Original Article

Observational studies of traditional Chinese medicine may provide evidence nearly consistent with the randomized controlled trials: A meta-epidemiological study

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A B S T R A C T

Background: In traditional Chinese medicine (TCM) field, the benefits of observational studies were more significant. Whether the evidence from observational studies agreed with RCTs in the field of TCM was still unclear.

Methods: A meta-epidemiological study was conducted. Meta-analyses and systematic reviews including cohort studies and case-control studies of TCM were included. Ratio of odds ratio (ROR) of randomized controlled trials and observational studies were calculated individually and intercomparisons were conducted by pool analysis.

Results: A total of 11 studies and 30 outcome pairs were included in the pool analysis. Using results from the observational studies as the reference group, the pooled ROR comparing randomized controlled trials with observational studies was 1.23 (95% confidence interval 1.05 to 1.44, and 95% prediction interval 0.90 to 1.68). The ROR by subgroup analysis were 1.15 (95% confidence interval 0.96 to 1.38; 95% prediction interval 0.95 to 1.39) and 1.12 (95% confidence interval 0.86 to 1.46; 95% prediction interval 0.51 to 2.47) for cohort studies and case-control studies, respectively.

Conclusions: There is difference in pooled results between randomized controlled studies and observational studies on TCM. However, the prediction interval shows the difference is small, which suggests observational studies of TCM can be included in data analysis to provide evidence for TCM. Future studies are needed to verify the above conclusion.

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1. Introduction

Traditional Chinese medicine (TCM), as a widely recognized alternative medicine around the world, has been proven effective over the long history. In prevention and treatment of diseases, especially stroke, low back pain, vertigo, diabetes et al., the effect had been significant. Furthermore, it was continuously developing with the application of evidence-based medicine. A range of evidence medicine methodologies have been widely adopted and achieved success, providing credible evidence for TCM.

Randomized controlled trials (RCTs) have the highest degree of evidence according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system. RCTs can overcome various biases, balance confounding factors, and improve statistical efficiency to the greatest extent possible because of its high authenticity, making it a gold standard for analyzing efficacy in clinical practice. Furthermore, with well-design and conduction, RCTs are often regarded as the best tool for causal inference. As a result, in the guideline development of TCM, evidence from RCTs is always highest level.

However, the proportion of high-quality RCTs for TCM was still limited. Difficulties in design were the major barrier. For ex-
ample, blind method in acupuncture and massage was difficult to perform, and both practitioners and patients might easily reveal the sham or real practice. Besides, it was difficult to show advantages of TCM in real-world such as its holistic view and comprehensive treatment measures in the strict test environment of RCTs.

Although various biases and confounding factors weaken the evidence level of observational studies, the advantages, such as larger sample size, longer follow-up period, higher feasibility and closer to real-world make them as a necessary addition to RCTs. Besides, different from RCTs, observational studies can track the effect of post-marketing drugs in the population and obtain the data of morbidity and mortality. In TCM field, the benefits of observational studies could be more significant, because observational studies match the principle of syndrome differentiation and holistic view better than RCTs. What’s more, in urgent situations, such as emerging infectious diseases, the simple and practicable characteristics of observational research could quickly draw conclusions and provide timely evidence.

Several studies were published to assess the agreement of evidence between RCTs and observational studies in the field of nutrition, healthcare, and COVID-19. However, whether the evidence from observational studies agreed with RCTs in the field of TCM was still unclear. To explore the role of observational studies in TCM, we conducted the current study to systematically compare the agreement of treatment effects between observational studies and RCTs in TCM.

2. Methods

We designed, conducted, and reported the study based on the guideline of reporting meta-epidemiological research.

2.1. Search strategy

PubMed, EMBase, Web of Science Core Collection, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), and WanFang Data were used for searching publications. Search terms for observational studies were cohort study and case-control study. Search terms for TCM included Traditional Chinese Medicine, Chung I Hseuh, Acupuncture, moxibustion, and names of TCM descriptions. We conducted a manual search for unpublished materials (including conference papers, master’s theses, doctoral dissertations, and gray literature). The search period was from the database establishment date to January 30, 2022, with no language restrictions.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: a) meta-analyses and/or systematic reviews with RCTs and observational studies (cohort studies and/or case-control studies) of TCM; b) No limitations were imposed on study setting, language, or publication type.

Exclusion criteria were as follows: a) Clinical experts experience; b) clinical trial protocols; c) meeting abstracts; d) full text unavailable; e) redundant publication; f) fundamental research or pharmacological research on TCM; g) animal studies.

2.3. Study selection and data extraction

Titles and abstracts were screened by one reviewer after removing duplicated results, and then relevant full-texts were screened by two independent reviewers. Any disagreement was resolved by discussion and checked by a third reviewer.

We extracted data from all eligible studies related to TCM, including names of first author, year of publication, age, intervention/exposure factor, comparator, definition of outcome, study design, effect estimate (risk ratio, hazard ratio, odds ratio, mean differences, 95% confidence interval), number of included RCTs and CSs, sample size, number of cases, duration of intervention/exposure, study quality rating, and risk of bias. Data were extracted by three reviewers and disagreements were resolved by discussion.

2.4. Quality assessment

The quality of included studies was individually assessed by two reviewers (SHQ and WMM). The methodological quality of all included SRs was evaluated using AMSTAR-2 tool, which was consisted of 16 questions. The rating was “Yes” when all the evaluation requirements were met. The rating was “Partially yes” when the requirements were partially met, and “No” when no relevant information met the requirements. The key item were item 2, item 4, item 7, item 9, item 11, item 13 and item 15. When none or only one non-critical item failed, the quality level would be high. If more than one non-critical item was not met, the quality level would be medium. With only one critical item was not met, the quality was low. The quality level would be rated very low when more than one key item was not met.

2.5. Statistical analysis

We recalculated the pooled effect estimates individually after removing non-cohort studies/case-control studies and non-randomized controlled trials when one meta-analysis (included both cohort studies and randomized controlled trials) was conducted using data from variable study designs. When a meta-analysis was conducted from only one type of study design, we converted all effect estimate measures into odds ratios (OR) with appropriate conversion formulas to ensure the comparability.

We compared the pooled estimate of RCTs with that of observational studies which served as the reference group. Therefore, the ratio of odds ratio (ROR) of our studies could be interpreted as differences between cohort studies/case-control studies and RCTs. When the ROR was larger than one, the estimate of RCTs would be higher than that of the reference group, and vice versa.

We used random effects model to obtain the pooled estimates, and I² and τ² statistics to assess the heterogeneity. Furthermore, to predict the range of possible values for the difference between RCTs and cohort studies/case-control studies observing in the future, we calculated the 95% prediction intervals of the comparisons. All meta-analyses of this study was conducted by the R package meta (version 5.2.0).

3. Results

3.1. Literature screening process and results

Initially, a systematic review of 1065 relevant cohort studies and case-control studies was conducted. After removing the duplicated studies, 697 studies were identified, from which 64 studies were further retained by screening the titles and abstracts. Finally, 53 studies were excluded after full-text assessment, and 11 studies were included (Figure 1).

3.2. The characteristics of the included studies

The characteristics of the included studies are shown in Table 1. Ten studies (90.9%) were from China and 1 (9.1%) from Netherlands. Six studies focused on COVID-19 and the rest focused on
Fig. 1. Literature screening process.

| Study | Disease                   | Number of RCTs | Number of CSs | Number of CCSs | Quality   |
|-------|---------------------------|----------------|---------------|----------------|-----------|
| Wang 2021 | COVID-19                  | 7              | 2             | 4              | Very low |
| Jia 2020  | Hepatocellular carcinoma | 5              | 0             | 11             | Very low |
| Liu 2021  | COVID-19                  | 2              | 0             | 5              | High     |
| Wang 2021  | COVID-19                  | 2              | 9             | 0              | High     |
| Ineke 2008 | Fetal malposition        | 7              | 4             | 0              | Very low |
| Qin 2019   | Chronic pelvic pain syndrome | 5            | 0             | 2              | Low      |
| Luo 2021  | COVID-19                  | 3              | 3             | 7              | High     |
| Jiang 2021 | COVID-19                  | 9              | 2             | 11             | High     |
| Ried 2011  | Infertility               | 3              | 0             | 5              | Low      |
| Wu 2021    | COVID-19                  | 4              | 4             | 0              | High     |
| Zheng 2015 | Cardiorespiratory fitness | 2              | 2             | 0              | Very low |

*RCT: randomized controlled trial; CS: cohort study; CCS: case-control study
hepatocellular carcinoma, fetal malposition, chronic pelvic pain syndrome, infertility, and cardiorenspiratory fitness, respectively. Each study contained more than 2 RCTs and cohort studies/ case-control studies. Certainty of evidence was rated for the 11 included studies using AMSTAR 2 tool: very low (n = 4), low (n = 2), moderate (n = 0), and high (n = 5).

3.3. Pooled estimate

Overall, 30 outcome pairs were included in the meta-analysis (Supplementary Table 1). 22 pairs of results were binary and 8 were continuous. The treatment effects were mostly larger in RCTs (n = 16) than cohort studies and case-control studies (n = 12), and comparable for two outcome pairs (Supplementary Table 1). The OR was less than one across 8 cohort studies and case-control studies with continuous results, whereas the OR was higher than one in the left 22 studies. The OR was less than one across 9 RCTs, whereas it was larger than or equal to one in 21 RCTs. As for continuous outcomes, the treatment effects were always larger in RCTs (n = 5) than cohort and case-control studies (n = 3).

Comparing to the reference group using cohort studies and case-control studies, RCTs had slightly different pooled estimates. The ROR was 1.23 with 95% confidence interval of 1.05 to 1.44, and the 95% prediction interval was 0.90 to 1.68 \( (I^2=0\%; t^2=0.0169) \) (Figure 2). The prediction interval indicated that the difference could be much more substantial in either direction. For binary outcomes where the 22 pairs of results were included, the ROR was 1.24 with 95% confidence interval of 1.05 to 1.47, and the 95% prediction interval was 1.04 to 1.48 \( (I^2=0\%; t^2=0) \) (Supplementary Figure 1). As for continuous outcomes where the 8 pairs of results were included, the ROR was 1.17 with 95% confidence interval of 0.65 to 2.09, and the 95% prediction interval was 0.23 to 5.94 \( (I^2=57\%; t^2=0.4175) \) (Supplementary Figure 2).

3.4. Subgroup analyses

In the subgroup analyses, cohort studies and case-control studies with an OR less than one was separately analyzed from those with an OR higher than or equal to one. When the OR of cohort studies and case-control studies was less than one, the 8 pairs of continuous results as mentioned above were included in the subgroup analysis. As a result, the ROR was 1.35 with 95% confidence interval of 1.01 to 1.82, and the 95% prediction interval was 0.83 to 2.19 \( (I^2=0\%; t^2=0.0163) \) (Supplementary Figure 3). When the OR of cohort studies and case-control studies was higher than one, 22 pairs of results were included, and the ROR was 1.18 with 95% confidence interval of 0.98 to 1.43, with the 95% prediction interval from 0.83 to 1.68 \( (I^2=0\%; t^2=0) \) (Supplementary Figure 4).

We also compared the effect in cohort studies with RCTs and that in case-control studies with RCTs. With 22 pairs of studies, we isolated and reviewed our results to specifically compare cohort studies and RCTs, from which the ROR was 1.15, with the 95% confidence interval from 0.96 to 1.38, and the 95% prediction interval from 0.95 to 1.39 \( (I^2=0\%; t^2=0) \) (Figure 3). With 15 pairs of studies, our study showed that the pooled ROR comparing effects from RCTs with effects from case-control studies was 1.12 with 95% confidence interval of 0.86 to 1.46, and the 95% prediction interval was 0.51 to 2.47 \( (I^2=47\%; t^2=0.1167) \) (Figure 4).

Subgroup analysis was also performed to analyze the studies of COVID-19. Comparing to cohort studies and case-control stud-
3.5. Heterogeneity

Across individual meta-analyses of RCTs, the mean $I^2$ was 28% ($\tau^2=0.028$), whereas the median $I^2$ was 3% ($\tau^2=0$). The heterogeneity was lower for binary outcomes (mean $I^2=21$%; median $I^2=0$%) than continuous outcomes (mean $I^2=31$%; median $I^2=23$%).

Across individual meta-analyses of cohort studies and case-control studies, the mean $I^2$ was 47% ($\tau^2=0.023$), whereas the median $I^2$ was 54% ($\tau^2=0.01$). The heterogeneity was lower for binary outcomes (mean $I^2=44$%; median $I^2=48$%) than continuous outcomes (mean $I^2=81$%; median $I^2=86$%).

4. Discussion

4.1. Summary of findings

Overall, 30 pairs of outcomes were identified in the meta-epidemiological study, and by reviewing and comparing the data, we determined that the results of RCTs and cohort studies/case-control studies of COVID-19 had different pooled estimates, the ROR were 1.29, with the 95% confidence interval from 1.06 to 1.56, and the 95% prediction interval from 1.04 to 1.59 ($I^2=0$%; $\tau^2=0$) (Figure 5).
Controlled studies in TCM were partly in agreement. For all the 30 pairs of studies, the difference between RCTs and cohort studies/case-control studies was significant. However, for continuous outcomes from case-control studies only, there was no significant difference when we performed subgroup analyses for the OR of cohort studies and case-control studies <1 and >1, separately. The risks of bias in the included reviews were generally high. More than half of included reviews ranked low (two of 11 reviews) and very low (four of 11 reviews) by using AMSTAR 2 tool, which might attribute to the relative low quality and high risk of bias in TCM studies. However, the quality of included studies published in recent 3 years was relatively higher, which suggested that the quality of TCM meta-analyses and systematic reviews had improved and gradually standardized.

4.2. Comparison with other studies

Schwingshaldl et al. conducted a meta-epidemiological study to evaluate the agreement between diet-disease effect estimates from RCT evidence and those from cohort studies in nutrition research, which showed that the difference in the pooled results was small, and the prediction intervals (0.81 to 1.46) was wide. Their results on the difference between RCTs and cohort studies (ROR 1.09 (95% confidence interval 1.04 to 1.14)) was less than ours (ratio of risk ratios 1.23 (1.05 to 1.44)). This diversity might attribute to the difference of research fields. In nutrition research, the strength of intervention was not as effective as medical research. Thus, for different results between control and case groups, long-term follow-up was necessary. However, RCTs of dietary interventions were difficult to conduct because of low adherence to long term interventions. As a result, the difference in the nutrition field was less than that from the TCM field. Osman et al. conducted a meta-epidemiological study that evaluated the agreement between treatment effects of hydroxychloroquine, lopinavir-ritonavir and dexamethasone for COVID-19 from observational studies and that of RCTs. They didn’t pool ROR for different kinds of intervention, however, in the 11 matched pairs, the median ROR was 0.96 (RCTs as the reference group). When exchanging the reference to observation studies, the median ROR was 1.04. Although comparing the pooled results was available because they employed different methods, however, the direction of ROR was consistent with the current study.

4.3. Potential implications

Observational studies, different from randomized controlled trials, provide methodologically less robust information about causality. However, they might be more applicable than RCTs for TCM research design from a certain point of view, especially when randomized controlled trials could not be conducted well or patient relevant outcomes such as morbidity or mortality are needed. Most of the diseases responding specifically to TCM were chronic diseases with high recurrence rates and often needed complex and long-term treatments. To provide insights of prevention and recurrence of these diseases, they were often followed up for a long time, which was difficult for randomized controlled trials. Although there were many observational studies of TCM, such as cancer, psoriasis, diabetes, asthma and AIDS, some of which have been high-quality and had large sample sizes, meta-analysis has been rarely performed on them. Partially due to the insufficient randomized controlled trials about COVID-19 treatments with TCM, some studies included cohort studies and case-control studies into meta-analysis. However, there has been no studies included observational studies in the field of TCM except for COVID-19. As a result, more than half of the included studies in our study were for treatment of COVID-19.

The results suggested that observational studies need to move a step further to be valued in the field of TCM. In research design, more observational studies and meta-analysis of observational studies are needed. In guidelines development, it is worthwhile to pay more attention to the evidence of observational studies. The current study could promote the development and application of observational studies and meta-analysis of observational studies, which would provide a theoretical basis for the inclusion of observational studies in TCM guidelines.
4.4. Strengths and limitations

Our study had several strengths. Firstly, meta-analysis was performed for each pair of outcomes, which means every RCTs and observational studies in each pair matched very well. Secondly, this is the first study comparing randomized controlled studies with observational studies in the field of TCM. Thirdly, we conducted various statistical analyses, including converting risk ratios into OR, recalculating pooled estimates of cohort studies, case-control studies, RCTs and combination of cohort studies and case-control studies, and pooling the estimates across all TCM outcome pairs.

Our study had several limitations as well. Firstly, we performed our search with no language limitations and two reviewers screened individually to reduce the likelihood of bias. Nevertheless, the potential for introduction of unknown bias in the process still exist through our methods of searching and data collection. Although we included 11 studies after screening 1065 systematic reviews of observation studies of TCM, the relative moderate quantity of studies may lead to bias when the conclusion is transplanted to all TCM studies. Secondly, the meta-analyses in the present study could have their own limitations, from the primary data and how the evidence had been summarized. Third, there were retrospective studies in our comparison, where relative risk was not available, so we converted relative risk to OR for comparison, which might exaggerate the difference between randomized controlled studies and observational studies, although this limitation would be unlikely to change the conclusion.

4.5. Conclusion

There is difference in pooled results between RCTs and observational studies in TCM. However, the prediction interval indicated that the difference was small, which suggests that observational studies of TCM need to be paid more attention and more meta-analysis of observation studies should be conducted in the future to provide evidence in the TCM field.

Conflict of interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Haigi Song: Formal analysis, Data curation, Writing – original draft, Writing – review & editing. Nian Li: Methodology, Formal analysis, Writing – review & editing. Wenjie Yang: Methodology, Formal analysis. Miaomiao Wu: Validation, Data curation. Xiaoyang Liao: Methodology, Validation, Conceptualization, Supervision, Writing – review & editing. Yonggang Zhang: Conceptualization, Supervision, Validation, Methodology, Writing – review & editing.

Ethical statement

This study did not require any ethical approvals.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2022.100889.

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