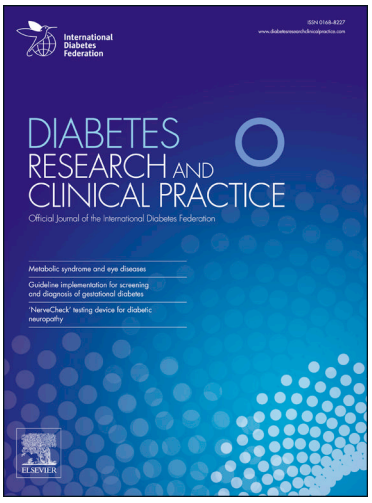

Review

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Bing Pang, Feng-mei Lian, Xi-yan Zhao, Xue-min Zhao, De Jin, Yi-qun Lin, Yu-jiao Zheng, Qing Ni, Xiao-lin Tong

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Prevention of type 2 diabetes with the traditional Chinese patent medicine: a systematic review and meta-analysis

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Abstract:

Aim: Early interventions in prediabetes can prevent or delay the incidence of type 2 diabetes mellitus (T_2DM). The aim of this review was to assess the efficacy and safety of traditional Chinese patent medicine (TCPM) on the prevention of T_2DM.

Methods: Seven electronic databases were searched to identify eligible trials published until June 1, 2016. Randomized controlled trials (RCTs) that compared TCPM plus lifestyle modification (LM) versus LM alone were included for in the. RCTs that used TCPM plus LM compared with placebo plus LM were also included. Methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool. A random- or fixed-effect model was used to analyze outcomes that were expressed as risk ratios (RRs) or mean differences (MD), and the I^2 statistic was used to assess heterogeneity.

Results: Twenty-six trials with a total of 4169 participants met the inclusion criteria. Subgroup analysis confirmed that, compared with LM alone, TCPM and LM together were significantly better at reducing diabetes (RR, 0.47; 95% CI, 0.38 to 0.59) and normalizing blood glucose (RR, 0.76; 95% CI, 0.69 to 0.85). They also caused a greater reduction in fasting plasma glucose (FBG) (MD, –0.37; 95% CI, –0.62 to –0.13), 2-hour plasma glucose (2h PG) (MD, –0.91; 95% CI, –1.35 to –0.47) and body mass index (BMI) (MD, –0.45; 95% CI, –0.76 to –0.14). Compared with placebo plus LM, TCPM plus LM was superior at reducing diabetes (RR, 0.55; 95% CI, 0.45 to 0.68) and normalizing blood glucose (RR, 0.62; 95% CI, 0.50 to 0.76). The interventions were also associated with a decline in FBG levels (MD, –0.68; 95% CI, –1.25 to –0.11) and 2h PG levels (MD, –1.07; 95% CI, –1.85 to –0.29). There were no significant differences in adverse events in either group. Subgroup and sensitivity analyses found no significant difference in overall effects among all study characteristics, indicating that the overall effects were stable. Generally, the quality of evidence was low for the effect of TCPM on the incidence of diabetes and normalization of blood glucose, and was very low for the effects of TCPM on FBG, 2h PG, and BMI.

Conclusions: Based on this systematic review, TCPM may reduce the risk of progression to T_2DM and increase the possibility of regression toward normoglycemia. As a result of the methodological drawbacks of the included studies, more rigorously designed RCTs are required to more reliably assess the efficacy of TCPM and long-term follow-up is needed before TCPM can be recommended for prediabetic patients.

Introduction

Diabetes (DM) is a severe and increasingly burdensome disease, with a current prevalence of 4150 million that is estimated to swell to 6420 million by 2040 [1]. In China, 1139 million adults (aged ≥20 years) have DM, which accounts for 11.6% of the adult population. In addition, 4934 million adults (50.1%) have prediabetes [2]. Prediabetes is characterized by both mild impaired fasting blood glucose (IFG) and/or impaired glucose tolerance (IGT). People with IGT show abnormal fasting plasma glucose levels (FBG <7.0 mmol/L) and abnormal 2-hour postprandial blood glucose levels (2h PG, 7.8–11.0 mmol/L). People with IFG only demonstrate abnormal FBG values (FBG, 6.1–6.9 mmol/L and 2h PG <7.8 mmol/L, if measured) [3]. The risk of DM is greatly increased in subjects with prediabetes, with recent estimates suggesting that 93% of subjects with prediabetes may develop DM within 20 years [4]. Furthermore, prediabetes also significantly increases the risk of cardiovascular disease. Early interventions in prediabetes, especially in subjects with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and previous gestational diabetes and obesity, can prevent or delay the progression of prediabetes to type 2 diabetes (T_2DM) and the development of complications [3-4]. Several systematic reviews suggest that lifestyle interventions are effective for preventing T_2DM [5-7]. However, many people are unwilling to change their lifestyle (diet and exercise) and maintain such changes for the long-term. For high-risk target subjects, lifestyle modification alone is not enough to delay or prevent DM. As for drug interventions, metformin and acarbose are inexpensive and popular drugs to treat prediabetes, and they have some mild gastrointestinal reaction. Other oral anti-diabetic and anti-obesity drugs are not currently recommended for diabetes prevention, although randomized controlled trials (RCTs) have shown some effectiveness [8-10].

One of the most appreciable distinctions between China and the West in treating prediabetes is the use of Traditional Chinese patent medicine (TCPM). In recent years, TCPMs have become increasingly popular in China. Proprietary TCPMs are developed by combining modernized pharmaceutical technologies with ancient TCM theories. Refined dosage forms and relative standardization in composing the main effective components are considered advantages of TCPMs compared with herbal decoctions [11]. Currently, more than 100 TCPMs are used for the prevention and treatment of diabetes; these TCPMs have been used in clinical practice for more than 15 years in China [12]. Although the included TCPMs vary in their herbal components, they form part of a “group” of herbal medicines with anti-hyperglycemic effects designed to prevent diabetes and decrease blood glucose levels. The main therapeutic principle in the field of TCM includes fortifying qi, clearing heat, nourishing yin, activating blood, and drying dampness.

Many patients with prediabetes are willing to choose TCPMs because their disease has not yet reached the stage that requires long-term use of anti-diabetic drugs, and the use of anti-diabetic drugs is also often accompanied by adverse events. Also, TCPMs are more conveniently administered and easier to take along.

Pharmacological investigations have indicated that TCPMs have beneficial effects on

reducing body weight, enhancing insulin sensitivity, protecting beta-cells, simulating insulin secretion, correcting glucose and lipid metabolism disorders, and improving the microcirculation and the immune system [13]. Although several studies [14-39] have suggested that TCPMs or TCPMs combined with lifestyle modifications (LMs) were effective for treating prediabetes, few systematic reviews have been published that summarized the effects of TCPMs for treating prediabetes. We performed a systematic review and meta-analysis to assess the strength of the current evidence to support the efficacy and safety of TCPMs for the treatment of prediabetes, which might be a complementary therapy for diabetes.

Methods

The review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42016046553; available online: http://www.crd.york.ac.uk/PROSPERO/myprospero.php). This article was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [40].

Search strategy

The following seven electronic databases were searched to identify eligible trials published from inception to June 1, 2016: Cochrane Central Register of Controlled Trials (searched in May 2016), Cochrane Database of Systematic Reviews (searched in May 2016), PubMed (1959–2014), EMBASE (1980–2014), Chinese Biomedical Literature Database (1978–2014), Chinese National Knowledge Infrastructure (1979–2014), and the Wanfang database (1985–2014). Because TCPMs are mainly used in China, a literature search was conducted in the four Chinese electronic databases to include the maximum possible number of clinical trials. The search was restricted to trials published in Chinese and English, and the search terms are listed in **Supplementary Table 1**. To include unpublished studies, the websites of the international clinical trial registry provided by the U.S. National Institutes of Health (available at http://clinicaltrials.gov/) and the Chinese clinical trial registry (available at http://www.chictr.org.cn/index.aspx) were also searched. Furthermore, the reference lists of relevant retrieved articles were searched manually to identify any additional eligible studies. The authors of significant publications or experts in the relevant field were contacted for potential studies, and the pharmaceutical companies that manufacture TCPMs were also contacted to identify further published and unpublished studies. Two reviewers (Pang B and Lian FM) independently screened the titles and abstracts for eligibility and examined the full text of the articles. Any discrepancies were resolved by consensus or after consulting a third party (Tong XL).

Study selection

All included trials met the following selection criteria: (1) the study was a randomized controlled trial (RCT); (2) the study examined prediabetic participants who received TCPM as a co-intervention with lifestyle modification (LM) in comparison with those receiving LM alone or placebo plus LM; and (3) the study included participants irrespective of gender, age, or ethnicity, and prediabetes was diagnosed by clearly defined or internationally recognized criteria. The exclusion criteria were as follows:

(1) studies describing interventions combined with other TCM therapies such as Chinese herbal medicine, acupuncture, acupoint injection, or herbal extracts; (2) and studies that were non-randomized controlled trials and quasi-randomized controlled trials. The primary outcomes were the incidence of diabetes and adverse events; the incidence of diabetes refers to the number of participants who had progressed to T_2DM according to standard Western medicine diagnostic criteria by the end of the trial. The secondary outcomes included normalization of blood glucose (the number of participants who returned to a normal blood glucose range by the end of the trial), fasting glucose, 2-hour postprandial blood glucose levels, and reduction in body mass index (BMI).

Data extraction

Two reviewers (Zhao XY and Zhao XM) independently extracted data using a predesigned collection form. The following data were extracted: general trial characteristics (title, authors, year); baseline patient and disease data (sample size, age, gender); interventions (component and dose TCPM, details of control interventions); and outcomes (follow-up length, outcome measures, adverse events). Discrepancies were settled by consensus or a third party (Ni Q).

Quality assessment

Two reviewers (Lin YQ and Zheng YJ) independently assessed the methodological quality of the RCTs using the Cochrane Collaboration Risk of Bias tool. The risk of bias was assessed according to the Cochrane Handbook [41], which consists of six items: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting and other sources of bias. Each item was categorized “high risk” (at least one item had a high risk of bias), “low risk” (all items had a low risk of bias), or “unclear” (at least one item had an unclear risk of bias). Other bias included the sample calculation and profit bias. If the placebo effect could not be ruled out, the positive finding should be interpreted conservatively, which is also another type of bias. Discrepancies in this interpretation were resolved by consensus or after discussion with a third party (Tong XL).

Assessment of the quality of the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to assess the quality of the evidence for each outcome. According to GRADE, the outcomes of an intervention are categorized into four levels of evidence quality: +very low, ++ low, +++ moderate, and ++++ high. In GRADE, the confidence assessment addressed the risk of bias (in individual studies), inconsistency (heterogeneity in estimates of an effect across studies), indirectness (related to the question or due to intransitivity), imprecision, and publication bias. Bodies of evidence from RCTs start as high quality evidence, whereas those from observational studies start as low quality evidence. Defined criteria are applied to either decrease or increase the quality of evidence rating. The GRADE profiler (GRADEPRO) was applied to create the summary of evidence table.

Statistical analysis

The data were analyzed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). Publication bias was examined using funnel plots. For outcomes, data regarding incidence were dichotomous, and others were continuous. Risk ratios (RRs) were calculated using the Mantel-Haenszel method for dichotomous outcomes, and weighted mean differences (MDs) were calculated using the inverse variance method for continuous variables. ITT (intention-to-treat) analysis was also applied. For all estimates, 95% confidence intervals (CIs) were calculated. I^2 statistics were used to assess heterogeneity. A fixed-effects (FE) model was used if there was no significant heterogeneity in the data (I^2<50%), and a random-effects (RE) model was used if significant heterogeneity was present (I^2>50%). Sensitivity analysis was performed to assess the stability of conclusions. Where heterogeneity was detected, accepted methods were used to explore the statistical heterogeneity using clinical parameters such as treatment duration, sample size, publication year, diagnostic criteria, publication language, and TCM syndrome. Publication bias was assessed using funnel plots. Egger's tests and Begg's tests [42-43] were conducted using R version 3.3.2 to determine whether the funnel plots were symmetrical.

Results

The search results are displayed in **Fig. 1**. The primary searches identified a total of 4992 references using the search strategy. A total of 2718 articles were screened after 444 duplicates of the same articles in different databases were removed. According to the inclusion criteria, 1993 articles were excluded based on the title and abstract because the title and abstract were not appropriate (n=1125) or because the studies were literature reviews (n=336), case reports (n=109), animal experiments (n=254), or molecular biology experiments (n=169). After a detailed evaluation of the full text, an additional 255 references were excluded. Finally, 26 RCTs [14-39] met the eligibility criteria and were included in the systematic review.

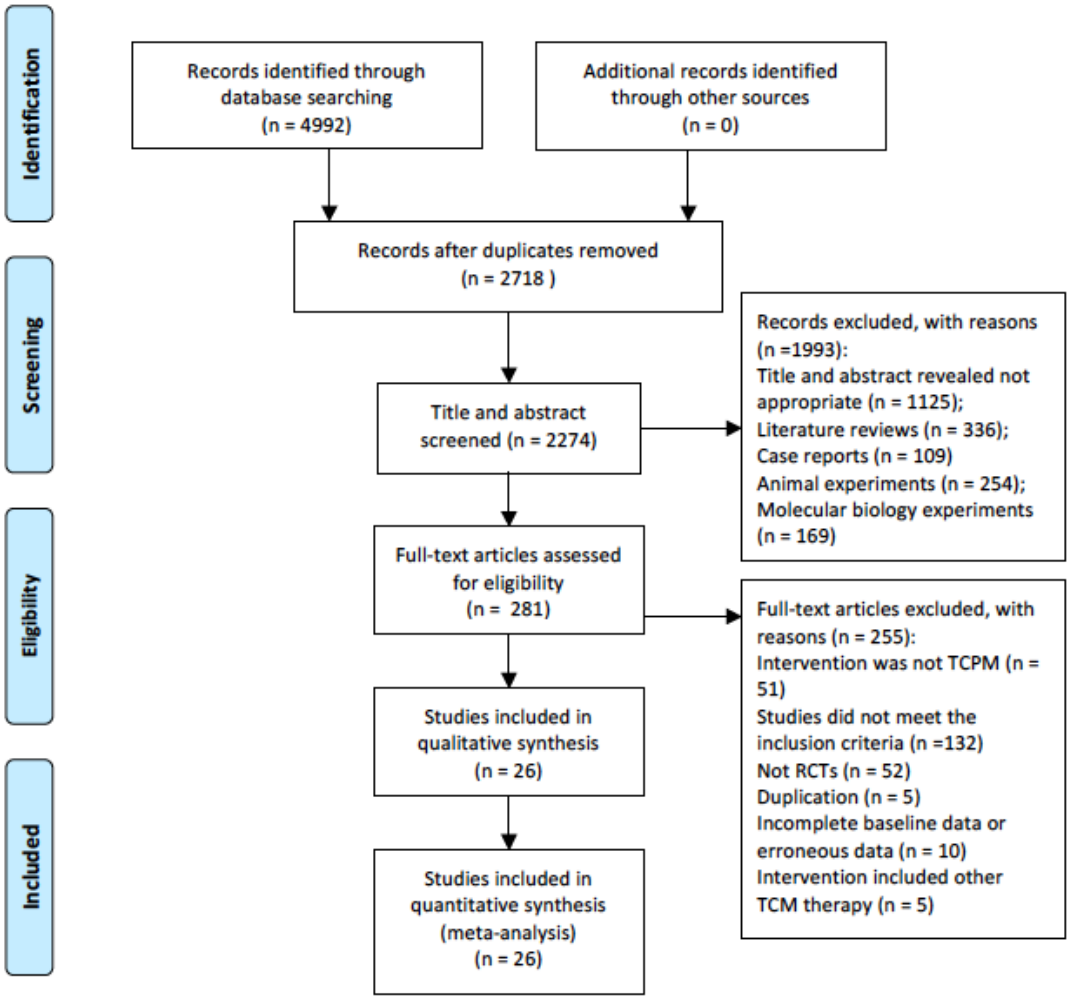


Figure 1. Flow diagram of literature search.

Characteristics of the included trials

The characteristics of the included trials are summarized in **Table 1.** Twenty-six trials that investigated 15 TCPMs were included. Six trials [14-19] were published in English and the rest were published in Chinese. A total of 4169 participants were involved (2127 and 2042 in the treatment and control groups, respectively). The trial sample size ranged from 58 to 514 participants. Standard diagnostic diabetic criteria for prediabetes were applied to all included trials, including World Health Organization (WHO) DM criteria (1999). Additionally, many trials used TCM diagnostic criteria according to TCM theory [15, 17, 20, 22, 26, 32, 34]. The components of the 15 included TCPMs are shown in **Table 2**.

Methodological quality assessment

An overview of the judgment regarding each risk of bias item in the included trials is shown in **Fig. 2.** Twelve trials reported the method of random sequence generation, and the remaining 14 trials reported "randomly allocating" without providing the detailed method of randomization. Seven trials reported the method of allocation

concealment, and eight trials reported the blinding of participants and personnel. All the included trials provided completed baseline information and described similarities between comparison groups. Twelve trials reported drop-outs or withdrawals. Furthermore, four trials were judged to be at a low risk of selective reporting bias because their trial protocols were available. Relevant information regarding sample calculation and conflicts of interest could not be acquired, so other bias was judged to be "unclear".

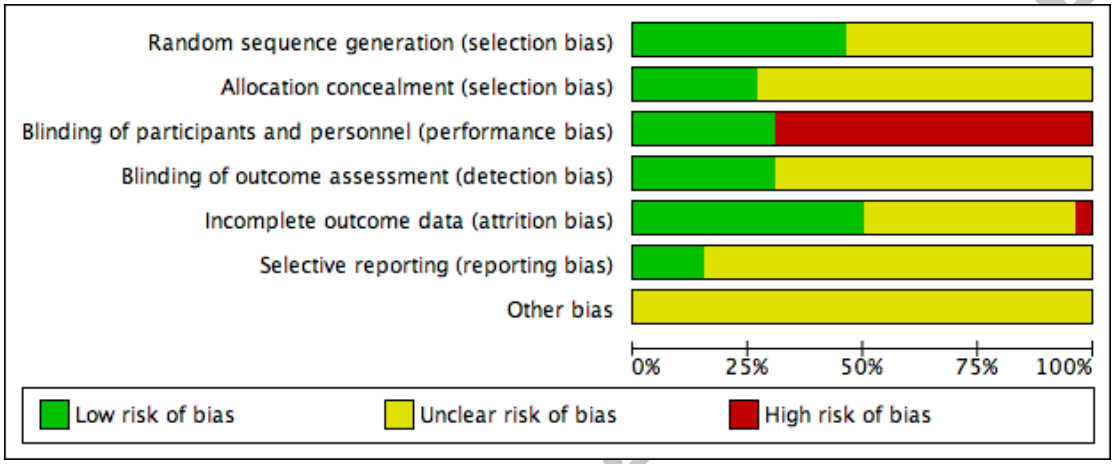


Figure 2. Risk of bias graph.

Primary outcomes

Incidence of diabetes

The incidence of diabetes is shown in **Fig. 3**. The results of the 17 trials (n = 3424) were included, and demonstrated a significant difference in the incidence of diabetes between the treatment groups and the control groups. These trials showed insignificant heterogeneity; thus, a fixed-effects model was used for statistical analysis. To compare the incidence of diabetes with TCPM compared with the control group, subgroup analysis was performed.

Eleven trials assessed the incidence of diabetes with TCPM + LM compared with LM alone and there were significant differences that favored the combination treatment (n = 2009; RR, 0.47; 95% CI, 0.38 to 0.59; $p < 0.00001$; $I^2 = 0\%$). Six trials compared the incidence of diabetes with TCPM+LM with placebo + LM (n = 1415), and there was also a significant difference in reducing the incidence of diabetes in favor of the TCPM + LM combination (RR, 0.55; 95% CI, 0.45 to 0.68, $p < 0.00001$; $I^2 = 0\%$).

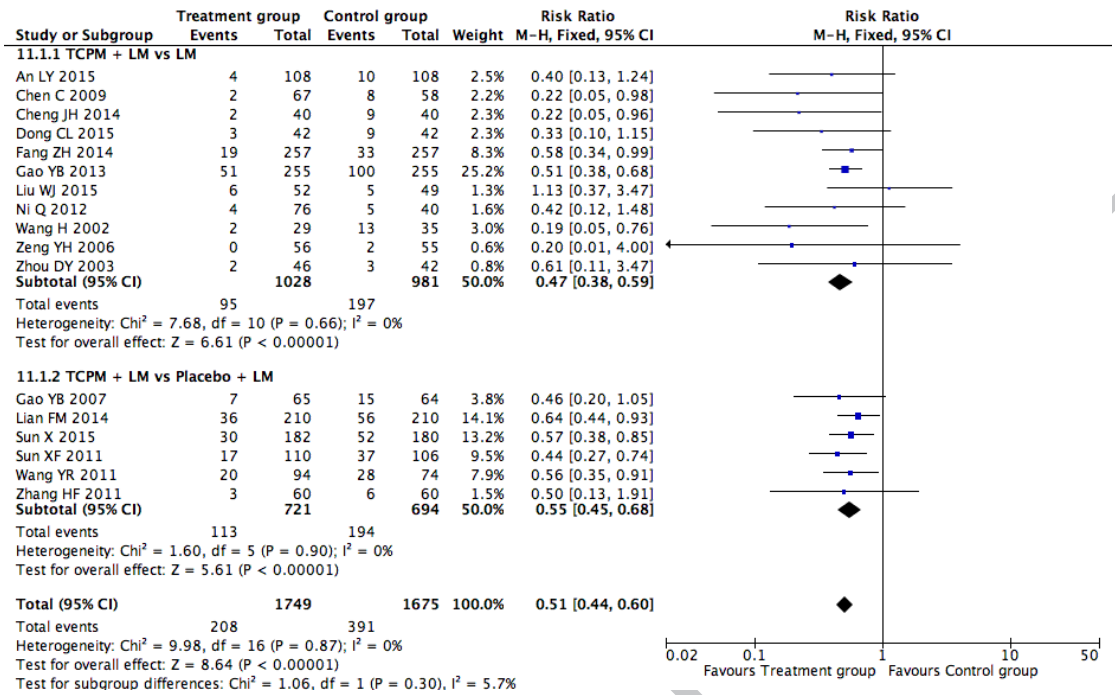


Figure 3. T_2DM incidence comparison.

Adverse events

Of the 17 trials that documented adverse events (AEs), seven reported no AEs and 10 trials recorded AEs, as shown in **Fig. 4**. These trials exhibited insignificant heterogeneity; thus, a fixed-effects model was used for statistical analysis. To compare the frequency of AEs between TCPM and the control group, subgroup analyses were performed. A meta-analysis of seven trials that compared TCPM + LM with LM showed that there was no significant difference in the frequency of AEs (RR, 1.03; 95% CI, 0.62 to 1.72; p = 0.91; I^2 = 42%). A meta-analysis of three trials also indicated that there were no significant differences in AEs between TCPM + LM and placebo + LM (RR, 1.46; 95% CI, 0.76 to 2.81; p = 0.25; I^2 = 0%).

Regarding individual AEs, the most frequent AE was gastrointestinal reactions in each group (**Table 3**). Eleven types of AE were reported in seven trials that compared TCPM + LM with LM. Cardiovascular events were significantly more frequent in patients receiving TCPM + LM (RR, 0.36; 95% CI, 0.14 to 0.93; one study, I^2 = NA), which was probably caused by the inclusion criteria. Twelve types of AE were reported in two trials that compared TCPM + LM with placebo + LM, and there were no significant differences between groups. There were also no significant differences in blood, urine, liver and renal function, or electrocardiogram (ECG) outcomes between treatment groups before and after treatment.

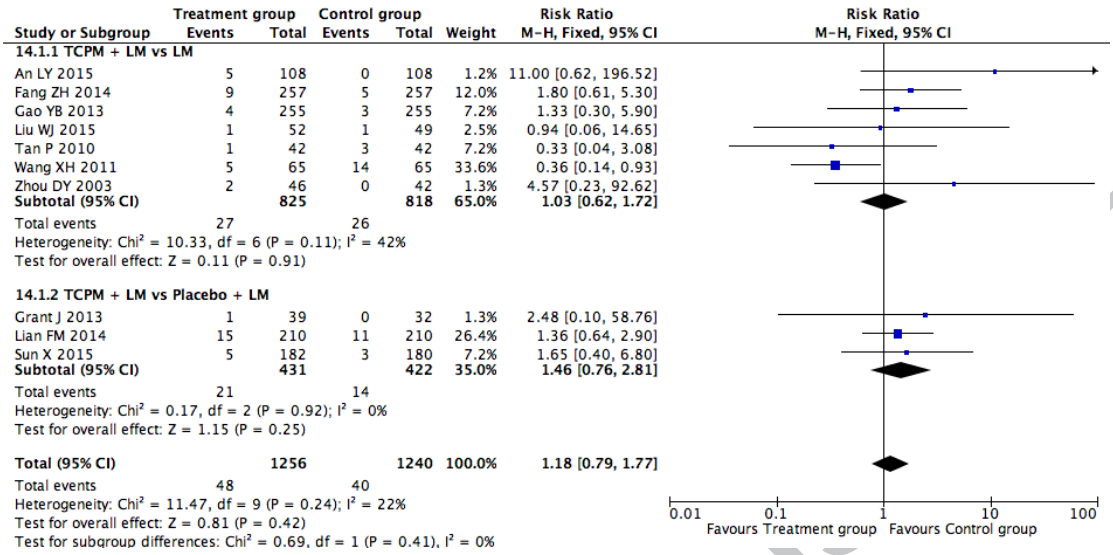


Figure 4. Frequency of adverse events comparison.

Table 3. Incidence of adverse events.

	Total events/ total number		Risk ratio (95% CI)
	TCPM + LM	LM	
Borborygmus	1/108	0/108	3.00 (0.12–72.83)
Cardiovascular events	5/65	14/65	0.36 (0.1– 0.93)
Elevated transaminase	0/42	1/42	0.33 (0.01–7.96)
Gastrointestinal reactions	11/355	5/348	2.16 (0.76–6.14)
Hypoglycemia	0/52	1/49	0.31 (0.01–7.54)
Loss of appetite	1/108	0/108	3.00 (0.12–72.83)
Mild abdominal distension	4/255	3/255	1.33 (0.30–5.90)
Mild diarrhea	2/150	0/150	5.00 (0.24–103.28)
Nausea	1/150	2/150	0.50 (0.05–5.46)
Pruritus	1/257	0/257	3.00 (0.12–73.30)
Stool changes	1/108	0/108	3.00 (0.12–72.83)
Incidence of any adverse event	–	–	Pooled rate ratio: 1.03 (0.63–1.68); P=0.92
	TCPM + LM	Placebo + LM	
Decreased hemoglobin	1/210	0/210	3.00 (0.12–73.22)
Elevated blood white blood cell	1/210	0/210	3.00 (0.12–73.22)
Elevated urine protein	0/210	1/210	0.33 (0.01–8.14)
Elevated urine white blood cell	2/210	0/210	5.00 (0.24–103.52)
Frequently urination	1/210	0/210	3.00 (0.12–73.22)
Gastrointestinal reactions	6/210	9/210	0.67 (0.24–1.84)
Genital swelling	0/210	1/210	0.33 (0.01–8.14)
Moderate dizziness	1/39	0/32	2.48 (0.10–58.76)
Rash	1/210	0/210	3.00 (0.12–73.22)
Tinnitus	1/210	0/210	3.00 (0.12–73.22)

Weakness	1/210	0/210	3.00 (0.12–73.22)
Weight loss	1/210	0/210	3.00 (0.12–73.22)
Incidence of any adverse event	-	-	Pooled rate ratio: 1.29 (0.68–2.44); P=0.43

Secondary outcomes

Normalization of blood glucose

Data regarding the normalization of blood glucose are shown in **Fig. 5**. The results of 16 trials (n = 3313) were included, and the results revealed a significant difference in the normalization of blood glucose between the treatment and control groups. To compare blood glucose normalization with TCPM and the control groups, subgroup analyses were performed.

Ten trials reported the normalization of blood glucose, and the data suggested that TCPM + LM was better at normalizing glucose than LM alone (n = 1898; RR, 0.76; 95% CI, 0.69 to 0.85, $p < 0.00001$; $I^2 = 61\%$). Although there was obvious heterogeneity among trials, the results were similar when analyzed using a fixed-effects model (RR, 0.79; 95% CI, 0.75 to 0.84, $p < 0.00001$). Six trials assessed blood glucose normalization with TCPM + LM compared with placebo + LM; there were significant differences between groups, with TCPM + LM being favored (n = 1415; RR, 0.62; 95% CI, 0.50 to 0.76; $p < 0.00001$; $I^2 = 74\%$).

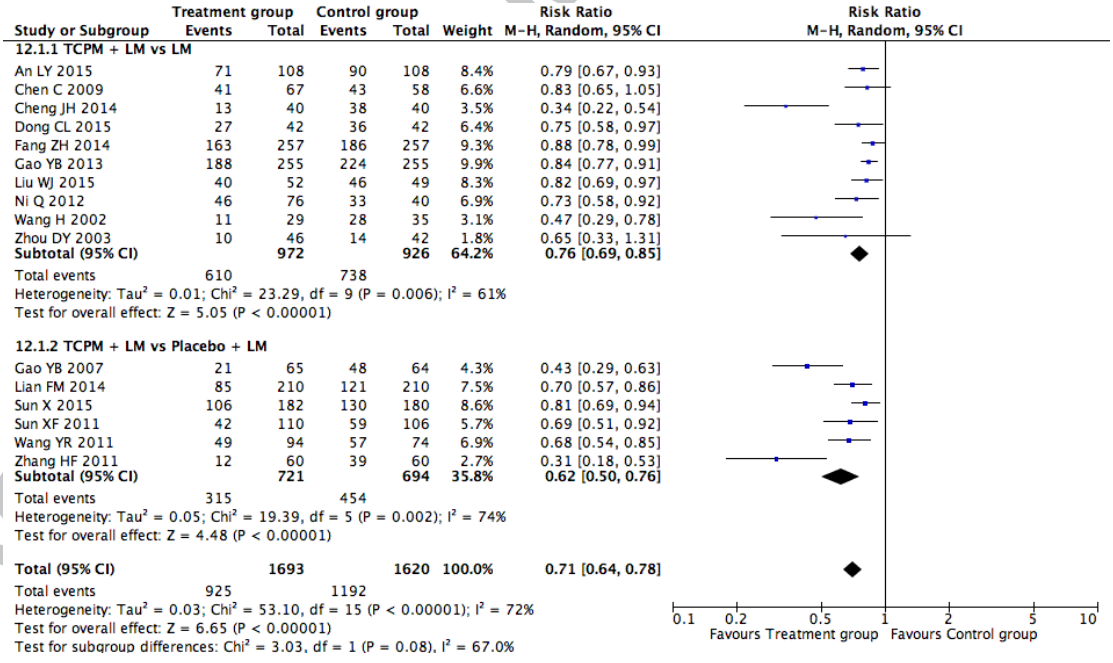


Figure 5. Blood glucose normalization comparison

Fasting blood glucose

A comparison of FBG levels is shown in **Fig. 6.** Twenty-four trials involving a total of 3387 participants reported FBG as an outcome. Significant heterogeneity between trials was observed, and so a random-effects model was used for statistical analysis. To compare changes in FBG levels between the treatment and control groups, subgroup analyses were performed.

Eighteen trials compared the effects of TCPM + LM with LM, and pooled analysis indicated that FBG decreased significantly more in the treatment group than the control group (n = 2602; MD, –0.37; 95% CI, –0.62 to –0.13; $p < 0.00001$; $I^2 = 98\%$). A pool analysis of six trials revealed no significant difference in FBG levels between TCPM + LM and placebo + LM (n = 785; MD, –0.68; 95% CI, –1.25 to –0.11; p = 0.02; $I^2 = 98\%$).

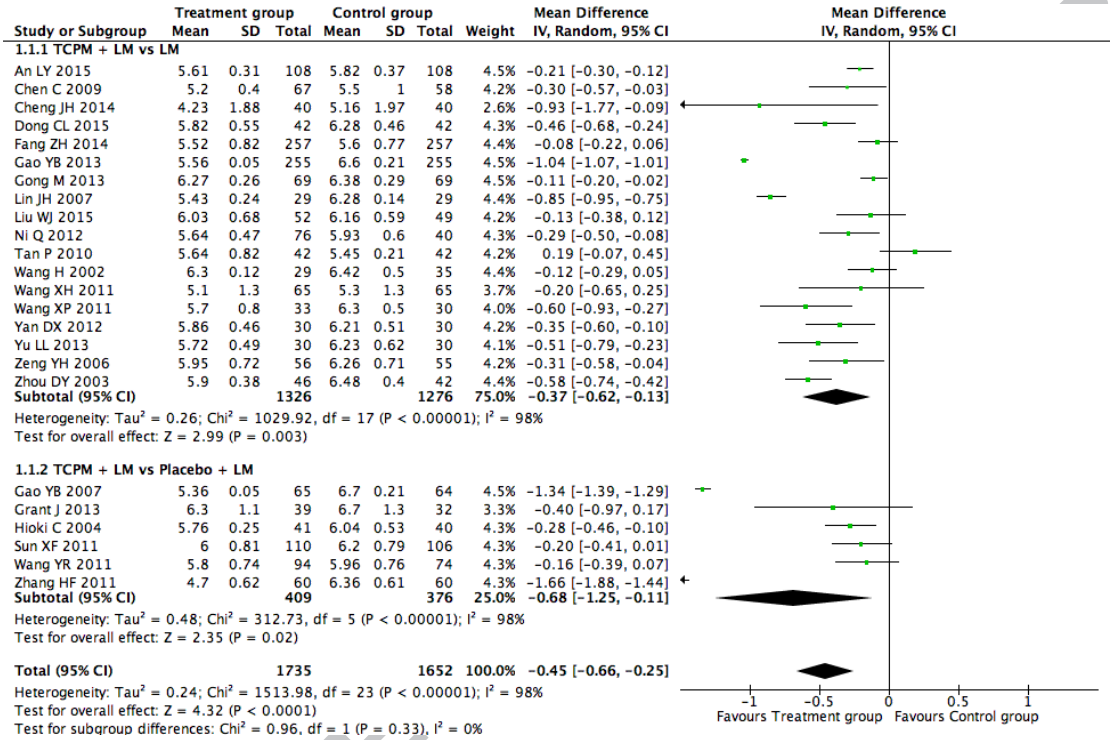


Figure 6. FBG comparison.

Two-hour postprandial blood glucose levels

A comparison of 2-hour PG levels is shown in **Fig. 7.** Twenty-four trials evaluated changes in 2h PG levels. Significant heterogeneity between trials was observed; therefore, a random effects model was used for statistical analysis. To compare changes in 2h PG levels between the treatment and control groups, subgroup analyses were performed. Eighteen trials compared 2h PG levels between TCPM+LM and LM alone. The results showed significant differences in favor of TCPM + LM (n = 2602; MD, –0.91; 95% CI, –1.35 to –0.47; $p < 0.0001$; $I^2 = 99\%$). There was also a statistically significant difference between TCPM + LM and placebo + LM (n = 785; MD, –1.07; 95% CI, –1.85 to –0.29; p = 0.007; $I^2 = 94\%$).

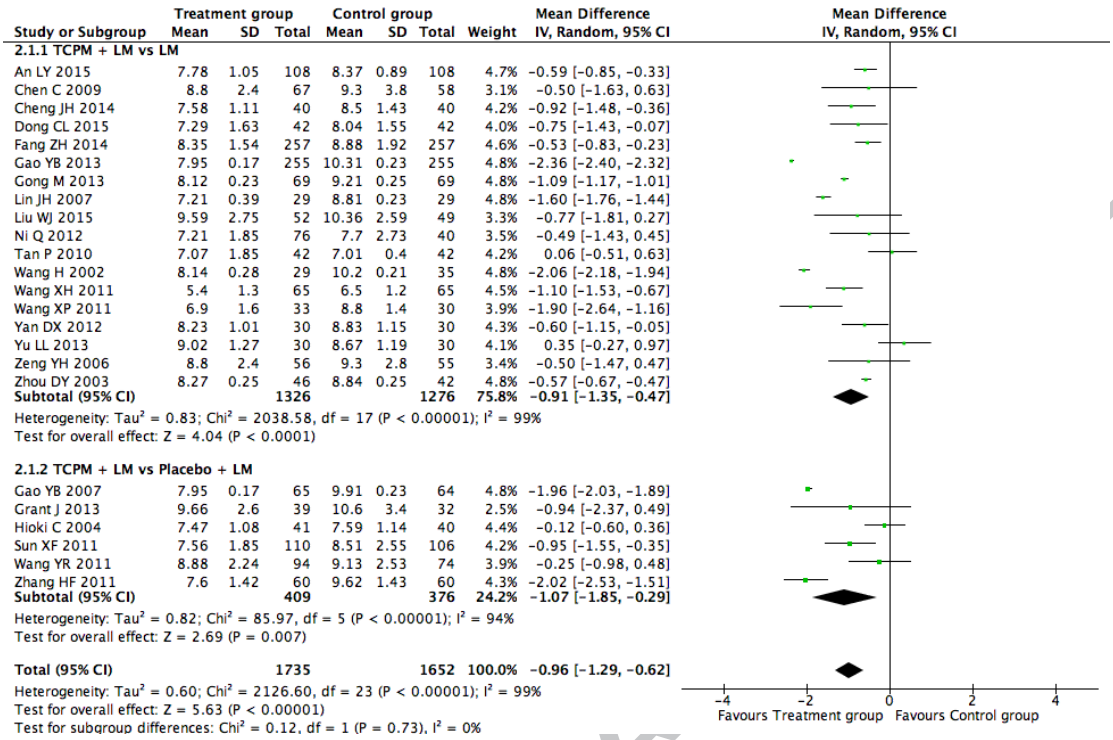


Figure 7. 2hPG comparison.

BMI

The BMI data are shown in **Fig. 8**. Thirteen trials reported BMI as an outcome. There was significant heterogeneity between trials; therefore, a random effects model was used for statistical analysis. Subgroup analyses indicated that TCPM + LM elicited a larger reduction in BMI than LM alone (eight trials; n = 1589; MD, –0.45; 95% CI, –0.76 to –0.14; p = 0.005; I^2 = 85%). However, there was no significant difference in BMI improvement between TCPM + LM and placebo + LM (five trials; n = 860; MD, –0.03; 95% CI, –1.50 to 1.44; p = 0.97; I^2 = 89%).

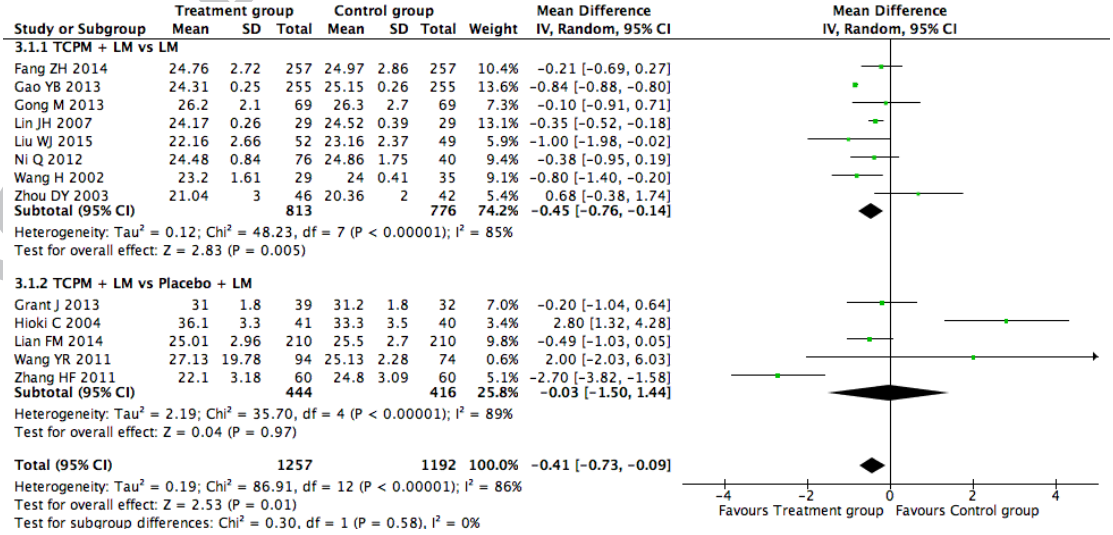


Figure 8. BMI comparison.

Sensitivity and subgroup analyses

Post hoc sensitivity analysis was performed by limiting the meta-analysis to 11 trials that compared TCPM +LM with LM. To investigate specific factors affecting the

overall efficacy of RCTs, subgroup analyses were performed on treatment duration, sample size, publication year, diagnostic criteria, publication language, and TCM syndrome. There were few differences (or much overlap in confidence intervals) in the overall risk ratios of incident diabetes (**Table 4**). All I^2 values were less than 50% and most groups were 0%, indicating low heterogeneity. There were no significant differences ($P > 0.05$) in the overall risk ratios in all subgroup analyses.

Table 4 Sensitivity and subgroup analysis based on the incidence of diabetes.

	Group	No. of studies	No. of participants	RR	95% CI	Z	P (effect)	I^2	Chi^2	P (het)
Treatment duration	≥12 months	8	1708	0.46	[0.37–0.59]	6.41	P<0.00001	0%	5.09	0.65
	<12 months	3	301	0.56	[0.29–1.09]	1.70	P=0.09	16%	2.39	0.30
Sample size	≥100	7	1693	0.51	[0.41–0.65]	5.60	P<0.00001	0%	4.02	0.67
	<100	4	316	0.28	[0.14–0.56]	3.57	P=0.0004	0%	1.27	0.74
Publication year	≥2010	7	1621	0.51	[0.40–0.64]	5.77	P<0.00001	0%	4.09	0.66
	<2010	4	388	0.25	[0.11–0.57]	1.24	P=0.001	0%	1.24	0.74
Diagnostic criteria	WHO criteria	9	1729	0.50	[0.39–0.62]	5.98	P<0.00001	0%	5.59	0.69
	Not WHO criteria	2	280	0.28	[0.12–0.68]	2.84	P=0.005	0%	2.84	0.40
Publication language	English	2	1024	0.53	[0.41–0.68]	4.93	P<0.00001	0%	0.15	0.70
	Chinese	9	985	0.37	[0.23–0.57]	4.42	P<0.00001	0%	6.28	0.62
TCM syndrome	Spleen qi deficiency	4	947	0.58	[0.38–0.87]	2.59	P=0.010	0%	2.03	0.57
	Others	7	1062	0.43	[0.33–0.56]	6.22	P<0.00001	0%	4.81	0.57

Note: The incidence of diabetes was analyzed according to different criteria based on treatment duration, sample size, publication year, diagnostic criteria, publication language, and TCM syndrome. RR, risk ratio; CI, confidence interval. Z and P (effect) evaluated the statistics of overall effect; I^2 and P (het) were used to assess heterogeneity.

A meta-analysis was also performed to include some TCPMs more than one trial in this review. The results indicated that seven TCPMs decreased FBG by 0.18–1.19 mmol/L and 2h PG by 0.50–2.16 mmol/L. The detailed effect sizes of TCPM compared with the control groups are summarized in **Table 5**.

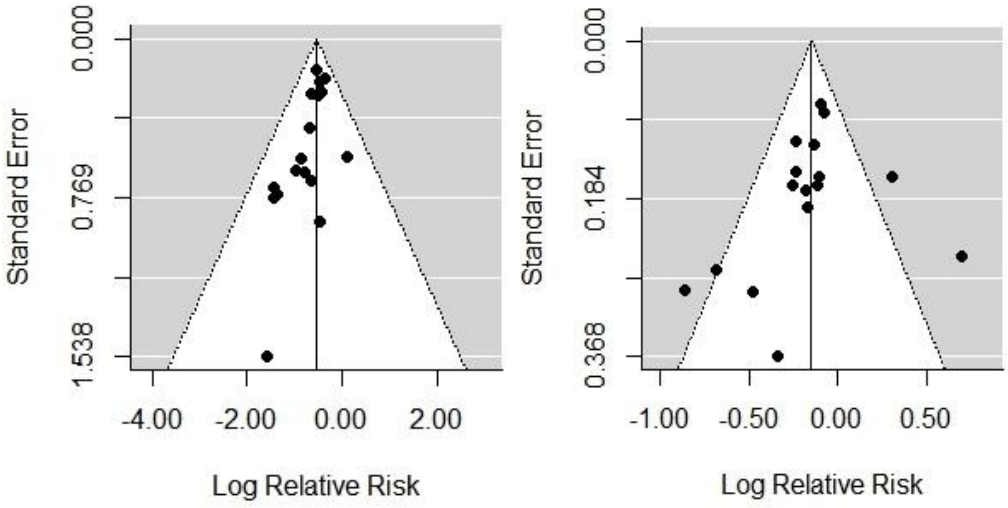
Table 5. Effect sizes of TCPM + LM or TCPM compared with the control group.

TCPM	**No. of**	**No. of**	**Outcomes**

	trials	participants	FBG (mmol/L)	2h PG (mmol/L)
Tianqi capsule + LM	3	804	MD, –0.18 (–0.34 to –0.33)	MD, –0.63 (–1.32 to 0.05)
Tang zhi ping + LM	2	639	MD, –1.19 (–1.48 to –0.90)	MD, -2.16 (–2.55 to –1.77)
Jin qi jiang tang tablet + LM	3	534	MD, –0.20 (–0.96 to 0.55)	MD, –0.32 (–0.92 to 0.28)
Jin li da granule + LM	3	291	MD, –0.29 (–0.54 to –0.03)	MD, –0.50 (–1.51 to 0.50)
Liu wei dihuang pill + LM	3	255	MD, –0.27 (–0.53 to 0.00)	MD, –1.23 (–2.25 to –0.21)
Tianmai Xiaoke tablet + LM	2	204	MD, –1.06 (–2.24 to 0.12)	MD, –1.41 (–2.65 to –0.16)
Shenqi Jiang Tang granule + LM	2	118	MD, –0.61 (–1.10 to –0.12)	MD, –1.14 (–2.11 to –0.16)

Publication bias

Publication bias regarding the incidence of diabetes and the normalization of blood glucose was assessed using funnel plots (**Fig. 9**). For the incidence of diabetes (**Fig. 9A**), there was significant publication bias in the results of Egger's test (t = –0.47, p < 0. 01) and Begg's test (Z = –1.71, p = 0.09). For the normalization of blood glucose (**Fig. 9B**), there was no significant publication bias in the results of Egger's test (t = –0.30, p = 0.12) and Begg's test (Z = –1.24, p = 0.22).



a. Incidence of diabetes b. Normalization of blood glucose

Figure 9. Funnel plot of the trials that compared treatment and control groups. (a) Incidence of diabetes. (b) Normalization of blood glucose.

Assessing the quality of the evidence

Figure 10 shows the summary of the overall evidence for each outcome (with the exception of adverse events), as assessed using the GRADE method. Generally, the quality of evidence was low for the effects of TCPM on the incidence of diabetes and the normalization of blood glucose and was very low for the effects of TCPM on FBG, 2h PG, and BMI.

Question: Should Traditional Chinese patent medicine be used for prediabetes?

Bibliography: . Traditional Chinese patent medicine for prediabetes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Control	With Traditional Chinese patent medicine		Risk with Control / Risk difference with Traditional Chinese patent medicine (95% CI)
Incidence of diabetes (CRITICAL OUTCOME)										
3424 (17 studies) 12 months	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias strongly suspected[2]	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, publication bias	391/1675 (23.3%)	208/1749 (11.9%)	**RR 0.51** (0.44 to 0.6)	**Study population** **233 per 1000** — **114 fewer per 1000** (from 93 fewer to 131 fewer) **Moderate** **214 per 1000** — **105 fewer per 1000** (from 86 fewer to 120 fewer)
Normalizaton of blood glucose (IMPORTANT OUTCOME)										
3313 (16 studies) 12 months	serious[1]	serious[3]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**[1,3] due to risk of bias, inconsistency	1192/1620 (73.6%)	925/1693 (54.6%)	**RR 0.71** (0.64 to 0.78)	**Study population** **736 per 1000** — **213 fewer per 1000** (from 162 fewer to 265 fewer) **Moderate** **760 per 1000** — **220 fewer per 1000** (from 167 fewer to 274 fewer)
FBG (IMPORTANT OUTCOME; Better indicated by lower values)										
3387 (24 studies) 12 months	serious[1]	serious[3]	no serious indirectness	no serious imprecision	reporting bias strongly suspected[2]	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, publication bias	1652	1735	-	The mean fbg in the intervention groups was **0.45 lower** (0.66 to 0.25 lower)
2h PG (IMPORTANT OUTCOME; Better indicated by lower values)										
3387 (24 studies) 12 months	serious[1]	serious[3]	no serious indirectness	no serious imprecision	reporting bias strongly suspected[2]	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, publication bias	1652	1735	-	The mean 2h pg in the intervention groups was **0.96 lower** (1.29 to 0.62 lower)
BMI (IMPORTANT OUTCOME; Better indicated by lower values)										
2449 (13 studies) 12 months	serious[1]	serious[3]	no serious indirectness	no serious imprecision	reporting bias strongly suspected[3]	⊕⊖⊖⊖ **VERY LOW**[1,3] due to risk of bias, inconsistency, publication bias	1192	1257	-	The mean bmi in the intervention groups was **0.41 lower** (0.73 to 0.09 lower)

[1] Most of the included trials were included as high risk of bias

[2] We detected significant asymmetry according to funnel plot, suggesting a negligible publication bias.

[3] Meta-analysis for the outcome had high heterogeneity.

Figure 10. Summary of the evidence for each outcome.

Discussion

Summary of the evidence and explanation of the results

The past decades have witnessed an unprecedented expansion in the fields of anti-diabetic drugs and insulin discovery and development. Thus, Western medications have become the dominant medical treatment worldwide. However, it has been increasingly acknowledged that TCM, which possess the characteristic of "preventive treatment of disease", may have an important role in primary healthcare in China and other Asian countries, especially in the field of disease prevention. Therefore, TCPM is becoming frequently used among patients with prediabetes [44-45]. However, few reviews have evaluated their effectiveness systematically and comprehensively according to current international standards. To our knowledge, this is the first systematic review of the English and Chinese literature to discuss the efficacy and safety of TCPM for prediabetes. This systematic review identified 26 RCTs investigating TCPM in patients with prediabetes. The main findings were that

subjects who received TCPM as a co-intervention with lifestyle modification (LM) were less likely to progress to T_2DM compared LM alone and placebo + LM. Subjects that received TCPM as a co-intervention with LM had an increased possibility of regression toward normoglycemia. TCPM as an adjuvant therapy did not have more AEs compared with controls. Merlotti et al.[10] assessed the effectiveness of different strategies for preventing T_2DM. Fifteen different strategies were included, such as diet plus/or physical activity, metformin, α-glucosidase inhibitors, glitazones, beta-cell stimulating drugs, lipid-affecting drugs, ACE inhibitors, and calcium antagonists. The results showed that twelve different strategies may prevent T_2DM, with different effectiveness (RR ranging from 0.37 [95%CI, 0.26 to 0.52] to 0.85 [95% CI, 0.77 to 0.93]).The overall efficacy of TCPM (RR, 0.51; 95% CI, 0.44 to 0.60) on the incidence of diabetes incidence was similar to that of diet (RR, 0.51; 95% CI, 0.39 to 0.68) and α-glucosidase inhibitors (RR, 0.54; 95% CI, 0.39 to 0.75).

Similar findings were published to evaluate Chinese herbal medicine in prediabetes [46], which concluded that Chinese herbal medicine plus LM was more effective at reducing the incidence of diabetes compared with LM alone. A strength of the current review is that we collected more recent data and included higher quality trials that only investigated TCPM, which made it convenient to evaluate efficacy. This systematic review suggested that TCPM plus LM was more beneficial for achiving glycemic control than LM alone. The overall interventions were associated with a decline in FBG and 2h PG by 0.45 mmol/L and 0.96 mmol/L, respectively, which was similar to lifestyle modification (physical or dietary interventions or both) [47]. However, confirmation of the efficacy was limited due to poor methodological quality, insufficient placebo-controlled trials, and significant heterogeneity in the included trials. Most trials did not include a placebo, so the effect of TCPM is likely to be attributed to a placebo effect or other psychological effects. In addition, the reported AEs were not severe and required no additional special treatment. Although the aggregated results indicated no difference between the compared groups, the safety of TCPMs must still be rigorously monitored and appropriately reported in future clinical trials.

Regarding the study limitations, 14 trials mentioned only “randomly allocating” the participants but did not provide the detailed method of randomization. Moreover, only seven trials described the allocation concealment method; inadequate allocation concealment might have created potential selection bias and exaggerated any estimates of therapeutic effects. Eighteen trials did not use a placebo; these trials were likely influenced by either the placebo effect or psychological effects. Additionally, most of the included trials have not been registered, and so we could not acquire the also not long enough to evaluate the long-term effects of TCPMs. The results of GRADE assessment were provided for all outcomes except for adverse events. The risk of bias in most of the included trials was high, which led to a reduced rating for the outcomes. Regarding inconsistency, a meta-analysis for the outcomes “normalization of blood glucose”, “FBG”, “2h PG” and “BMI” had high heterogeneity, so the ratings for these outcomes were reduced. As for indirectness, the aim of this review was to explore traditional Chinese medicine for early glucose

impairment, and so we did not include indirect comparisons. We also did not find any imprecise evidence. For publication bias, significant asymmetry was detected in funnel plots for the normalization of blood glucose, FBG, 2h PG, and BMI, suggesting negligible publication bias. In conclusion, the evidence level for the outcomes was low regarding the incidence of diabetes and normalization of blood glucose was low and very low for FBG, 2hPG, and BMI (**Fig. 10**).

Limitations

The current systematic review and meta-analysis was limited by the trials identified. We could not perform no pooled analyses due to the high heterogeneity. Better accuracy would be obtained with pooled analysis based on the course of treatment, follow-up duration, and different formulations and dosage of TCPM. Additionally, different TCPM prescriptions and formulations would undoubtedly differ in terms of mechanism of action and putative efficacy, which we did not measure. Additionally, the long-term effects of TCPMs on the prevention of T_2DM in patients with prediabetes are unknown and we have no data regarding the improvement in diabetes after treatment.

Implications for research

Although the present evidence is insufficient to support the effectiveness of TCPM, it may warrant further study. Concerns regarding the methodological quality suggest that the CONSORT 2010 statement should be recommended as a guideline [48-49], which consists of a 25-item checklist to confirm the trial quality. Double-blinded, placebo-controlled RCTs are necessary, as are standardization of all TCMs used, documentation of the dosing regimen, and the strength of each compound. Then, a longer follow-up with TCPMs should be performed to assess the long-term effects on diabetes and the progression to diabetic complications.

Implications for clinical practice

TCM may hold promise in the prevention of diabetes. On one hand, holistic concepts are a characteristic and advantage of TCM. It takes a disease as a whole, considers the whole disease process, and focuses on adjusting the imbalance of qi, blood, yin, and yang [50-51]. TCPM contains various active ingredients that could exert multiple therapeutic effects on multiple targets such as enhancing insulin sensitivity, stimulating insulin secretion, or reducing body weight and other cardiovascular risk factors (hyperlipidemia and hypertension) [52]. Therefore, each abnormality could be treated as a whole. On the other hand, the thought of “treat disease before it arises” is the unique feature and essence, which includes two parts of “prevent disease before it arises” and “control the development of existing disease”. “Prevent disease before it arises” means that strengthening the body constitution regulation and closely monitoring the high-risk target group of diabetes is necessary. “Control the development of existing disease” means that early diagnosis and intervention play important roles, and aims to reverse the risk factors leading to diabetes and delay diabetic complications. Prediabetes may fall under the TCM patterns of “spleen pyretic abundance” and “stagnation” [53]. The main pathogenesis lies in the spleen and stomach congestion, damp-heat accumulation in the spleen, and qi stagnation due to liver depression leading to spleen qi deficiency in the body; blood stasis and

phlegm retention are often also present. If prolonged qi deficiency impairs yin, dual deficiency of qi and yin will occur [54]. Fifteen TCPMs were examined in 26 included trials. The most frequently used ten herbs were Huangqi (*Astragali Radix*), Dihuang (*Radix Rehmanniae Glutinosae*), Huanglian (*Rhizoma Coptidis*), Shanyao (*Dioscoreae Rhizoma*), Tianhuafen (*Trichosanthis Radix*), Gegen (*Radix Puerariae*), Danshen (*Radix Salviae Miltiorrhizae*), Cangzhu (*Rhizoma Atractylodis*), Shanzhuyu (*Corni Fructus*), and Fuling (*Scierotium Poriae Cocos*). The main therapeutic principle included fortifying qi, clearing heat, nourishing yin, activating blood, and drying dampness.

Conflict of interest statement

The authors declare that they have no conflicts of interest related to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Author contributions

Bing Pang and Feng-mei Lian conceived the study and wrote the manuscript; they contributed equally to this work. Xi-yan Zhao and Xue-min Zhao collected the data. De Jin and Yi-qun Lin assessed the risk of bias in the included studies. Bing Pang and Yu-jiao Zheng performed the statistical analysis. Xiao-lin Tong, Qing Ni, and Feng-mei Lian participated in the study design and coordination. Xiao-lin Tong and Qing Ni are co-corresponding authors.

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Table 1 Characteristics of trials included in this review

Study ID	Sample Size(randomized/drop-out); Sex: M/F	Age（year）	Diagnostic criteria	Intervention	Treatment duration (month)	Follow-up duration (month)	Outcome measure	
				Treatment group	Control group			
An LY 2015	216/26 T:108 (70/38) C:108 (72/36)	T: 41.8 ± 7.7 C:39.6 ± 7.5	ADA 2008	Yue Ju pill (6g ,po, bid) + LM	LM	12	12	A-E
Chen C 2009	125/12 T:61 (32/29) C:52 (29/23)	T: 57.7 ± 12.9 C: 56.3 ± 12.8	WHO 1999	Shen qi jiang tang capsule (2 capsules/ 0.7 g, po, tid) + LM	LM	24	24	A, B, D
Cheng JH 2014	80/0 T:40 (25/15) C:40 (23/17)	T: 52.8 ± 6.2 C: 49.4 ± 4.2	WHO 1985	Liu wei dihuang pill (6 g, po, bid) + LM	LM	12	12	A-E
Dong XL 2015	84/0 T:42 (18/24) C:42 (20/22)	T: 52.4 ± 8.6 C: 54.1 ± 7.9	WHO 1999	Tianmai Xiaoke tablet (2 tablet, 0.24 g, po, bid)+ LM	LM	6	6	A, B, D, E
Fang ZH 2014	514/75 T:157 (136/21) C:157 (142/15)	T:54.95 ± 9.50 C:54.61 ± 10.51	WHO 1999	Shen zhu tiaopi granule (8.8 g, po, bid) + LM	LM	12	12	A-F
Gao YB 2013	510/52 T:255 (110/145) C: 255 (112/143)	T: 49.3 ± 1.2 C: 51.12 ± 1.3	WHO 1999	Tang zhi ping (5 g, po, bid) + LM	LM	36	36	A-F
Gong M 2013	138/17 T:69 (24/35) C:69 (26/36)	T: 45.2 ± 10.6 C: 46.5 ± 10.2	WHO 1999	Zhi bai dihuang pil (3 g, po, tid) + LM	LM	3	3	D, E, F
Lin JH 2007	58/0 T:29 C:29	T: 53.6 ± 4.4 C: 52.9 ± 5.8	WHO 1999	Shenqi Jiang Tang granule (3 g, po, tid) + LM	LM	6	6	A, C, D, E, F
Liu WJ 2015	101/8 T:52 (24/25) C:49 (22/22)	T: 49.68 ± 11.31 C: 47.93 ± 11.82	WHO 1999	Jin Li Da granule (9 g, po, tid) + LM	LM	3	3	A-F
Ni Q 2012	116/0 T:76 (40/36) C:40 (19/21)	T: 48.2 ± 10.1 C: 45.8 ± 10.5	WHO 1999	Qiyao Xiaoke capsule (2.4 g, po, tid) + LM	LM	3	6	A-F
Tan P 2010	84/0 T:42 (20/22) C:42 (21/21)	T: 58.4 ± 2.1 C: 54.8 ± 1.6	ADA 2008	Jin qi jiang tang tablet (3.36 mg, po, tid)+	LM	3	3	C, D, E

Note: A: Incidence of diabetes; B: Normalization of blood glucose; C: Adverse events; D: Fasting blood glucose; E: 2-hour postprandial blood glucose; F: Body mass index; G: Cost-effectiveness ratio.

Table 2 Components of the included TCPMs

TCPMs	Components
Yue Ju pill	Nutgrass galingale rhizome (Xiangfu, Rhizoma Cyperi), Szechuan Lovage Root (Chuanxiong, Rhizoma Ligustici Chuanxiong), Cape jasmine fruit (Zhizi, Fructus Gardeniae), Atractylodes rhizome (Cangzhu, Rhizoma Atractylodis), Massa Medicated leaven (Shenqu, Medicata Fermentata)
Shen qi jiang tang capsule	Panax Ginseng Leaves Extract (Renshen jing ye zaogan, Panax ginseng C. A. Meyer), Chinese magnolivine fruit (Wuweizi, Fructus Schisandrae Chinensis), Astragalus root (Huangqi, Astragali Radix), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Chinese raspberry (Fupenzi, Fructus Rubi), Dwarf lilyturf tuber (Maidong, Radix Ophiopogonis), Poria (Fuling, Scierotium Poriae Cocos), Trichosanthes root (Tianhuafen, Trichosanthis Radix), Alisma (Zexie, Rhizoma Alismatis), and Chinese Wolfberry Fruit (Gouqizi, Fructus Lycii Chinensis).
Liu wei dihuang pill	Rehmannia root (Dihuang, Radix Rehmanniae Glutinosae), Cornus Fruit (Shanzhuyu, Corni Fructus), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Poria (Fuling, Scierotium Poriae Cocos), Alisma (Zexie, Rhizoma Alismatis), and Cortex of the Peony Tree Rote (Danpi, Cortex Radicis Moutan).
Tian mai xiaoke tablet	Chrome acid chrome, Chinese magnolivine fruit (Wuweizi, Fructus Schisandrae Chinensis), Dwarf lilyturf tuber (Maidong, Radix Ophiopogonis), Trichosanthes root (Tianhuafen, Trichosanthis Radix).
Shen zhu tiaopi granule	Codonopsis root (Dangshen, Radix Codonopsis), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Atractylodes rhizome (Cangzhu, Rhizoma Atractylodis), Poria (Fuling, Scierotium Poriae Cocos), Aged tangerine peel (Chenpi, Pericarpium Citri Reticulatae) and Liquoric Root (Gancao, Radix Glycyrrhizae).
Tang zhi ping granule	Coptis root (Huanglian, Coptidis Rhizoma), Giant knotweed (Huzhang, Rhizoma Polygoni Cuspidati), Alisma (Zexie, Rhizoma Alismatis), White atractylodes rhizome (Baizhu, Rhizoma Atractylodis Macrocephalae), Atractylodes rhizome (Cangzhu, Rhizoma Atractylodis), Astragalus root (Huangqi, Astragali Radix), Crataegus Fruit (Shanzha, Crataegi Fructus), Salvia Root (Danshen, Radix Salviae Miltiorrhizae), Pueraria (Gegen, Radix Puerariae), Ningpo Figwort Root (Xuanshen, Radix Scrophulariae Ningpoensis), Fleeceflower Root (Heshouwu, Radix Polygoni Multiflori), Polygonati officinalis (Yuzhu, Rhizoma Polygonati Odorati), Psoralea fruit (Buguzhi, Fructus Psoraleae), and White mulberry root-bark (Sangbaipi, Cortex Mori).

Shen qi jiang tang granule	Panax Ginseng Leaves Extract (Renshen jing ye zaogan, Panax ginseng C. A. Meyer), Chinese magnolivine fruit (Wuweizi, Fructus Schisandrae Chinensis), Astragalus root (Huangqi, Astragali Radix), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Chinese raspberry (Fupenzi, Fructus Rubi), Dwarf lilyturf tuber (Maidong, Radix Ophiopogonis), Poria (Fuling, Scierotium Poriae Cocos), Trichosanthes root (Tianhuafen, Trichosanthis Radix), Alisma (Zexie, Rhizoma Alismatis), and Chinese Wolfberry Fruit (Gouqizi, Fructus Lycii Chinensis).
Zhi bai dihuang pil	Anemarrhena rhizome (Zhimu, Rhizoma Anemarrhenae), Phellodendron bark (Huangbai, Cortex Phellodendri Chinensis), Rehmannia root (Dihuang, Radix Rehmanniae Glutinosae), Cornus Fruit (Shanzhuyu, Corni Fructus), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Poria (Fuling, Scierotium Poriae Cocos), Alisma (Zexie, Rhizoma Alismatis), and Cortex of the Peony Tree Rote (Danpi, Cortex Radicis Moutan).
Jin Li Da granule	Ginseng (Renshen, Radix et Rhizoma Ginseng), Siberian Solomon Seal Rhizome (Huangjing, Rhizoma Polygonati), Atractylodes rhizome (Cangzhu, Rhizoma Atractylodis), Light yellow sophora root (Kushen, Radix Sophorae Flavescentis), Dwarf lilyturf tuber (Maidong, Radix Ophiopogonis), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Fleeceflower Root (Heshouwu, Radix Polygoni Multiflori), Cornus Fruit (Shanzhuyu, Corni Fructus), Poria (Fuling, Scierotium Poriae Cocos), Eupatorium (Peilan, Herba Eupatorii), Coptis root (Huanglian, Coptidis Rhizoma), Anemarrhena rhizome (Zhimu, Rhizoma Anemarrhenae), Epimedium (Yinyanghuo, Herba Epimedii), Salvia Root (Danshen, Radix Salviae Miltiorrhizae), Pueraria (Gegen, Radix Puerariae), Lychee seed (Lizhihe, Semen litchi), Chinese wolfberry root-bark (Digupi, Cortex Lycii).
Qiyao Xiaoke capsule	American ginseng (Xiyangshen, Radix Panacis Quinquefolii), Astragalus root (Huangqi, Astragali Radix), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Cornus Fruit (Shanzhuyu, Corni Fructus), Chinese Wolfberry Fruit (Gouqizi, Fructus Lycii Chinensis), Dwarf lilyturf tuber (Maidong, Radix Ophiopogonis), Anemarrhena rhizome (Zhimu, Rhizoma Anemarrhenae), Trichosanthes root (Tianhuafen, Trichosanthis Radix), Pueraria (Gegen, Radix Puerariae), Chinese magnolivine fruit (Wuweizi, Fructus Schisandrae Chinensis), Gallnut of Chinese sumac (Wubeizi, Galla Chinensis).
Jin qi jiang tang tablet	Astragalus root (Huangqi, Astragali Radix), Coptis root (Huanglian, Coptidis Rhizoma), and Honeysuckle flower (Jinyinhua, Flos Lonicerae Japonicae),etc.
Fufang yuanqi granule	Astragalus root (Huangqi, Astragali Radix), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Chinese wolfberry root-bark (Digupi, Cortex Lycii), Anemarrhena rhizome (Zhimu, Rhizoma Anemarrhenae), Ningpo Figwort Root (Xuanshen, Radix Scrophulariae Ningpoensis), Honeysuckle flower (Jinyinhua, Flos Lonicerae Japonicae), Peach seed (Taoren, Semen Persicae), (Notoginseng root (Sanqi, Radix et Rhizoma Notoginseng).
Bofu-tsusho-san	Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Liquoric Root (Gancao, Radix Glycyrrhizae), Platycodon root (Jiegeng, Radix Platycodonis), Gypsum (Shigao, Gypsum Fibrosum), Atractylodes rhizome (Cangzhu, Rhizoma Atractylodis), Rhubarb root (Dahuang, Radix et Rhizoma Rhei), Fineleaf schizonepeta spike (Jingjiesui, Spica Schizonepetae), Cape jasmine fruit (Zhizi, Fructus Gardeniae), White peony root (Baishao, Radix Paeoniae Alba), Szechuan Lovage Root (Chuanxiong, Rhizoma Ligustici Chuanxiong), Chinese angelica (Danggui, Radix Angelicae Sinensis), Field mint (Bohe, Herba Menthae), Saposhnikovia root (Fangfeng, Radix Saposhnikoviae), Ephedra herb (Mahuang, Herba Ephedrae), Forsythia fruit (Lianqiao, Fructus Forsythiae), Dried ginger rhizome (Ganjiang, Rhizoma Zingiberis), Talcum (Huashi, Talcum), and Natrium Sulphuricum.

Tianqi capsule	Astragalus root (Huangqi, Astragali Radix), Coptis root (Huanglian, Coptidis Rhizoma), Trichosanthes root (Tianhuafen, Trichosanthis Radix), Privet Fruit (Nvzhenzi, Fructus Ligustri Lucidi), Eclipta (Hanliancao, Herba Ecliptae Prostratae), Dendrobe (Shihu, Dendrobii Caulis), Ginseng (Renshen, Radix et Rhizoma Ginseng), Chinese wolfberry root-bark (Digupi, Cortex Lycii), Gallnut of Chinese sumac (Wubeizi, Galla Chinensis), and Cornus Fruit (Shanzhuyu, Corni Fructus).
Jiangtang Xiaozhi granule	Privet Fruit (Nvzhenzi, Fructus Ligustri Lucidi), Astragalus root (Huangqi, Astragali Radix), Coptis root (Huanglian, Coptidis Rhizoma), Lyechee nut (Lizhihe, Litchi chinensis), Kelp (Kunbu, Ecklonia kurome), Turmeric root tuber (Jianghuang, Rhizoma Curcumae Longae), Lactose, Magnesium stearate.

Note: TCPMs: Traditional Chinese patent medicine

Highlights

1.The efficacy and safety of traditional Chinese patent medicine on preventing type 2 diabetes are evaluated.

2.Traditional Chinese patent medicine may bring a new approach for preventing type 2 diabetes.

3.Traditional Chinese patent medicine reduce the risk of progression to T_2DM and increase the possibility of regression toward normoglycemia.

4.The quality of randomized controlled trials is evaluated rigorously.