Heliyon 8 (2022) e12112

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The efficacy of Chinese patent medicine intervention on blood glucose and lipid in prediabetes: A meta-analysis

Kaile Ma [a,1], Chuanxi Tian [a,1], Can Guo [b], Min Li [a,*]

[a] Institute of Metabolic Diseases, Guang'anmen Hospital, China Academy of Chinese, 100053, China
[b] Nanjing University of Chinese Medicine, Nanjing, China

ARTICLE INFO

Keywords:
Prediabetes
Chinese patent medicine
Blood glucose
Meta-analysis
BMI
Routine lifestyle intervention

ABSTRACT

Objective: The purpose of this study was to analyze the efficacy and safety of Chinese patent medicine in the treatment of blood glucose, blood lipid and insulin resistance in prediabetic patients through a meta-analysis of clinical trials.

Methods: Randomized controlled trials of Chinese patent medicine in the treatment of prediabetes were searched in the databases of CNKI, WanFang, VIP, CBM, PubMed, Web of Science and Embase using the computer with the search deadline on June 2, 2022. The two researchers independently screened the literatures based on the inclusion and exclusion criteria, and the fasting blood glucose, postprandial blood glucose, glycated hemoglobin, insulin resistance index, blood lipids, prediabetes reversal rate and diabetes conversion rate were used as outcome indicators. The quality of the study was evaluated according to the Cochrane scale, and data were analyzed by RevMan software.

Results: Sixteen clinical trial studies were eventually fitted into, and a meta-analysis was conducted on the included studies, and the final results showed as follows: Compared with conventional lifestyle intervention, the remedy of Chinese patent medicine intervention in prediabetes patients had significant effects on the outcome indicators, such as fasting blood glucose [MD = -0.36, 95%CI = (-0.45,-0.26), $P < 0.00001$], 2 h postprandial blood glucose [MD = -0.71, 95%CI = (-0.99,-0.42), $P < 0.00001$], glycated hemoglobin [MD = -0.33, 95%CI = (-0.48,-0.19), $P < 0.00001$], BMI [MD = -0.82, 95%CI = (-1.20,-0.44), $P < 0.0001$], insulin resistance index [MD = -0.20, 95%CI = (-0.29,-0.11), $P < 0.00001$], diabetes conversion rate [MD = 0.49, 95%CI = (0.34,0.70), $P < 0.0001$], and the differences were indicated as a statistically significant. However, the outcome indexes of TC, TG, HDL-C and LDL-C in blood lipid exhibited no significant effect, and no significant difference.

Conclusions: The results indicated that Chinese patent medicine intervention could ameliorate the outcome indicators of prediabetes with significant efficacy and good safety. Its therapeutic effect was mainly manifested in blood glucose, insulin, body weight, and diabetes conversion rate. Chinese patent medicine maybe a promising avenue for prediabetes.

1. Introduction

Diabetes, a metabolic disease, is mainly characterized by hyperglycemia. In recent years, the incidence of diabetes has been increasing, and diabetes has become a global epidemic. Diabetes often causes a series of hazards (blindness, kidney failure, heart attack, stroke, or lower limb amputation), and has a very high risk in humans hyperglycemia [1]. According to the estimation of the International Diabetes Federation (IDF), the number of people with diabetes worldwide is expected to increase to nearly 700 million by 2045 [2]. Multiple data suggest that the high prevalence of diabetes makes it a plaguing disease all over the world. Due to its serious complications, early detection, early prevention, and early treatment are required, it's a key to prevent the development of prediabetes. Prediabetes also strongly increases the risk of cardiovascular disease and all-cause mortality. And cure of prediabetes to normoglycemia decreases the risk of both diabetes and cardiovascular disease. Identifying modifiable factors exerts crucial clinical significance for help reverse prediabetes to normoglycemia. At present, the commonly agents used for treatment of diabetes in clinic includes as the first-line dipeptide peptidase - 4 (DPP4 inhibitor), glucagon like peptide 1 agonists, sulfonylureas and

* Corresponding author.
E-mail address: limin-72114@163.com (M. Li).
[1] Equal contribution.

https://doi.org/10.1016/j.heliyon.2022.e12112
Received 19 July 2022; Received in revised form 24 October 2022; Accepted 28 November 2022

metformin. Meanwhile, increasing studies are also reported in clinical Chinese medicine treatment, especially related researches of the Chinese patent medicine in treatment of diabetes and prediabetes are into the field of vision gradually. Prediabetes involves two stages of the progress: impaired fasting glucose and impaired glucose tolerance. The American Diabetes Association defines prediabetes as the control scope of glycated hemoglobin A1c (HbA1c) between 5.7% and 6.4%, and divides prediabetes into such two types, partially impaired fasting glucose (IFG) and partially impaired glucose tolerance (IGT), according to 2-hour postprandial blood glucose [3]. Therefore, it is urgent to explore the more therapeutic regimens for the treatment of prediabetes.

The present study, a meta-analysis was conducted on the efficacy and safety of target Chinese patent medicine in the treatment of patients with prediabetes. Here, the Chinese patent medicine, Jinlida granule, Jinqi Glucose-lowering tablet, Shenqi glucose-lowering granule, Tianqi glucose-lowering capsule, and Tangmaikang granule were included in the study. Their main components are shown in Table 1. Jinlida granule, an innovative Chinese patent medicine (CPM), is developed with the guidance of collateral disease theory, and based on the human experience. It plays a positive role in improving insulin resistance and regulating the disorder of glucose and lipid metabolism [4]. Several studies have shown that ginsenoside is the imperial ingredient in the prescription contained the ginsenoside analogues such as ginsenoside, ginsenoside Rb1, ginsenoside CK and polysaccharides, and those all are reported to have the effect of anti-hyperglycemia [5]. And ginsenoside, as a CPM active compound, is often used to treat type 2 diabetes mellitus with deficiency of both Qi and Yin. And Jinqi glucose-lowering tablet is a CPM developed by The Institute of Materia Medica, Chinese Academy of Medical Sciences for the treatment of diabetes. It is reported that Jinqi glucose-lowering tablet also exerts a certain effect on the pre-diabetic population, which can promote the blood glucose level of pre-diabetic patients, according to the formula Coptis pill in "Prepare for Emergencies, Qianjin Yaofang" and combined with modern pharmacology [6]. The therapeutic regime Jinqi glucose-lowering tablet combined with conventional lifestyle exhibits a good performance on reducing the blood glucose level of diabetic patients and improving insulin resistance. Its main active ingredients kaempferol, luteolin and β-carotene can promote the metabolism and secretion of insulin by regulating the absorption of calcium via mitochondria, significantly improve glucose and lipid metabolism, reduce insulin resistance, which are indicated that Jinqi glucose-lowering tablet has obvious effect on prediabetes [6].

Tianqi glucose-lowering capsule is a CPM compound preparation [7], It is shown that Tianqi glucose-lowering capsule has the functions of improving lipid, reducing blood glucose, improving blood rheology, insulin sensitivity and regulating amino acid metabolism disorder, suggesting a promising effect on the treatment of prediabetes [8]. Furthermore, Shenqi glucose-lowering granule can effectively treat type 2 diabetes, the previous study found that the main ingredients of ginseng saponin, astragalus root, etc, could reduce glucose production, ameliorate the impact in insulin resistance, regulating lipid, meanwhile, effectively reverse the low blood sugar, plasma insulin concentrations and glycated hemoglobin level [9]. As for Tangmaikang granule, modern pharmacological studies have uncovered that it has the functions of regulating glucose and lipid metabolism, scavenging oxygen free radicals, reducing the body's stress response, regulating vascular endothelin, and effectively reducing blood glucose [10]. Collectively, this study mainly explored the therapeutic effect of CPM on prediabetes through literature retrieval and a integrated meta analysis.

Table 1. Classification of proprietary Chinese medicines and their constituent components.

The name of the proprietary Chinese medicine	Composition
Jinlida granule	Ginseng, Huang Jing, Zhi Mu, Huang Huang, Mai Dong, Kudzu, Cang Shu, Peran, Bitter Ginseng, Epimedium Weed, He Shou Wu, Mountain Flesh, Salvia, Lychee Kernel, Ground Bone Skin, Poria Root, Huang Lian
Jinqi glucose-lowering tablet	Astragalus, Astragalus, Honeysuckle
Shenqi glucose-lowering granule	Ginseng, Schizandra, Astragalus, Yam, Rehmannia, Goji Berry
Tiaqi gucose-lowering capsule	Astragalus, smallpox pollen, female virgin, dendrobium, ginseng, ground bone skin, huanglian, dogwood, ink lotus, pentagram
Tangmaikang granule	Astragalus, Rehmannia, Red Peony, Salvia, Beef Knee, Mai Dong, Kudzu Root, Mulberry Leaf, Yellow Lian, Yellow Essence, Epimedium Weed

2. Methods

This meta-analysis was conducted step by step in accordance with the PRISMA statement and was registered using PROSPERO International Prospective Systems Evaluation with the registration number (CRD 42022341750).

2.1. Search strategy

We searched the clinical randomized controlled trials for CPM in the treatment of prediabetes patients in the past decade, including the databases of CNKI, WanFang, VIP, CBM, Web of Science, PubMed, and Embase, and the search time span was limited from January 2012 to June 2022. Chinese search terms included "prediabetes", "abnormal glucose tolerance", "impaired glucose tolerance", "abnormal glucose regulation", "abnormal glucose tolerance", "abnormal glucose tolerance", "Abnormal glucose tolerance", "Jinlida granule", "Jinqi glucose-lowering tablet", "Tianqi glucose-lowering capsule", "Shenqi glucose-lowering granule", "Tangmaikang granule", "randomized controlled trial", "randomization", etc. The English retrieval words are "prediabetes", "Prediabetic States", "Jinlida", "Jin Qi", "Shenqi", "Tianqi" and "RCT", etc, which all use subject words + free words for retrieval. Two independent researchers (reviewers) conducted a preliminary screening according to the title and abstract of the literature, and then read the full text of the collected articles to conduct a secondary screening. Then the article data was evaluated further according to the inclusion and exclusion criteria. Any differences between reviewers during the full text evaluation, they should reach an agreement through discussion and consensus. If no decision is made, the third reviewers will participate in the decision.

2.2. Inclusion and exclusion criteria

The expected inclusion criteria of the meta-analysis were as follows: 1, Randomized Controlled Trials (RCTs) in prediabetes patients. 2, All comorbidities such as heart disease, and liver, and kidney dysfunction were excluded. 3, The intervention measures were CPM such as Jinlida granule, Shen qi glucose-lowering granule, Jinqi glucose-lowering tablet, Tianqi glucose-lowering capsule, and Tangmaikang granule. The control group received routine life intervention, including diet, exercise, and mental health education.

Conversely, non-intervention, non-intervention drugs, observational studies, animal studies and non-randomized clinical trials were excluded.

2.3. Data extraction

After two researchers independently extracted all the data, they discussed and resolved the differences. If they could not be resolved, a third researcher would participate in and resolve the differences. We unified extraction contents, including: first author, publication year, number of patients participating in clinical trials, age, sex, intervention and timing, outcome indicators, etc. In the form of mean ± standard deviation, the blood glucose, blood lipids and insulin resistance index were evaluated as continuous variables. And dichotomous variables were used to evaluate diabetes conversion rate, prediabetes reversal rate and adverse reactions of diabetes mellitus [11].

2.4. Bias risk assessment

The quality of the included literatures was assessed using the Cochrane tool for bias risk assessment, and data was extracted independently by two researchers using preplanned tables. The evaluation items for each literature were as follows: whether there were deviations in the randomization process, deviations in the allocation hiding process, deviations from the expected outcome of the intervention, and whether the outcome indicators were complete, etc [12].

2.5. Data analysis

We aimed to explore whether the results of meta-analysis meet the expectations of our study through data analysis of the extracted literatures. The present meta-analysis mainly used Review Manager 5.4 (RevMan) software, the forest map was used for study the effect of CPM in the treatment of prediabetes, and quality evaluation map was used for highlight the overall quality of the research literatures. The I^2 index and *P*-value were performed to test heterogeneity between studies, and 95% *CI*, *OR*, and *MD* values was shown to test efficacy of studies. For the analysis of I^2 index results, we believe that an I^2 value less than 25% represented as low heterogeneity, a value between 26% and 50% represented as medium heterogeneity, and a deal greater than 50% represented as high heterogeneity. Cochran's *Q* statistic *P*-value below 0.05 was considered an indicator of significant heterogeneity [12]. For the results with excessive high heterogeneity, meta-analysis was re-conducted to find the causes of high heterogeneity by eliminating the literatures item by item. And then the original literatures were reviewed again to explore the differences between the literatures with the whole, and carefully considered its clinical effects further. After sensitivity analysis, we considered the reasons for the high heterogeneity of several outcome indicators, and conducted subgroup analysis according to the type of CPM that had the greatest possible influencing factor.

3. Results

3.1. The process of literature retrieval and the basic characteristics of the included studies

According to the retrieval strategy we formulated, 204 kinds of literatures were retrieved from CNKI, WanFang, VIP, CBM, PubMed, Web of Science, and Embase databases, which were exported to the literature management software NoteExpress (Version), and 116 kinds of literatures were obtained after eliminating the duplication. After careful perusal of the titles and abstracts, 24 articles not accordant with the inclusion criteria were screened out (including the literatures as non-subjects, non-interventions, reviews, conferences, and animal experiments). The full text of the above 24 literatures was read, and 16 literatures were finally still included after the screening of repeated publications, incomplete data, non-randomized controlled trials and non-conforming literatures. The whole process of literature retrieval was shown in Figure 1. And the retrieval process of PubMed database is shown in Figure 1.

A total of 16 clinical trial RCTs were retrieved, and the two independent researchers read the full text of the included literatures. Data such as first author, publication year, average age, sample size, intervention measures, intervention duration, and outcome indicators were extracted, respectively, and a table was designed and formed according to the extracted data. There were eight articles reported on the comparison of the efficacy between jinlida granule and conventional lifestyle

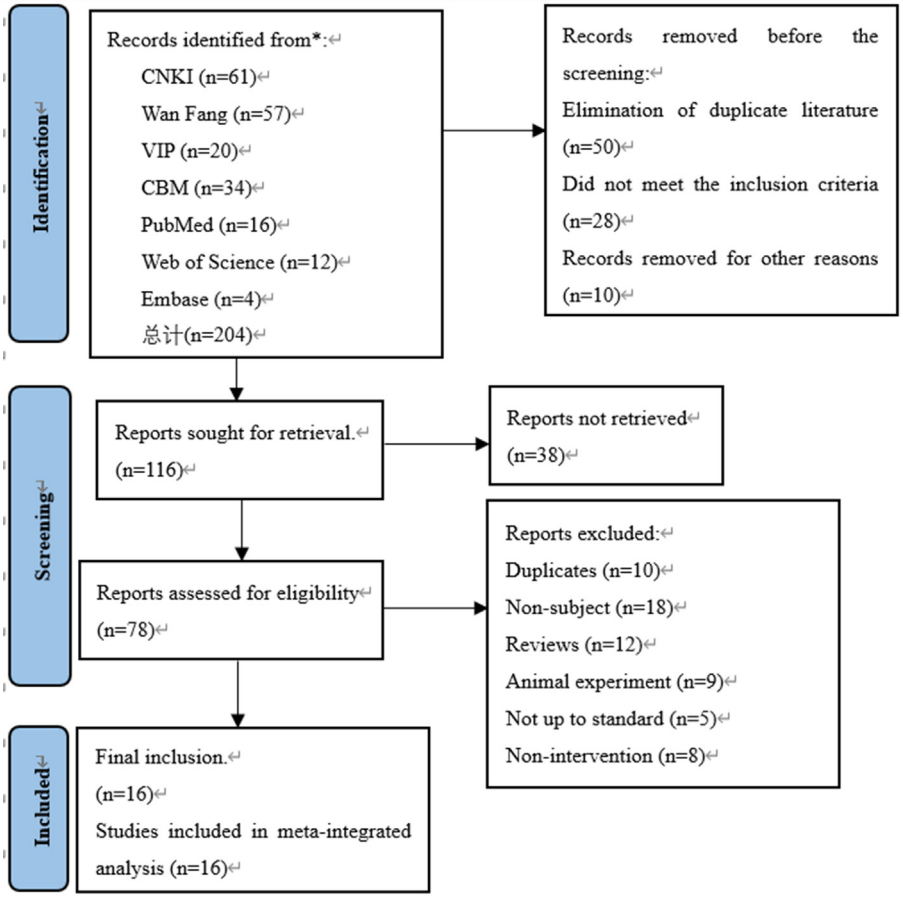

Figure 1. Document retrieval flow chart and the retrieval process of PubMed database.

intervention; Two articles were covered about the comparison between Jinqi glucose-lowering tablets and routine lifestyle intervention; And another two articles were described about the comparison between Shenqi Jiang tang granule and conventional lifestyle intervention; There were three articles were delivered about the comparison between Tianqi glucose-lowering capsules and routine lifestyle intervention; Only ones were shown about tangmaikang granule and traditional intervention of lifestyle, and the essential characteristics of the included study were shown in Table 2.

3.2. Risk of bias

Based on the extracted data, bias risk assessment was conducted for each study, and the results were shown in Figure 2. The quality of the included literatures were evaluated by random-sequence generation, assignment concealment, blind use of investigators and subjects, incomplete outcome measures, selective reporting results, and other biased results.

4. Meta-analysis

According to the inclusive literatures, we conducted an integrated meta-analysis of FBG, 2hPG, HbA1c, FINs, HOMA-IR, BMI, TG, TC, HDL-C, LDL-C, prediabetes reversal rate, and diabetes conversion rate, respectively.

4.1. Influence of Chinese patent medicine on FBG in prediabetic patients

A total of 14 studies, including 1022 patients, used FBG as an outcome measure in prediabetic patients. As shown in Figure 3a, after the heterogeneity test analysis of these 14 studies, the results showed that the heterogeneity among the included studies was very small ($P = 0.29$, $I^2 =$ 15%), so the fixed-effect model was adopted. The result showed that the effect of CPM in improving fasting blood glucose was significantly better than that of the control group [MD = -0.36, 95%CI = (−0.45,-0.26), $P <$ 0.00001], as shown in Figure 3a.

4.2. Influence of Chinese patent medicine on 2-hour postprandial blood glucose in prediabetic patients

A total of 949 participants were included in 13 studies, and the 2-hour postprandial blood glucose was used as an outcome measure in prediabetic patients. As shown in Figure 3b, the heterogeneity test exhibited a large heterogeneity among the included studies ($P < 0.0001$, $I^2 = 70\%$), thus, the random effect model was used for analysis. The results of the meta-analysis suggested that the combined effect level [MD = -0.71,95% CI=(−0.99,-0.42), $P < 0.00001$], indicating that the intervention effect of TCM was better than that of the conventional lifestyle intervention group. Due to the large heterogeneity, subgroup analysis was performed on the included literatures to find out the reasons for the heterogeneity among these studies. Through a comprehensive review and analysis of each article, we found that the types of TCM affected the clinical intervention effects. Therefore, it was divided into five subgroups of shenqi glucose-lowering granule, jinqi glucose-lowering tablet, jinlida granule, tianqi glucose-lowering capsule, and tangmaikang granule for analysis according to the various types of TCM. And the effect level was combined with the random effect model. The result showed that the heterogeneity of six studies in the jinlida granule subgroup was 50% ($P = 0.07$, $I^2 =$ 50%), and the difference of combined effect amount was statistically significant [MD = -0.62, 95%CI = (−1.01, -0.23), P = 0.002]. Two studies in the subgroup of jinqi glucose-lowering tablet demonstrated a minimal heterogeneity after merger ($P = 0.50$, $I^2 = 0\%$), and the difference in effect amount after merger was statistically significant [$MD =$

Table 2. The basic characteristics of the included study.

Study	Sample size	Mean age (years) E/C	Man/ Woman	Intervention	Intervention time	Outcome
Jing Cai 2017 [13]	60	46.4 ± 10.8/48.2 ± 9.8	30/30	Jinlida granules and routine lifestyle Interventions	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)
Xiujuan Ji 2018 [14]	79	57.1 ± 10.6/55.6 ± 11.4	42/37	Jinlida granules and routine lifestyle interventions	16 weeks	(1)(2)(3)(5)(7)(8)(10)
Wenjuan Liu 2015 [15]	93	49.7 ± 11.3/47.9 ± 11.8	49/44	Jinlida granules and routine lifestyle interventions	12 weeks	(1)(2)(3)(4)(5)(7)(8)(9)(10)(11)
Ya-Lin Shi 2016 [16]	61	47.1 ± 7.1/49.9 ± 7.2	32/29	Jinlida granules and routine lifestyle interventions	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)(11)
Enuo Qian 2018 [17]	72	53.86 ± 7.87/ 52.63 ± 8.92	43/29	Jinlida granules and routine lifestyle interventions	8 weeks	(1)(5)
Leilei Yu 2013 [18]	60		30/30	Jinlida granules and routine lifestyle interventions	12 weeks	(1)(2)(4)(5)
Jing Cai 2017 (2) [19]	120	46.4 ± 10.6/48.2 ± 9.7	60/60	Jinlida granules and routine lifestyle interventions	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)
Qingcheng Jiang 2015 [20]	62	59.1 ± 3.86/59.6 ± 3.9	30/32	Jinqi glucose-lowering tablets, diet combined with exercise therapy	12 weeks	(1)(2)(3)
Dongxue Yan 2012 [21]	60			control diet, exercise, improve lifestyle intervention, and give Shenqi glucose-lowering granules	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)
Shouguang Sun 2015 [22]	100	53.6 ± 9.6/50.8 ± 8.6	50/50	Jinqi glucose-lowering tablets, diet combined with exercise therapy		(1)(2)(3)(5)(7)(8)(10)
Fengmei Lian 2013 [23]	389		198/191	Tianqi glucose-lowering capsule		(1)(2)(3)(4)(5)(7)(8)(9)(10)(11)
Shaodong Hong 2013 [24]	60	44 ± 9.3/43 ± 10.1	29/31	control diet, exercise, improve lifestyle intervention, and give Tianqi glucose-lowering capsule	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)(11)
Wenzhen Tian 2012 [25]	60	50.6 ± 6.4/51.2 ± 6.2	30/30	control diet, exercise, improve lifestyle intervention, and give Shenqi glucose-lowering granule	24 weeks	(1)(5)
Yanrong Wang 2012 [26]	84			control diet, exercise, improve lifestyle intervention, and give Tianqi glucose-lowering capsule	3 years	(1)(2)(4)(5)
Lewei Tao 2012 [27]	55	55.1 ± 10.4/55.4 ± 7.7	27/28	control diet, exercise, improve lifestyle intervention, and give Tangmaikang granule	12 weeks	(1)(2)(3)(4)(5)(6)(7)(8)(9)(10)
Hua Zhao 2019 [28]	56			Jinlida granules androutine lifestyle interventions		(1)(2)(3)

(1)FPG(2)2hPG(3)HbA1c(4)FINs(5)HOMA-IR(6)BMI(7)TC(8)TG(9)HDL-C(10)LDL-C(11)Diabetic conversion rate.

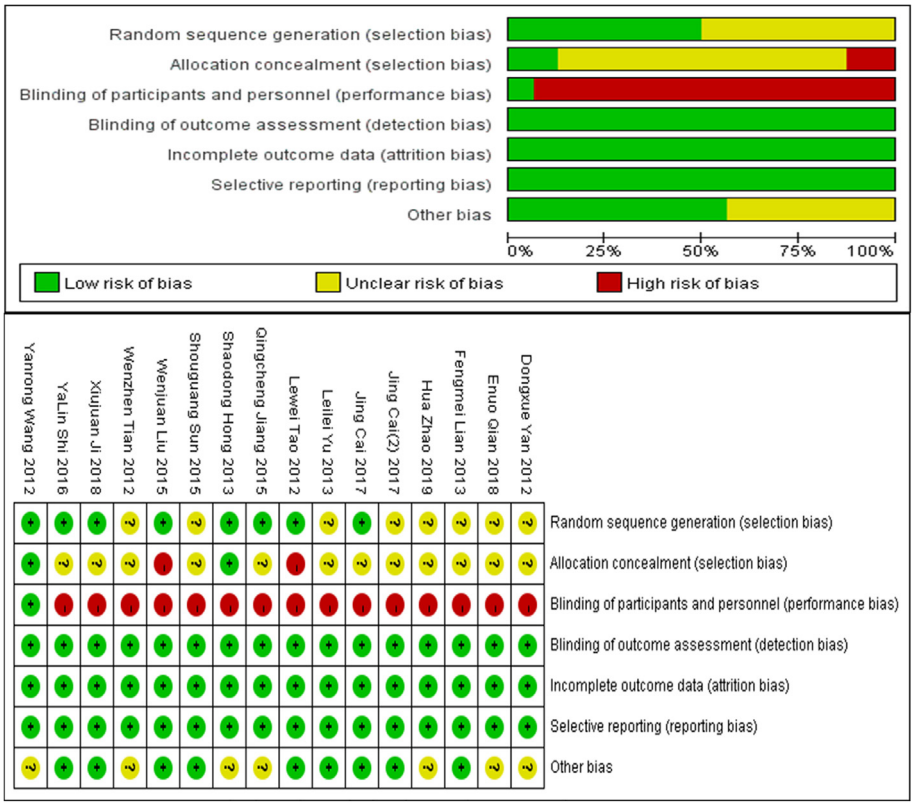

Figure 2. Risk of bias in the included literature.

-0.73, 95%*CI* = (−1.07,-0.39), $P < 0.0001$]. The subgroup heterogeneity of shenqi glucose-lowering granule was large ($P = 0.03$, $I^2 = 78\%$), and the difference in the combined effector of the two studies was statistically significant [*MD* = -0.97, 95%*CI* = (−1.57, -0.37), $P = 0.001$]. The subgroup heterogeneity of tianqi glucose-lowering capsule was 0% ($P = 0.61$, $I^2 = 0\%$), and the difference in the combined effector of the two studies was statistically significant [*MD* = -1.25, 95%*CI* = (−1.25, 95%*CI* = (−2.17, -0.33), $P = 0.008$]. A study in the tangmaikang granule subgroup indicated no statistically significant difference [*MD* = -0.00, 95% *CI* = (−0.78, 0.78), $P = 1.00$]. The analysis of the comprehensive research result showed that the subgroups of jinlida granules, jinqi glucose-lowering tablet, shenqi glucose-lowering granule and tianqi glucose-lowering capsule had a significant effective action on reducing fasting blood glucose in prediabetic patients, and had a certain guiding effect on clinical medication. The results were shown in Figure 3b.

4.3. Influence of Chinese patent medicine on glycated hemoglobin in prediabetic patients

A total of 651 subjects were included in 9 studies using HbA1c as an outcome measure in prediabetic patients. As shown in Figure 3c, the heterogeneity test showed large heterogeneity among the included studies ($P = 0.01$, $I^2 = 58\%$), so the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [*MD* = -0.33, 95%*CI* = (−0.48,-0.19), $P < 0.00001$], indicating that the intervention effect of CPM in the treatment of prediabetes patients was better than that of the conventional lifestyle intervention group. We analyzed the subgroups of CPM according to their different types, and the effect size was combined with the random effect model. Results showed that six studies in the jinlida granule subgroup had the least heterogeneity ($P = 0.46$, $I^2 = 0\%$), and the difference in the combined effect amount was significant [*MD* = -0.39, 95%*CI* = (−0.51, -0.28), $P <$ 0.00001]; Two studies in the subgroup of shenqi glucose-lowering granule were highly heterogeneous ($P = 0.10$, $I^2 = 64\%$), and there was no significant difference in the combined effect amount [*MD* = -0.16, 95%*CI* = (−0.44, 0.11), $P = 0.25$]; There was a statistically significant difference in the combined effect size of one study in jinqi glucose-lowering tablet subgroup [*MD* = -0.56, 95%*CI* = (−1.03, -0.09), $P =$ 0.02]. According to the comprehensive results analysis, jinlida granule and jinqi glucose-lowering tablet had more significant effects on reducing HbA1c content in patients with prediabetes when CPM intervention was carried out, as shown in Figure 3c.

4.4. Effects of Chinese patent medicine on FINs in prediabetic patients

A total of 412 participants were enrolled in 5 studies using FINs as an outcome measure in prediabetic patients. As shown in Figure 4a, the heterogeneity test showed great heterogeneity among the included studies ($P < 0.00001$, $I^2 = 93\%$), so the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [*MD* = -1.71, 95%*CI* = (−3.28,-0.14), $P = 0.03$], indicating the intervention effect of CPM in the treatment of prediabetes patients was better than that of conventional lifestyle intervention. Due to the large heterogeneity, we removed literature one by one to find possible factors that might cause excessive heterogeneity. Finally we found that the type of CPM was the cause of excessive heterogeneity in the results of FINs. Therefore, subgroup analysis was conducted according to the types of CPM, divided into jinlida granule, tianqi hypoglycemic capsule, and tangmaikang granule. The results showed that the heterogeneity of the three studies in the jinlida granule subgroup was 0% ($P = 0.93$, $I^2 = 0\%$), and the difference was statistically significant [*MD* = -1.76, 95%*CI* = (−2.50, -1.02), $P < 0.00001$]; One study in the subgroup of tianqi glucose-lowering capsule showed that the difference was statistically significant [*MD* = -3.82, 95%*CI* = (−5.15, -2.49), $P < 0.00001$]; One study in the subgroup of tangmaikang granules showed no significant difference [*MD* = 0.05, 95% *CI* = (−0.08, 0.18), $P = 0.44$]. The comprehensive results were analyzed, and the intervention of jinlida granules and tianqi glucose-lowering capsule had a significant effect on the FINs of patients with prediabetes, and the results were shown in Figure 4a.

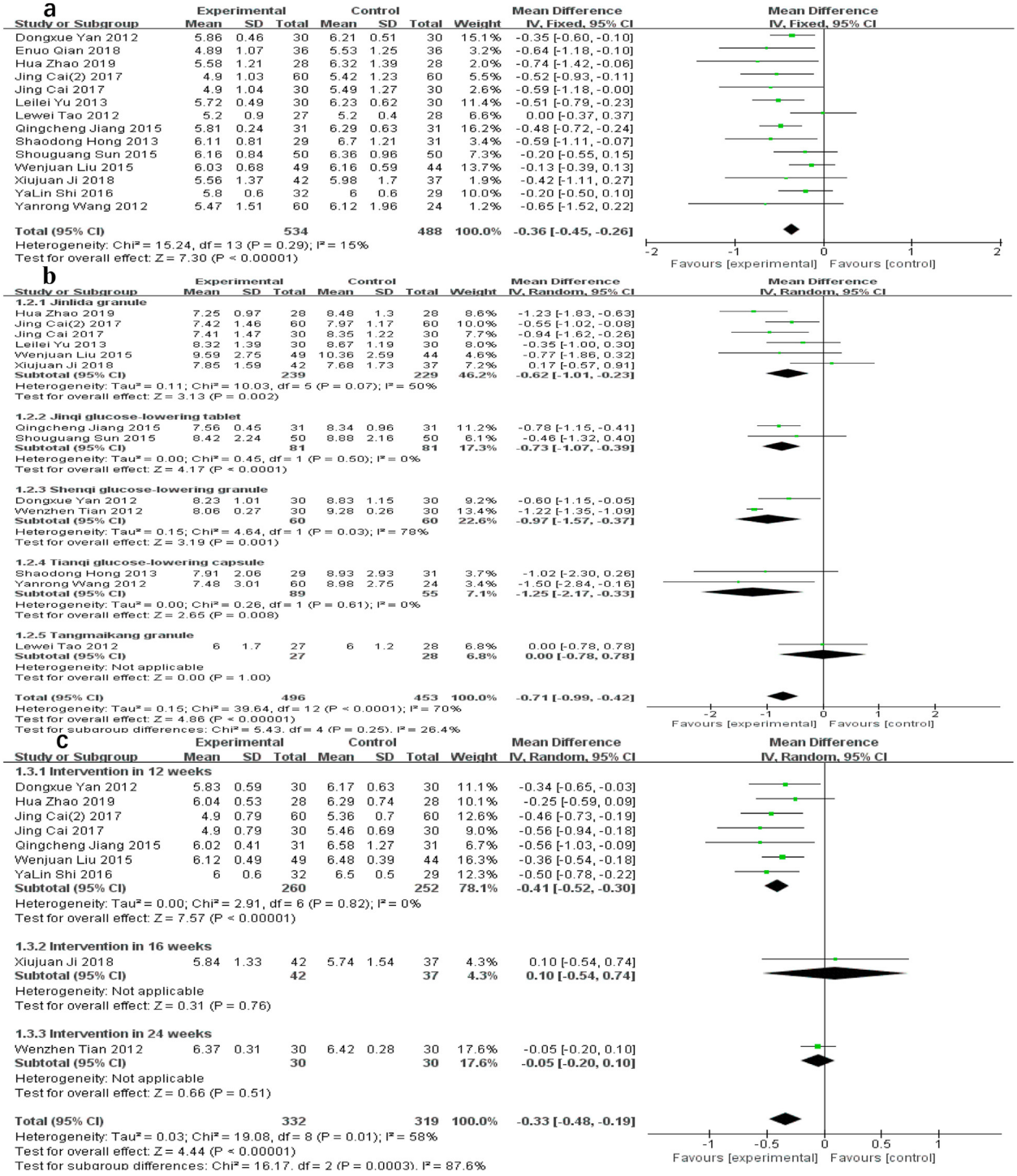

Figure 3. Forest plot summary of Chinese patent drugs' intervention in prediabetes glucose indicators. a: FBG forest map b: 2hPG forest map c: HbA1c forest map.

4.5. Influence of Chinese patent medicine on HOMA-IR in prediabetic patients

There were 8 studies in the included literatures, including 644 subjects, and HOMA-IR was used as an outcome measure in prediabetic patients. As shown in Figure 4b, the heterogeneity test revealed a large heterogeneity among the included studies ($P < 0.00001$, $I^2 = 91\%$), then the random effect model was used for analysis. Meta-analysis results indicated that the combined effect level [$MD = -0.20$, 95%$CI = (-0.29, -0.11)$, $P < 0.00001$] suggested that the intervention effect of CPM in prediabetes patients was better than that in the conventional lifestyle intervention group in terms of HOMA-IR outcome index. Due to the large heterogeneity, subgroup analysis was performed on the included literatures to explore the possible sources of heterogeneity among studies. Thorough review and analysis of each piece of literature, it was found that the clinical effects of various studies had significant differences among the types of CPM. Thus, four subgroups were divided according to the types of CPM (Respectively, jinlida granules, jinqi glucose-lowering tablets, tianqi glucose-lowering capsules and tangmaikang granule). And effect levels were combined using a random-effects model. The results exhibited that a less heterogeneity of five studies in the subgroup of jinlida granules ($P = 0.22$, $I^2 = 31\%$), and the clinical effect was

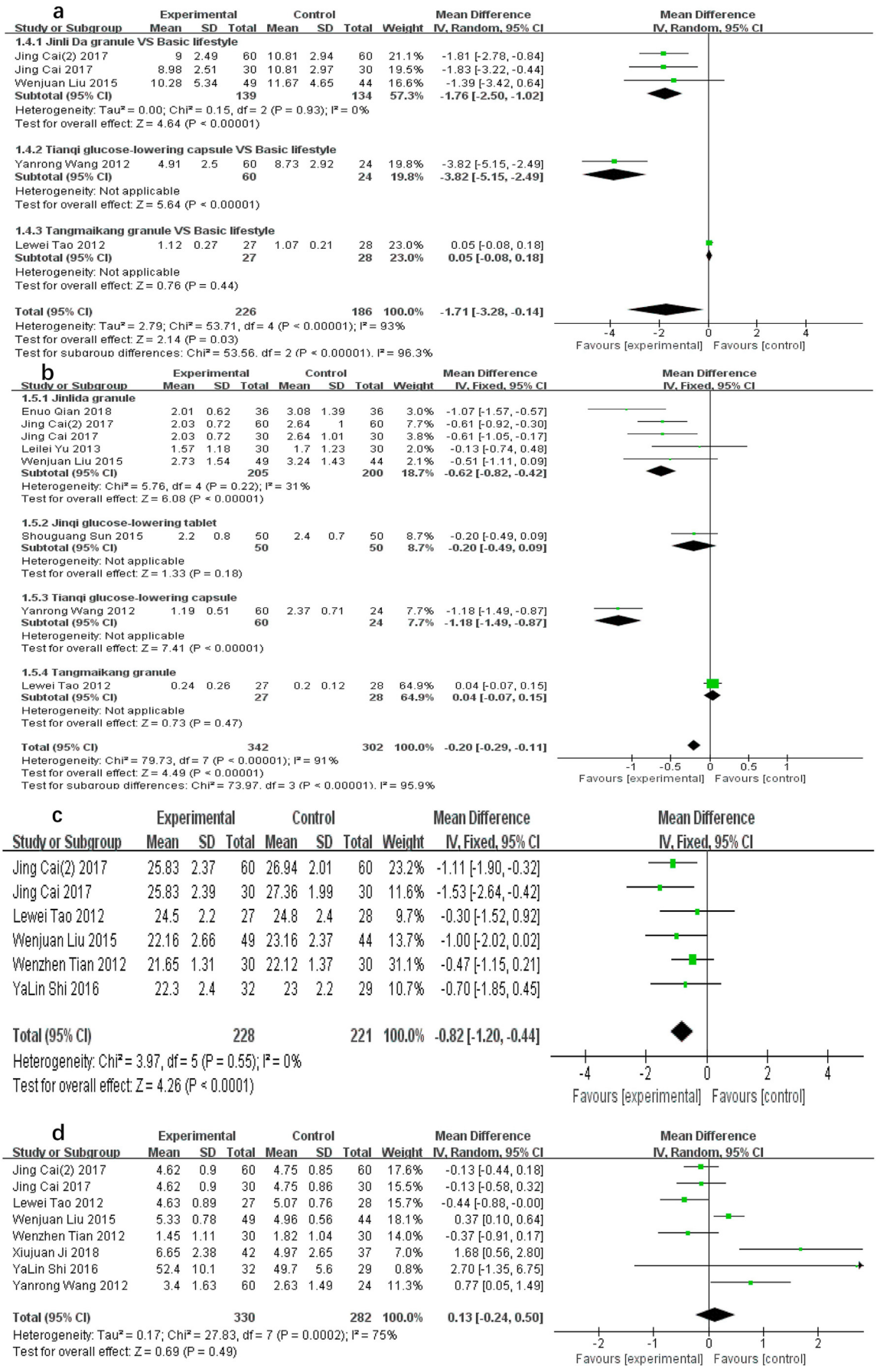

Figure 4. Forest map of Chinese patent medicine outcome indicators. a: FINs forest map b: HOMA-IR forest map c: BMI forest map d: TC forest map.

significant, and the difference was statistically significant [*MD* = -0.62, 95%*CI* = (−0.82, -0.42), *P* < 0.00001]; One study in the subgroup of jinqi glucose-lowering tablet showed no significant difference [*MD* = -0.20, 95%*CI* = (−0.49, 0.09), *P* = 0.18]; Another one study in the subgroup of tianqi glucose-lowering capsule showed a statistically significant difference [*MD* = -1.18, 95%*CI* = (−1.49, -0.87), *P* < 0.00001]; And there was one study in the subgroup of tangmaikang granule showing no significant difference [*MD* = 0.04, 95% *CI* = (−0.07, 0.15), *P* = 0.47]. The results indicated that the effect of CPM intervention on prediabetes patients via HOMA-IR was more conducive to the treatment of prediabetes than traditional lifestyle intervention. And the intervention effects among the CPM, jinlida granule and tianqi glucose-lowering capsule were more significant, as shown in Figure 4b.

4.6. Influence of Chinese patent medicine on BMI of prediabetic patients

A total of 449 subjects were included in 6 studies using BMI as an outcome measure in prediabetic patients. As shown in Figure 4c, the heterogeneity test showed that the heterogeneity between the included studies was 0%, so the fixed-effect model was used [*MD* = -0.82, 95%*CI* = (−1.20,-0.44), *P* < 0.0001]. The result suggested that CPM intervention had a more significant effect on the BMI of prediabetic patients than conventional lifestyle intervention, as shown in Figure 4c.

4.7. Influence of Chinese patent medicine on TC in prediabetic patients

612 subjects were included in 8 studies using TC in prediabetic patients as the outcome measure. As shown in Figure 4d, the heterogeneity test showed significant heterogeneity among the included studies (*P* = 0.0002, I^2 = 75%), therefore, the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [*MD* = 0.13, 95%*CI* = (−0.24,0.50), *P* = 0.49], indicating that there was no statistical significance in the intervention effect of CPM in the treatment of prediabetes patients compared with the conventional lifestyle intervention group. Due to the large heterogeneity, we conducted a sensitivity analysis of the literature step by step. Finally, we found that CPM had no significant effect on TC in prediabetic patients, as shown in Figure 4d.

4.8. Influence of Chinese patent medicine on TG in prediabetic patients

In the included literature, there were 7 studies were using TG of prediabetic patients as the outcome measurement index, involving 551

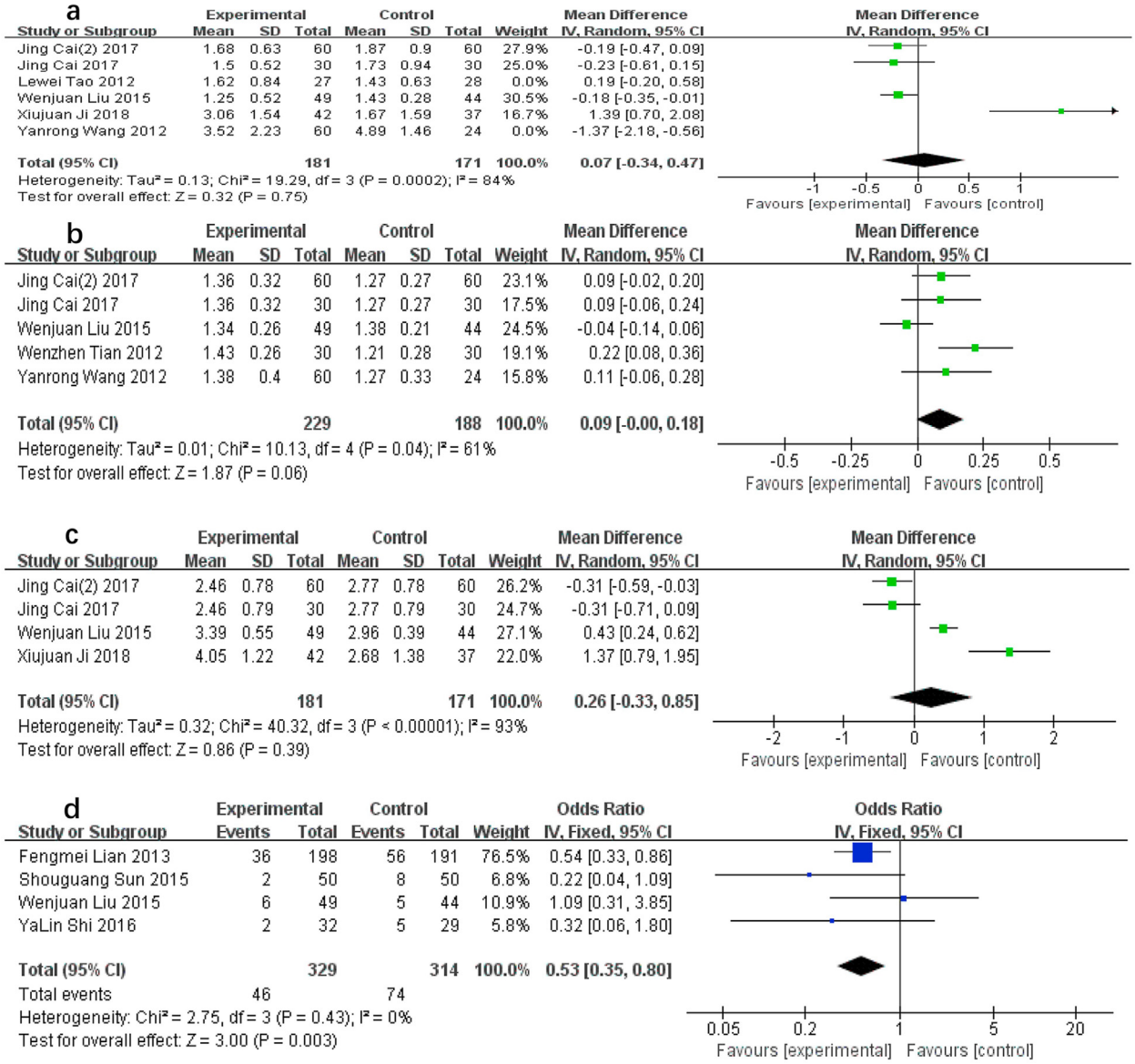

Figure 5. Forest map of Chinese patent medicine outcome indicators. a: TG forest map b: HDL-C forest map c: LDL-C forest map d: diabetic conversion rate.

patients. As shown in Figure 5a, the heterogeneity test showed large heterogeneity among the included studies ($P < 0.00001$, $I^2 = 87\%$), so the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [$MD = -0.01$, 95%$CI = (-0.31, 0.29)$, $P = 0.96$]. The result showed no statistical significance in the intervention effect of CPM in treating TG in prediabetic patients compared with the conventional lifestyle intervention group. Due to the large heterogeneity, we conducted a sensitivity analysis of the literature step by step, and finally found that CPM had no significant effect on TG in prediabetic patients, as shown in Figure 5a.

4.9. Influence of Chinese patent medicine on HDL-C in prediabetic patients

A total of 417 subjects were included in 5 studies using HDL-C as an outcome measure in prediabetic patients. As shown in Figure 5b, the heterogeneity test showed large heterogeneity among the included studies ($P = 0.04$, $I^2 = 61\%$), so the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [$MD = 0.09$, 95%$CI = (-0.00, 0.18)$, $P = 0.06$]. The result showed that there was no statistical significance in the intervention effect of CPM on TG in prediabetic patients compared with the conventional lifestyle intervention group. Due to the large heterogeneity, we conducted a sensitivity analysis of the literature step by step. Finally, we found that CPM had no significant effect on HDL-C in prediabetes patients, as shown in Figure 5b.

4.10. Effects of Chinese patent medicine on LDL-C in prediabetic patients

In the included literature, 4 studies used HDL-C as an outcome measure in prediabetes patients, involving 352 subjects. As shown in Figure 5c, the heterogeneity test showed large heterogeneity among the included studies ($P < 0.00001$, $I^2 = 93\%$), so the random effect model was used for analysis. Meta-analysis results suggested that the combined effect size [$MD = 0.26$, 95%$CI = (-0.33, 0.89)$, $P = 0.39$]. The result showed no statistical significance in the intervention effect of CPM on LDL-C in prediabetic patients compared with the conventional lifestyle intervention group. Due to the large heterogeneity, we conducted a sensitivity analysis of the literature step by step. Finally, we found that CPM had no significant effect on LDL-C in prediabetic patients, as shown in Figure 5c.

4.11. Influence of Chinese patent medicine on the diabetic conversion rate of prediabetes patients

Among the included literature, 7 studies using prediabetes conversion rate as an outcome measure involving 847 subjects. As shown in Figure 5d, the heterogeneity test showed that $I^2 = 0$ between the included studies, so a fixed-effect model was used for analysis. Meta-analysis results indicated that the combined effect size [$MD = 0.49$, 95%$CI = (0.34, 0.70)$, $P < 0.0001$], showed the intervention effect of CPM on the conversion rate of prediabetes patients was significantly better than that of the conventional lifestyle intervention group, as shown in Figure 5d.

4.12. Effect of proprietary Chinese medicine on the rate of reversal to normal in patients with prediabetes

Four studies included a total of 259 patients, and the prediabetes reversal rate was used as an outcome to measure the clinical efficacy of CPM. The results of meta-analysis showed that the heterogeneity was large ($P = 0.08$, $I^2 = 56\%$), and the difference was not statistically significant [$MD = 1.61$, 95%$CI = (0.73, 3.53)$, $P = 0.24$]. Comprehensive analysis showed that the intervention of CPM in the treatment of prediabetic patients had no obvious effect on the outcome index of prediabetes reversal to normal, and the results were shown in Figure 6.

5. Discussion

5.1. Analysis of the research significance

Diabetes is a global magnitude disease that seriously endangers public health. Its major complications of diabetes is regard as related large and small vessel diseases and a leading cause of disability and death. Taking corresponding measures to effectively treat the early stage of diabetes and preventing the development of its source could exert the crucial role in reversing prediabetes. Currently, the reports about the treatment of prediabetes with CPM are uncovered rarely. In the present study, the literatures of CPM treatment of prediabetes were searched from the main databases. In the part, the included CPM is a clinical early a certain basis, and for the treatment of diabetes or prediabetes have more significant effect of Chinese herbal medicine, the sifting of high quality research. Then the clinical effect of CPM intervention was comprehensively analyzed in order to provide a certain theoretical basis for the clinical treatment of prediabetes.

5.2. Efficacy analysis of outcome indicators

In present study, the diabetes conversion rate, prediabetes reversal rate, blood glucose, blood lipid and insulin content were mainly selected as the main outcome indicators. Diabetes conversion rate and the probability of prediabetes reversal to normal can reflect the clinical effect of CPM intervention well, which might help for clinical medication guidance. Guideline research was conducted in the early stage of this study, and as seen from the clinic expert consensus that the conversion rate of diabetes and the reversal rate of prediabetes are of great significance for the clinical treatment of prediabetes.

A total of 16 studies were included in the study. The outcomes of the included studies were integrated and analyzed via Meta, the indicators included diabetes conversion rate, pre-glucose reversal rate, fasting blood glucose, 2-hour postprandial blood glucose, HbA1c, fasting insulin, insulin resistance index, BMI, TC, TG, HDL-C, and LDL-C. The results showed that Chinese patent medicine intervention exerted a significant effect on the conversion rate of diabetes in the treatment of prediabetes, which can reduce the conversion rate of diabetes, obviously suggesting that the treatment of CPM was more instrumental in than conventional lifestyle intervention, which could inspiration for clinical practice. However, there was no significant effect on pre-glucose reversal rate, considering that there were few records of this outcome index in the relevant literatures. CPM intervention in the treatment of prediabetes

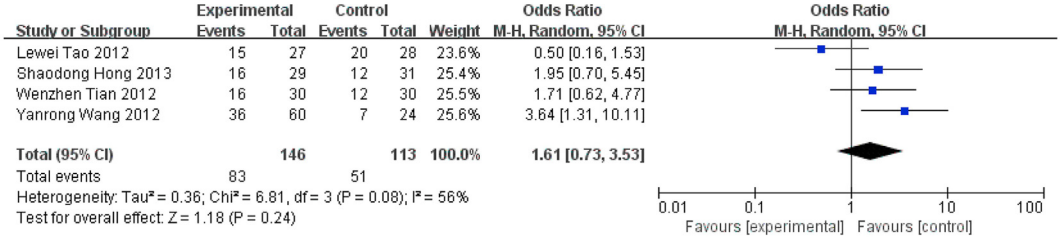

Figure 6. Forest map of prediabetes reversal rate.

played significant effects on fasting blood glucose, 2-hour postprandial blood glucose and glycosylated hemoglobin, and its clinical efficacy was significantly better than conventional lifestyle intervention. Blood glucose is a crucial clinical indicator of diabetes, and the intervention effect of CPM in our study also reflected from the side. According to FINs and HOMA-IR indexes, CPM intervention could improve prediabetic symptoms and reduce insulin resistance. The heterogeneity of TC, TG, HDL-C, and LDL-C was considerable, and the difference was not statistically significant. However, considering the few studies on blood lipid were included, several better and higher-quality studies on blood lipid indicators could be included in the future to explore the influence of CPM on blood lipid. All the above results indicated that compared with the traditional lifestyle intervention, the intervention of CPM has a more significant therapeutic effect on blood glucose and diabetes conversion rate in patients with prediabetes.

5.3. Analysis of the advantages and limitations of the study

In this study, the efficacy of CPM in the intervention of prediabetes analyzed in detail, and the expected conclusion is obtained, which provides a treatment strategy for diabetes and prediabetes in clinic. However, several inclusive studies were of relative low quality. In order to obtain more reliable results, more clinical trials with higher quality should be considered in the future, and further research can focus on how traditional Chinese medicines improve the related mechanisms of prediabetes.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This work was supported by Beijing-Tianjin-Hebei Project, Beijing Natural Science Foundation of J200019.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

Acknowledgements

The author would like to thank the team for their help and discussion.

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