sub-health has its strength in improving people's QOL, which is consistent with the results of preceding systemic reviews.[15] Through further analysis, it was also found that in the comparison between groups using CM and blank control groups and placebo control groups, the comparison between groups using CM and groups of CM combined with NMI, and the comparison groups of CM combined with CM-featured sleep guidance and groups using CM only, either the experimental groups had lower scores than the control groups in the aspect of environment or the difference was not statistically significant. This shows possible connection between sub-health status and environment, which has barely been reported in earlier systematic reviews. Doctors could use this information to give patients advice on changing living or working environment during treatment of sub-health. There are studies reporting that the occurrence of sub-health syndromes are closely connected with environment.[14,18,94]

Five studies[56,73,74,79,88] reported ICG scores in their continuous and dynamic observation lasting for 4 weeks and it showed that ICG scores decreased with the extension of course of treatment, and the scores in experimental groups were lower than those of control groups. Among them the result of a study[56] was statistically significant, and results of the other 4 studies were not. Although we still need to make further analyses of the results as there are too few studies with rather varied interventions, their methods of continuous and dynamic observation help us to know the changes of patients' body conditions so as to facilitate CM doctors in pattern differentiation and treatment. In this research, the overall effective rate of the 5 trials of the 3 studies[18,40,71] were calculated, which continued their follow-ups after finishing the treatment. The results of the 5 experimental groups were 79.54%, 73.8%, 50%, 64.45%, 60.71% respectively while the results of the control groups were 64.28%, 35%, 31.25%, 35.48%, 32.14%. From these data, it was seen that participants in experimental groups had higher overall effective rates than those in control groups after follow-ups, but not higher than the rates when the participants just finished their treatment, which indicated that sub-health patients are prone to suffer relapses. It is recommended that doctors can prolong the course of treatment based on patients' conditions so as to improve therapeutic effect and prevent recurrence. More attention should be attached to follow-ups of sub-health patients. The outcome indicators in the other 6 studies vary too much, and thus we did not make any analysis. In our study, there was no RCT studying the relation between dosage and therapeutic effect among the published literature of CM treatment of sub-health studies. If the treatment dosage was increased, will it help to reach effective concentration in short time, achieve better treatment effect, and further shorten course of treatment? This might be a breakthrough point for later clinical studies.

In conclusion, it was found in our studies that interventions in the included studies were quite various. Despite all kinds of CM used in different forms, there were also external treatment methods such as ear acupuncture, foot bath, acupoint application, acupoint injection, and some other treatments including acupuncture, moxibustion, Tuina, cupping, eight-sectioned exercise, and Chinese five tones therapy. Different CM treating methods can provide patients with similar therapeutic effects. It is recommended that doctors provide patients with various and suitable treating plans according to their physical condition to enhance the therapeutic effect and help patients remain healthy.

Conflict of Interest: None.

Author Contributions

Zhao H was responsible for the overall conception and study design; Zhao J wrote the article and participated in the whole research process; Liao X guided the systemic evaluation; Li ZG, Wang NY and Wang LM were responsible for literature checking and data entry.

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