Should acupuncture-related therapies be considered in prediabetes control? Results from a systematic review and meta-analysis of randomized controlled trials

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Should Acupuncture-Related Therapies be Considered in Prediabetes Control?

Results From a Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

To assess the effects and safety of acupuncture-related therapy (AT) interventions on glycemic control for prediabetes, we systematically searched 14 databases and 5 clinical registry platforms from inception to December 2020. Randomized controlled trials involving AT interventions for managing prediabetes were included (PROSPERO registration no. CRD42020209809). Of the 855 identified trials, 34 articles were included for qualitative synthesis, 31 of which were included in the final meta-analysis. Compared with usual care, sham intervention, or conventional medicine, AT treatments yielded greater reductions in the primary outcomes, including fasting plasma glucose (FPG) (standard mean difference [SMD] = −0.83; 95% confidence interval [CI], −1.06, −0.61; \( P < .00001 \)), 2-hour plasma glucose (2hPG) (SMD = −0.88; 95% CI, −1.20, −0.57; \( P < .00001 \)), and glycated hemoglobin (HbA\textsubscript{1c}) levels (SMD = −0.91; 95% CI, −1.31, −0.51; \( P < .00001 \)), as well as a greater decline in the secondary outcome, which is the incidence of prediabetes (RR = 1.43; 95% CI, 1.26, 1.63; \( P < .00001 \)). AT is thus a potential strategy that can contribute to better glycemic control in the management of prediabetes. Because of the substantial clinical heterogeneity, the effect estimates should be interpreted with caution. More research is required for different ethnic groups and long-term effectiveness.

KEY WORDS: acupoint, acupuncture, glycemic control, meta-analysis, prediabetes, systematic review

Authors’ Contributions: M.Z., C.W., and J.L. were involved in design, data collection, analysis, and manuscript writing. All authors in this article meet the criteria for authorship and have approved the final draft of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The current study received an Industry Engagement PhD Scholarship (G1004815) from Golden Sunflower Pty Ltd and Edith Cowan University. Date of award: February 24, 2020. The continuous variable data supporting this meta-analysis are from previously reported studies and data sets, which have been cited. The processed data are available in the supplementary files. The authors declare that they have no competing interests.

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INTRODUCTION

Prediabetes, defined by blood glucose levels higher than normal but not yet high enough to be diagnosed as diabetes, is increasing markedly in incidence and prevalence, and becoming a major global health issue.\(^1\) Statistically, about 88 million Americans -1 in 3 adults have prediabetes.\(^2\) In China, the standardized prevalence of prediabetes was 35.2\% (33.5\% to 37.0\%), diagnosed by the American Diabetes Association (ADA) criteria.\(^3\) The high prevalence of prediabetes imposes a significant burden on healthcare worldwide. Individuals with prediabetes have a significantly higher risk for a long list of other serious health problems, including heart disease, stroke, blindness, kidney failure, and loss of toes, feet, or legs.\(^1,\,2\) Accordingly, medical expenditures associated with prediabetes are increasing due to greater health care services, medications, and other health care products.\(^4\) In Australia, for example, 4.7\% of the total burden of disease was attributed to high blood plasma glucose levels, including diabetes and prediabetes.\(^5\) Without intervention, 93\% of people with prediabetes will develop Type 2 diabetes mellitus (T2D) within 20 years.\(^6\) The annual expenditures for individuals who transition from prediabetes to diabetes is nearly one third higher than those who do not develop diabetes in subsequent years.\(^4\) Therefore, to mitigate the medical and economic burden associated with diabetes, it is imperative to prevent or delay the development of prediabetes.

Prediabetes is reversible.\(^6\) According to ADA standards,\(^7\) the strategies include pharmacologic interventions, lifestyle interventions, prevention of cardiovascular disease, and diabetes self-management education and support are recommended for prevention or delay of T2D. However, compared to pharmacologic interventions, which are not approved by the US Food and Drug Administration (FDA) for prediabetes,\(^1,\,7\) different non-drug therapies, such as lifestyle interventions, psychotherapy, acupuncture and moxibustion therapies, are used for diabetes prevention efforts.\(^6,\,8\) Although World Health Organization\(^9\) proposed that the more effective way of preventing T2D is lifestyle interventions, there is a lack of adherence for people with prediabetes to change their lifestyle (diet and exercise) and maintain such changes for the long-term. Making active lifestyle changes requires not only multiple sources of support from family and social networks, an enabling food system, and a physical environment, but enough individual desire and motivation to adhere to such changes for 2 to 6 years.\(^6,\,9\) The challenge is that lifestyle changes were unsustainable in preventing T2D in more than 50\% of cases, and some of them would get back into their old routine in 3 or 6 months.\(^10\) Traditional Chinese medicine (TCM) is gaining popularity as a complementary and alternative therapy for prediabetes control in Asian countries considering the risk of
drug-related implications and the low compliance lifestyle interventions.\textsuperscript{11,12} Acupuncture-related therapies (AT), such as acupuncture, acupressure, moxibustion, acupoint catgut embedding (ACE), auricular acupuncture, and acupoint application, have been used for T2D prevention through stimulating acupoints.\textsuperscript{13-17}

The main symptom of early diabetes is called 'Consumptive thirst' in the TCM classic - the 'Yellow Emperor’s Inner Canon'. The concept of 'preventing disease before it starts' in TCM theory, which works at preventing medical conditions and diseases before they happen, is suitable for intervening with prediabetes to prevent T2D.\textsuperscript{9} AT interventions can balance the body and strengthen the immune system to prevent T2D. In TCM, AT is performed on one or more of the 365 acupoints distributed along the meridians to modulate the physiology of the body through impulse transmission to the brain and other organs along nerves and meridian lines and improve the flow of Qi, thereby returning the body to a balanced state.\textsuperscript{18} From a western perspective, AT can assist with glycemic control by enhancing insulin production in pancreatic beta cells and the efficacy of insulin utilization.\textsuperscript{19} AT also has preventive effects on some T2D complications such as neurologic, vascular and retinal degeneration.\textsuperscript{19} All the aforementioned information above provides a sound theoretical and scientific basis to treat prediabetes with AT.

**PURPOSE OF THIS STUDY**

Although recent clinical trials using AT interventions have reported possible therapeutic value in prediabetes, whether AT can be an effective and safe therapy on prediabetes control remains unclear. This study aimed to assess the efficacy and safety of AT on glycemic control in prediabetes and to ascertain the best treatment regimen regarding AT for prediabetes control.

**METHODS**

This systematic review has been registered in PROSPERO (CRD42020209809) and reported following the preferred reporting items for a systematic review and meta-analysis guidelines.\textsuperscript{20}

**Information sources and search strategy**

We searched 14 databases, including Allied and Complementary Medicine Database (AMED), Cochrane Database, Cumulative Index to Nursing and Allied Health (CINAHL), China National Knowledge Infrastructure (CNKI), China Proceedings Conference Full-text database, China Doctor/Master Dissertation
Full-text database, Chinese Biomedical Literature database (CBM), Embase, Medline, PubMed, ProQuest, VIP Chinese Science and Technology Periodicals Full-Text Database, Wanfang database, Science Citation Index (SCI) to identify eligible trials, published in English or Chinese, from April 1921 to December 2020. Ongoing registered clinical trials were searched in the Australian New Zealand Clinical Trials Registry (ANZCTR), the ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. Citation searching was included to avoid publication bias. Potential grey literature was searched in OpenGrey.eu. The search strategy included MeSH terms in Pubmed, Emtree terms in Embase, and the CMeSH terms in the CBM database. The selected search strategy is presented in Supplemental Digital Content Appendix D (available at: http://links.lww.com/HNP/A7). All the references were managed by Endnote X9.3.3.

Selection process and data extraction

Two reviewers screened the studies by scanning the titles and or abstracts. All studies were included if they fulfilled the following eligibility criteria: (1) population—participants included people diagnosed with prediabetes, which involves separate impaired fasting glucose (IFG), separate impaired glucose tolerance (IGT) or both; (2) intervention—AT in the intervention group without restrictions on duration, manipulation, location or frequency; (3) comparison—randomized participants in the control group received usual care and or conventional medicine or sham AT; (4) outcomes—at least one outcome measure related to glucose blood level (such as FPG, 2hPG, or HbA1c%) evaluated after the intervention; (5) study design—RCTs. Acupoint injection as an intervention was excluded. Then a full-text assessment was conducted independently for eligibility. During the dual independent screening of full text, disagreements were resolved by discussion between two reviewers until consensus was reached. If consensus was not achieved, a final decision was reached after consultation with a third reviewer. The excluded studies were classified with reasons in Endnote.

Two authors extracted the following data from each selected study: first author, year, sample size, dropout rate, age, diagnostic criteria, background treatment in both groups, intervention regimen, control type, primary outcomes, adverse events (AEs), and information for the assessment of the risk of bias (RoB). The extracted outcomes included FPG, 2hPG, HbA1c and declining incidence of prediabetes. For studies with more than two intervention groups, we combined groups to create a single pair-wise comparison
according to the Cochrane Handbook recommendation. For the missing or unclear data, further information was collected by contacting the original authors.

**Data items**

The primary outcomes were the changes in FPG, 2hPG, and HbA1c levels and adverse events. The secondary outcome was the change in the incidence rate of prediabetes (PROSPERO registration CRD42020209809).

**Assessment of risk of bias**

We used the revised Cochrane risk-of-bias tool (RoB 2) for randomized trials to rate the methodological quality of the 34 included articles. When necessary, two reviewers (M.Z. and J.L.) consulted a third reviewer (C.W.) to resolve disagreements in overall risk-of-bias judgements. The RoB tool consists of the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias selecting the reported result and overall bias. Unconcealed allocation is the most important source of bias in randomized trials. For each study, each domain was rated as ‘low risk of bias’, ‘some concerns’, and ‘high risk of bias’. No exclusions were made based on the RoB 2 assessment.

**Measures of treatment effect**

For the continuous data, such as FPG, 2hPG, and HbA1c, standard mean differences (SMD) were used to measure the treatment effect with 95% confidence intervals (CIs). A SMD of 0.8 is considered a large effect size; 0.5, moderate; and 0.2, small. For the dichotomous data, the change in the incidence of prediabetes was determined by the risk ratio (RR) with 95% CIs. Forest plots were used to depict and summarize effect sizes with 95% CIs. Pre-specified subgroup analyses were conducted based on the type of AT interventions and the type of control. Data analyses were performed using RevMan V.5.3 and Stata V.12.0 (StataCorp, College Station, Texas, USA).

**Assessment of heterogeneity**

The $I^2$ index statistic (1-100%) was performed to assess the magnitude of the heterogeneity between studies. Where there was evidence of heterogeneity ($I^2>50\%, P<0.1$), a random-effects model was used to pool the data.
Assessment of publications bias

Potential publication bias was examined by Begg’s and Egger’s funnel plots. If asymmetry is evident in the funnel plot, a trim-and-fill test was used to adjust for publication bias in meta-analysis.\textsuperscript{24}

RESULTS

Study selection

We identified 855 studies, of which 34 met our inclusion criteria. Fig. 1. shows the study selection using a PRISMA flow diagram. In 6 articles, disagreements were resolved by discussion between the 2 review authors. After consensus-based discussion, 3 trials using a combination of AT with traditional Chinese herbal therapy for prediabetes were excluded from the meta-analysis.\textsuperscript{15,25,26} This is because the combination works through AT and medication, and the drug effect of Chinese herbs could have a large impact on the results. However, consensus was not achieved for the other 3 articles, and a third author was asked to provide a final decision. For example, we excluded one trial after contacting its authors due to the presence of duplicate data. After removing 14 articles with reasons, such as diabetic patients, study protocol, quasi-experimental design, blank control, no available data, data duplications, the remaining 34 articles were included in qualitative synthesis and 31 were included in the meta-analysis.
Study characteristics

We included 34 studies with a total of 3620 participants. These studies were all published between 2006 and 2020. There were 4 trials published in English, with the remaining in Chinese. The intervention duration ranged from 3 to 96 weeks. The mean age of the participants ranged from 33.5 to 71.3 years. Types of AT interventions that were conducted in the included studies were as follows: acupuncture (n = 14), auricular acupuncture (n = 2), acupoint catgut embedding (n = 6), acupressure (n = 2), moxibustion (n = 3), acupoint application (n = 2), combined therapies (acupuncture plus other AT therapy) (n = 2), and AT plus traditional Chinese herbal therapy (n = 3). The selection of acupoints was varied across the studies. The top 5 points that were used frequently in the included studies were Zu San Li (ST36) (18 studies), Pi Shu (BL-20) (16 studies), Shen Shu (BL-23) (14 studies), San Yin Jiao (SP-6) (11 studies), and Wei Shu (BL-21) (9 studies). Three
points, including Tian Shu (ST-25), Gan Shu (BL-18), and Weiwanxiashu (EX-B3), were all used in 8 studies. Other acupoints and the characteristics of studies are listed in Supplemental Digital Content Table 1 (available at: http://links.lww.com/HNP/A6).

**Risk of bias in the included studies**

Fig. 2 shows the RoB summaries. Methodological quality of the included 34 trials was generally satisfactory. An overall judgement for RoB indicated that 3 of the trials had a low risk of bias in all domains and 31 of them were at the level of “some concerns”. All trials reported random sequence generation, while 50.0% of the included studies were at “low RoB” and described adequate allocation concealment. All studies were at low RoB in domains of “measurement of the outcome” and “missing outcome data”. There were 32 (94.1%) studies at low RoB in domains of “deviations from intended interventions”. Moreover, we used the journal article, research protocol, statistical analysis plan, clinical study report, and study registry records in the database to help inform the RoB assessment. However, only 4 of the included studies reported the research protocols, statistical analysis plan, or study registry records. The prespecified analysis plan for the rest of the trials was not available. Therefore, 30 (88.2%) of these studies were at “some concerns” risk of selective reporting.
Meta-analysis for primary outcomes

Reduction of Blood Glucose Levels

There were 29 studies with 3189 participants contributing to the analysis of FPG (mmol/L) (Fig.3a). However, 2 reasonably independent pairwise comparisons were created from the multiple-treatment trial by Lin,\textsuperscript{27} which resulted in 30 trials. This approach to a multiple treatment trial is in line with the Cochrane Handbook for Systematic Reviews.\textsuperscript{21} AT groups produced a significantly greater reduction in FPG than the control group (SMD = \(-0.83; 95\% CI, 1.06, -0.61; p<.00001\)), with high heterogeneity ($I^2 = 89\%$, $P < .00001$). A pooled analysis of 28 trials involving 2957 participants demonstrated a more significant decrease in the level of 2hPG (mmol/L) than that of the control group (SMD = \(-0.88; 95\% CI, -1.20, -0.57; P < .00001\)), with substantial heterogeneity ($I^2 = 94\%$, $P < .00001$; Fig.3b). Nineteen trials assessed 1809 participants for the change in HbA1c levels after treatment (Fig.3c). AT intervention groups had a greater reduction in HbA1c than the control groups ($P < .00001$), with a mean reduction of about 0.91. Heterogeneity is high across the studies but not in a way that diminishes the fact that most studies have demonstrated that AT is effective.

Adverse events (AEs)

The potential AEs associated with AT were discussed in 17 studies. Fifteen of them reported no AEs. One trial reported that one patient felt dizzy during or after applying treatment,\textsuperscript{29} and one trial reported 5 categories of postoperative reactions of ACE treatment: dietary inhibition (44.6%), abnormal feeling (24.4%), local discomfort (13.7%), general malaise (12.5%), and other symptoms (4.8%).\textsuperscript{30}

Meta-Analysis for secondary outcomes

Changes in the incidence of prediabetes after treatment in both the intervention and control groups were reported in 19 RCTs (Fig.3d). For the overall effect of the declining incidence of prediabetes, the AT group produced a greater reduction in the incidence than the control group (RR = 1.43; 95\% CI, 1.26, 1.63; $P < .00001$). Heterogeneity of this secondary outcome was 85\% (Fig.3d).
Findings of subgroup analysis

Subgroup analysis was performed according to the type of AT interventions. The difference between subgroups of studies for FPG, 2hPG and HbA1c was significant (P < .001; see Supplemental Digital Content Appendix A, available at: http://links.lww. com/HNP/A7). Supplemental Digital Content Appendix Aa (available at: http://links.lww.com/HNP/A7) and Supplemental Digital Content Appendix Ab (available at: http://links.lww.com/HNP/A7) show that the subgroups of acupuncture in auricular acupuncture, ACE, moxibustion, and acupoint application were more effective in lowering FPG and 2hPG levels than in the control group (P < .05). The outcome HbA1c in Supplemental Digital Content Appendix Ac (available at: http://links.lww.com/ HNP/A7), however, only reached statistical significance in 2 of the subgroups: acupuncture (P < .00001) and ACE (P = .007). Furthermore, these 2 subgroups significantly lowered the incidence of prediabetes (P < .01; see Supplemental Digital Content Appendix Ad, available at: http://links.lww. com/HNP/A7). The acupressure subgroup was shown to be ineffective in lowering FPG, 2hPG, HbA1c and the incidence of prediabetes (P > .05). In most subgroups with 2 or more studies included, substantial heterogeneity was found (I^2 > 75%). We identified substantial heterogeneity in most subgroup analysis. For example, the acupuncture subgroup in FPG had considerable clinical heterogeneity due to different acupuncture modalities.

We also performed a subgroup analysis comparing AT with different types of control groups. The subgroup of “AT plus usual care versus usual care” and the subgroup of “AT versus usual care' showed an extremely significant reduction in blood glucose levels and the incidence of prediabetes (P < .01; see Supplemental Digital Content Appendixes Ae-h, available at: http://links.lww.com/HNP/A7). The AT group also showed a greater reduction in both the FPG outcomes and decline in the incidence of prediabetes than the sham group (P < .05; see Supplemental Digital Content Appendixes Ae-h, available at: http://links.lww.com/HNP/A7), while compared with conventional medicine, AT interventions were comparable in their impact on blood glucose or the incidence of prediabetes (P > .05; see Supplemental Digital Content Appendixes Ae-h, available at: http://links.lww.com/HNP/A7).

Low heterogeneity existed in most subgroup analysis for FPG (I^2 < 50%) in Supplemental Digital Content Appendix B (available at: http://links.lww. com/HNP/A7), except for the subgroup of “acupuncture plus usual care verse usual care” (I^2 = 94%; see Supplemental Digital Content Appendix Ba, available at: http://links.lww.com/HNP/A7) and “ACE plus usual care verse usual care” (I^2 = 91%; see Supplemental
The high heterogeneity may be due to the intervention characteristics of acupuncture or ACE, for example, the different acupoints selection. Compared with usual care, AT interventions, including acupuncture, auricular acupuncture, ACE, moxibustion, and acupoint application, plus usual care, showed a significant reduction in FPG (see Supplemental Digital Content Appendixes Ba-g, available at: http://links.lww.com/HNP/A7). Compared with usual care, acupuncture showed a significant mean reduction in FPG for about 0.95 mmol/l ($P < .0001$; see Supplemental Digital Content Appendix Ba, available at: http://links.lww.com/HNP/A7). Although the heterogeneity between studies is statistically significant ($I^2 = 52\%$; see Supplemental Digital Content Appendix Bb, available at: http://links.lww.com/HNP/A7), this is more in relation to the magnitude of the reduction in FPG rather than in conclusion. ACE and moxibustion indicated a more significant reduction in FPG than conventional medicine (see Supplemental Digital Content Appendixes Be and Bc, available at: http://links.lww.com/HNP/A7). Overall, there is evidence that it is effective to treat prediabetes with AT interventions in reducing the level of FPG.

### Table: Forest plot representing the effect of AT interventions on FPG (mmol/L)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV (Random, 95% CI)</th>
<th>Std. Mean Difference IV (Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2015</td>
<td>4.75</td>
<td>0.36</td>
<td>64</td>
<td>5.09</td>
<td>0.34</td>
<td>64</td>
<td>-0.35 [-0.47, -0.23]</td>
<td><strong>-0.35 [-0.47, -0.23]</strong></td>
</tr>
<tr>
<td>Chen 2019</td>
<td>5.39</td>
<td>0.38</td>
<td>46</td>
<td>6.29</td>
<td>0.86</td>
<td>46</td>
<td>-0.91 [-1.38, -0.43]</td>
<td><strong>-0.91 [-1.38, -0.43]</strong></td>
</tr>
<tr>
<td>Huang 2011</td>
<td>5.73</td>
<td>0.63</td>
<td>35</td>
<td>6.17</td>
<td>0.78</td>
<td>35</td>
<td>-0.43 [-0.61, -0.25]</td>
<td><strong>-0.43 [-0.61, -0.25]</strong></td>
</tr>
<tr>
<td>Ji 2018</td>
<td>5.14</td>
<td>0.63</td>
<td>18</td>
<td>5.89</td>
<td>0.03</td>
<td>16</td>
<td>-0.74 [-1.23, -0.24]</td>
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</tr>
<tr>
<td>Kang 2013</td>
<td>5.37</td>
<td>0.60</td>
<td>60</td>
<td>5.76</td>
<td>0.94</td>
<td>58</td>
<td>-0.43 [-0.48, -0.37]</td>
<td><strong>-0.43 [-0.48, -0.37]</strong></td>
</tr>
<tr>
<td>Li 2014</td>
<td>5.2</td>
<td>0.7</td>
<td>46</td>
<td>5.9</td>
<td>0.6</td>
<td>46</td>
<td>-0.10 [-0.44, 0.24]</td>
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</tr>
<tr>
<td>Liang 2018</td>
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<td>0.1</td>
<td>150</td>
<td>5.6</td>
<td>0.2</td>
<td>150</td>
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<td><strong>-0.03 [-0.46, 0.39]</strong></td>
</tr>
<tr>
<td>Lin 2019a</td>
<td>3.97</td>
<td>0.34</td>
<td>60</td>
<td>3.31</td>
<td>0.35</td>
<td>55</td>
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<td><strong>0.33 [0.14, 0.52]</strong></td>
</tr>
<tr>
<td>Lin 2019b</td>
<td>0.11</td>
<td>0.31</td>
<td>30</td>
<td>0.31</td>
<td>0.35</td>
<td>15</td>
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<td><strong>0.10 [0.01, 0.20]</strong></td>
</tr>
<tr>
<td>Liu 2016</td>
<td>5.02</td>
<td>0.28</td>
<td>32</td>
<td>5.35</td>
<td>0.17</td>
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</tr>
<tr>
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<td>6.21</td>
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</tr>
<tr>
<td>Liu 2020</td>
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<td>0.07</td>
<td>41</td>
<td>6.38</td>
<td>0.12</td>
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<tr>
<td>Nac 2016</td>
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<td>1.07</td>
<td>50</td>
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<td>1.1</td>
<td>50</td>
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<td><strong>-0.30 [-0.80, 0.20]</strong></td>
</tr>
<tr>
<td>Pan 2014</td>
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<td>0.13</td>
<td>32</td>
<td>6.12</td>
<td>0.26</td>
<td>30</td>
<td>-0.99 [-1.52, -0.46]</td>
<td><strong>-0.99 [-1.52, -0.46]</strong></td>
</tr>
<tr>
<td>Pan 2019</td>
<td>6.25</td>
<td>0.26</td>
<td>40</td>
<td>6.53</td>
<td>0.84</td>
<td>40</td>
<td>-0.66 [-1.11, -0.21]</td>
<td><strong>-0.66 [-1.11, -0.21]</strong></td>
</tr>
<tr>
<td>Su 2019</td>
<td>5.41</td>
<td>0.48</td>
<td>60</td>
<td>6.32</td>
<td>0.41</td>
<td>60</td>
<td>-1.97 [-2.50, -1.44]</td>
<td><strong>-1.97 [-2.50, -1.44]</strong></td>
</tr>
<tr>
<td>Wang 2013a</td>
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<td>0.76</td>
<td>105</td>
<td>5.86</td>
<td>1.05</td>
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<td><strong>0.37 [0.02, 0.73]</strong></td>
</tr>
<tr>
<td>Wang 2015b</td>
<td>3.65</td>
<td>0.35</td>
<td>30</td>
<td>6.18</td>
<td>0.44</td>
<td>30</td>
<td>-0.23 [0.01, 0.46]</td>
<td><strong>-0.23 [0.01, 0.46]</strong></td>
</tr>
<tr>
<td>Wang 2016</td>
<td>3.22</td>
<td>0.36</td>
<td>30</td>
<td>4.63</td>
<td>0.44</td>
<td>30</td>
<td>-0.31 [-0.62, 0.0]</td>
<td><strong>-0.31 [-0.62, 0.0]</strong></td>
</tr>
<tr>
<td>Xiang 2013</td>
<td>5.12</td>
<td>0.25</td>
<td>32</td>
<td>5.21</td>
<td>0.39</td>
<td>32</td>
<td>0.33 [0.24, 0.42]</td>
<td><strong>0.33 [0.24, 0.42]</strong></td>
</tr>
<tr>
<td>Xue 2011</td>
<td>5.67</td>
<td>0.34</td>
<td>33</td>
<td>6.87</td>
<td>0.43</td>
<td>33</td>
<td>-2.04 [-2.45, -1.63]</td>
<td><strong>-2.04 [-2.45, -1.63]</strong></td>
</tr>
<tr>
<td>Zhu 2010</td>
<td>5.73</td>
<td>0.36</td>
<td>30</td>
<td>5.83</td>
<td>0.12</td>
<td>30</td>
<td>-0.20 [-0.55, 0.05]</td>
<td><strong>-0.20 [-0.55, 0.05]</strong></td>
</tr>
<tr>
<td>Zhao 2012</td>
<td>3.49</td>
<td>0.68</td>
<td>36</td>
<td>5.88</td>
<td>0.38</td>
<td>56</td>
<td>1.40 [-0.02, 0.08]</td>
<td><strong>1.40 [-0.02, 0.08]</strong></td>
</tr>
<tr>
<td>Zhou 2016</td>
<td>4.1</td>
<td>0.3</td>
<td>35</td>
<td>4.7</td>
<td>1.4</td>
<td>35</td>
<td>0.33 [-0.39, 0.81 -0.17, 0.01]</td>
<td><strong>0.33 [-0.39, 0.81 -0.17, 0.01]</strong></td>
</tr>
<tr>
<td>Zhong 2020</td>
<td>5.8</td>
<td>0.39</td>
<td>31</td>
<td>5.88</td>
<td>0.4</td>
<td>31</td>
<td>0.22 [-0.60, 0.80]</td>
<td><strong>0.22 [-0.60, 0.80]</strong></td>
</tr>
<tr>
<td>Zhu 2016</td>
<td>5.82</td>
<td>0.61</td>
<td>160</td>
<td>6.16</td>
<td>0.57</td>
<td>160</td>
<td>-0.57 [-0.80, -0.35]</td>
<td><strong>-0.57 [-0.80, -0.35]</strong></td>
</tr>
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</table>

**Fig. 3a** – Forest plot representing the effect of AT interventions on FPG (mmol/L)

*Heterogeneity: Tau² = 0.35; Chi² = 264.72, df = 29 (P < 0.00001); I² = 89%

Test for overall effect: Z = 7.18 (P < 0.00001)
**Findings of publication bias**

We used Begg's and Egger's tests to analyze publication bias, and the funnel plot is presented in Supplemental Digital Content Appendixes Ca-g (available at: http://links.lww.com/HNP/A7). There is no
publication bias for 2hPG ($P = .156$) and HbA1c ($P = .234$). However, publication bias was noted for FPG as Egger's test ($P = .022$). Thus, a trim-and-fill test for FPG was performed to explore whether this publication bias would significantly impact the estimates. The result showed that no study was trimmed, indicating that weighting of the small studies with a large effect size was very low and the potential influence was minor. Therefore, we included all reviews when calculating the overall effect of the meta-analysis.

**DISCUSSION**

Our results showed that, compared with usual care or sham intervention or conventional medicine, AT interventions significantly reduced not only the levels of FPG, 2hPG and HbA1c but also the incidence of prediabetes. In addition, participants with prediabetes treated with acupuncture and ACE showed improved glycemic control and a reduction in the incidence of prediabetes. These data provided evidence of the efficacy of AT as a supplementary treatment in the management of prediabetes. Although no significant AEs were reported in the included studies, the information was insufficient to conclude the safety of AT for prediabetes.

To date, two relevant reviews have assessed the effect of acupuncture-related approaches for prediabetes. One systematic review of 11 RCTs with 970 participants had reported that acupuncture and moxibustion were ‘probably’ associated with the improvement in FPG and 2hPG levels. The efficacy and safety of acupuncture and moxibustion for this population, however, are still unclear due to generally poor methodological quality, publication bias, and small sample size.\(^8\) A recent meta-analysis of 791 participants reported that ACE might have great potentials for reducing levels of FPG, 2hPG, and HbA1c and improving clinical efficiency for prediabetes.\(^{16}\) Compared with previous reviews, the present study involved various AT interventions, recently published trials, and larger sample size to provide firm evidence for the potential role and safety of AT in the management of prediabetes.

Our data have yielded robust and consistent findings that support and expand the findings in the previous studies. From the meta-analysis of all included studies, we found that AT improved the glycemic control of prediabetes in comparison with participants undergoing usual care and/or conventional medicine or sham intervention. Standard care includes exercise, diet, and lifestyle modifications such as education, weight control, and quitting cigarettes smoking. Conventional medicine refers to antidiabetic drugs such as
metformin, rosiglitazone, and rosuvastatin. Sham intervention is a fake AS approach designed to prevent the participants from knowing whether they have received real AS. It includes “non-acupoints” stimulation and “true-acupoints” stimulation as the active AS group. Non-acupoints refer to ineffective body points not on established acupuncture point charts, while “true acupoints” stimulation such as superficial needling is considered minimal activity against diabetes. In addition, AT led to a significantly lower incidence rate of prediabetes (3–96 weeks) than in the control group. Moreover, the subgroup analysis provided a shred of comprehensive evidence that that acupuncture and ACE offered better results in glycemic control and in the incidence of prediabetes. However, the subgroup of acupressure and associated combined therapies failed to demonstrate any significant impact on 2hPG and HbA1c levels. This may be due to the small number of trials in the acupressure subgroup and positive medicine control in the subgroup of combined therapies, making the overall effect minor. Therefore, AT interventions such as acupuncture or ACE are a considerable selection for preventing prediabetes’s progression to T2D. In contrast, the long-term effects of auricular acupuncture, moxibustion, acupoint application, or the combination of acupuncture with other AT therapy still need further research.

Although AEs are rare, the evidence of the safety of AT for prediabetes is still insufficient since 15 of the trials did not provide any information on AEs. In our study, one patient who received auricular acupuncture felt dizzy during or after the treatment.\textsuperscript{29} Besides this, there were various reports of postoperative reactions of ACE, which included dietary inhibition, abnormal feeling, local discomfort, and general malaise.\textsuperscript{30} Xue et al.\textsuperscript{30} pointed out that the reactions of dietary inhibition have positive effects for treating prediabetes due to the effect of appetite suppressant. As a lack of reports on AEs and follow-up is the most dominant problem of TCM studies, we suggest that the AEs of AT should be seriously considered in clinical practice. Future research should attach more importance to the safety of AT for prediabetes.

Our review had several strengths. A key strength of our trial was the robust systematic approach, and many recently published trials were included. For instance, we conducted a current and comprehensive search across a large number of databases and performed stable analyses by adjusting for publication bias. In addition, all the included RCTs were of moderate to high methodological quality. Furthermore, for all the prespecified sensitivity analyses, the results had a very small difference as compared with the primary results, indicating that the primary results were robust and further actions to resolve the difference was not needed.
This review had some limitations. Given the substantial clinical heterogeneity, the effect estimates should be interpreted with caution. We identified that the high heterogeneity between studies is based on the different types of AT interventions, intervention characteristics, and type of control groups. The differences in AT manipulation techniques may be a source of heterogeneity in most subgroup analysis. As a therapy that stimulates the body surface, it is hard for the acupuncturist to perform completely standardized manipulation procedures for different participants. For example, many factors of moxibustion, such as the different acupoints selection, materials, treatment duration, number of sessions, frequency, and intensity, could affect the eventual outcomes. Moreover, since AT interventions originated in China, most of the included trials were conducted in China. There are also concerns that most Chinese trials reported unusually high proportions of positive results. Future studies should aim to apply this treatment in other regions for the clinical management of prediabetes.

CONCLUSION

Our findings showed that AT significantly reduced the levels of FPG, 2hPG, and HbA1c and improved the incidence of prediabetes, without significant AEs reported. In conclusion, AT is a potential strategy that could improve the management of prediabetes. For example, acupuncture or ACE could be a considerable selection for preventing prediabetes progression to T2D. Since the present findings have substantial clinical heterogeneity, the effect estimates should be interpreted with caution. More research is required for different ethnic groups and long-term effectiveness; also, future research should attach more importance to the safety of AT for prediabetes.

REFERENCE


49. Xiang QY, Li GA, Shen XH, Hong J. Clinical research on combined electroacupuncture and ear point for simple obesity with impaired glucose regulation. SHJ.TCM, 2013; 47(5): 31-33.