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Role of acupuncture in the treatment of insulin resistance: A systematic review and meta-analysis

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ABSTRACT

Background: and purpose Acupuncture has gained increasing attention in the treatment of insulin resistance (IR). This study systematically reviews the efficacy of acupuncture on clinical IR outcomes.
Methods: Cochrane Central Register of Controlled Trials, Embase, Medline (via OVID), China National Knowledge Infrastructure (CNKI), Wan Fang and China Science and Technology Journal Database (VIP) were searched to collect randomized controlled trials (RCTs) of patients with IR treated by acupuncture. Meta-analysis was performed by RevMan 5.3.
Results: With acupuncture, the homeostasis model assessment of insulin resistance (homa-IR) significantly decreased (mean difference (MD) = -1.04, 95% confidence interval (CI) −1.37 to −0.71; P < 0.00001), as did fasting blood glucose (FBG) (MD = −0.56, 95% CI -0.88 to −0.25; P = 0.0005), 2 h postprandial blood glucose (2hPG) (MD = −0.91, 95% CI -1.62 to −0.20; P = 0.01), and fasting insulin (FINS) (MD = −3.23, 95% CI -4.14 to −2; P < 0.00001). Meanwhile, the insulin sensitivity index (ISI) (MD = 0.36, 95% CI 0.18 to 0.53; P < 0.0001) increased, and fewer adverse events occurred.
Conclusion: Acupuncture may improve homa-IR, ISI, FBG, 2hPG and FINS with fewer adverse events than other treatments, making it a viable treatment for IR.

1. Background

Insulin resistance (IR) is a general term which means that insulin can not apply its power in insulin-sensitive target tissues, such as skeletal muscle, adipose tissue, the liver or the pancreas, for insulin action in glucose metabolism [1]. This failure is a result of the inhibition of the insulin signalling pathway [2]. Insulin resistance is not only a symptom of metabolic syndrome, obesity, and hyperlipidemia, but also a premonition to diabetes, cardiovascular disease, and some cancers [3]. With changes in lifestyles and environmental conditions, more and more people are at risk of metabolic problems, causing considerable economic, emotional and physical hardship [4]. The management of IR is a challenge to clinicians due to the complex pathology and multiple chronic complications associated with it [5]. The usual IR treatments include lifestyle modifications, exercise, diet therapy, and medications such as metformin and thiazolidinediones [6]. Thiazolidinediones can decrease IR by enhancing insulin's action in peripheral target tissues [7]. However, there are some shortcomings of drug application, such as hypoglycaemia, costs, bulky drug combinations and the deterioration of drug efficacy over time.[8] Acupuncture, an effective alternative therapy, has been widely applied for millennia in China, and it's value in IR-related diseases has been acknowledged internationally [9]. Animal experiments have shown that acupuncture can down-regulate P13K p85 overexpression in skeletal muscle and IR 52 mRNA in liver tissue, thus promoting glucose uptake in skeletal muscle and liver tissue. As a result, IR status is improved [10,11]. Acupuncture has also

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significantly reduced blood glucose levels in Otsuka Long-Evans Tokushima Fatty (OLETF) rats [12]. An RCT has shown that acupuncture can interfere with the occurrence and progression of IR by reducing the inflammatory factors related to it [13]. According to theoretical research on Traditional Chinese Medicine (TCM), an acupuncturist's needle can stimulate and regulate “Qi and Blood” when inserted into the requisite acupoints [14]. Empirical evidence has shown that the stimulation and regulation of Qi and Blood can modulate the immune, nervous, and endocrine systems. In turn, this affects the vitality of bodily substances, such as insulin [15]. Numerous clinical and practical studies have demonstrated acupuncture's potential value to IR treatment [16–18]. An RCT has illustrated that the combined therapy of electro-acupuncture and rosiglitazone can suppress endogenous insulin secretion, which then improves insulin activity by decreasing homa-IR [19]. Systemic reviews have shown that both and integrated acupuncture and acupuncture alone can improve outcomes such as homa-IR, FBG, FINS, and ISI in patients diagnosed with diabetes or Type-2 diabetes mellitus (T2DM) with depression or obesity or polycystic ovarian syndrome (PCOS) respectively [20–22]. However, these reviews contained limited patient samples for certain diseases and excluded many IR-related diseases [20–22,25]. Additionally, there is an ongoing debate on the effects of legitimate acupuncture versus those of sham acupuncture [23,24]. A systematic review has suggested that the acupuncture effect may be overestimated, given that some RCTs do not consider the placebo effect [25]. Thus, sham acupuncture control groups must be isolated to analyse this overestimation. Furthermore, few researchers have pointed out the unique effects of acupuncture on IR, with more regarding it as an endpoint to assess the role of acupuncture in related diseases [20–22,25]. Therefore, this systematic review and meta-analysis evaluates the effects of both acupuncture alone and acupuncture in combination with other treatments on IR. It also provides additional evidence that acupuncture reduces IR.

2. Methods

2.1. Literature search

The Cochrane Central Register of Controlled Trials, Embase, Medline (via OVID), China National Knowledge Infrastructure (CNKI), Wan Fang and China Science and Technology Journal Database (VIP) were searched up to October 2018. The search strategy for Embase was as follows: (“insulin resistance”/exp OR “glucose intolerance”/exp OR “diabetes mellitus”/exp OR “metabolic syndrome” OR “prediabetic state”/exp) AND (“acupuncture”/exp OR “acupuncture therapy”/exp OR “Medicine, Chinese Traditional”/exp) AND (“crossover-procedure”/exp OR “double-blind procedure”/exp OR “randomized controlled tria”/exp). Subject headings (Emtree) and free-terms were used in the primary search. We limited our search to human studies. The detailed search strategy is presented in Appendix 1.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

(a) All published RCTs of acupuncture for IR were included. (b) Participants diagnosed with IR-related diseases such as all types of diabetes mellitus (DM), obesity, PCOS, hyperlipidemia, metabolic syndrome, cardiovascular disease, specific cancers and other diseases leading to IR were included. The age, sex, and ethnicity of participants was not limited. (c) Participants in the experimental groups received acupuncture with or without the same interventions performed in the control group. (d) Participants in the control groups received either the oral Western medication, as recommended by the latest Health and Care Excellence (NICE) guidelines, lifestyle modifications, or sham acupuncture. (e) Primary outcomes included a homeostasis model assessment of homa-IR, as well as ISI. Secondary outcomes included FBG, 2hPG, FINS and adverse events.

2.2.2. Exclusion criteria

(a) Non-randomized trials, quasi-experimental studies, animal experiments, reviews, case reports and conference abstracts were excluded. In instances where there were duplicate studies, we chose the most recent. (b) Trials in which one acupuncture method had been compared with another or with integrated methods, in which experimental groups received other types of acupuncture, such as acupressure, cutaneous needle or transcutaneous electrical stimulation, were excluded. Studies in which control groups had concurrently received other TCM therapies of uncertain efficacy, such as medicinal herbs, were excluded as well. (c) Trials for which outcomes were not available, not extractable, or not documented, or for which the authors did not respond to our inquiries, were excluded as well.

2.3. Study selection and data extraction

All articles retrieved from the databases were entered into Note Express. Duplicates were identified and eliminated. Then, two reviewers independently scanned the titles and abstracts of the database records. Full texts of potentially eligible studies were analysed further. A data extraction table was constructed which included the topic, author, year of publication, number of participants, samples, interventions, clinical outcomes, adverse events and assessments of risk of bias. These data were extracted and validated by two reviewers independently. Differences were resolved by discussing with another reviewer.

2.4. Risk of bias assessment

The risk of bias of the included studies was adopted by two reviewers independently using the Cochrane tool for quality assessment [26]. Each trial was scored as either high, low, or unclear risk for seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. If more than three of the items were scored low-risk, the overall quality of the trial was classified as low-risk. If more than three of the items were identified as high- or unclear-risk, the overall quality was classified as high-risk. When there were disagreements, a third reviewer was consulted.

2.5. Statistical analysis

The meta-analysis was conducted by Reviewer Manager, version 5.3 (Cochrane Collaboration, Oxford, UK) [27]. With a 95% confidence interval (CI), the mean difference (MD) was calculated for the continuous variables, and the risk ratio (RR) was calculated for the dichotomous variables. Data heterogeneity was assessed by a Chi-square and I^2 test. A fixed-effects model was conducted to analyse the pooled effects when heterogeneity was not significant ($P \geq 0.10$ or $I^2 \leq 50\%$); a random-effects model was used when heterogeneity was statistically significant ($I^2 > 50\%$ or $P < 0.10$) [28]. Subgroup analyses were conducted in order to explore the reasons for heterogeneity, as well as to investigate the effects of different acupuncture approaches and different forms of acupuncture for diseases related to IR. Forest plots were generated to illustrate the relative changes in treatment effects.

3. Results

3.1. Study selection

The literature selection process is shown in the flow diagram (Fig. 1). Our initial search identified 1144 reports in English, and 9116 reports from Chinese databases. After scanning the titles and abstracts, 283 articles were left and the full texts were downloaded for further assessment. After assessing the full texts, 41 articles were excluded because they were deemed not to be true RCTs; 27 were excluded

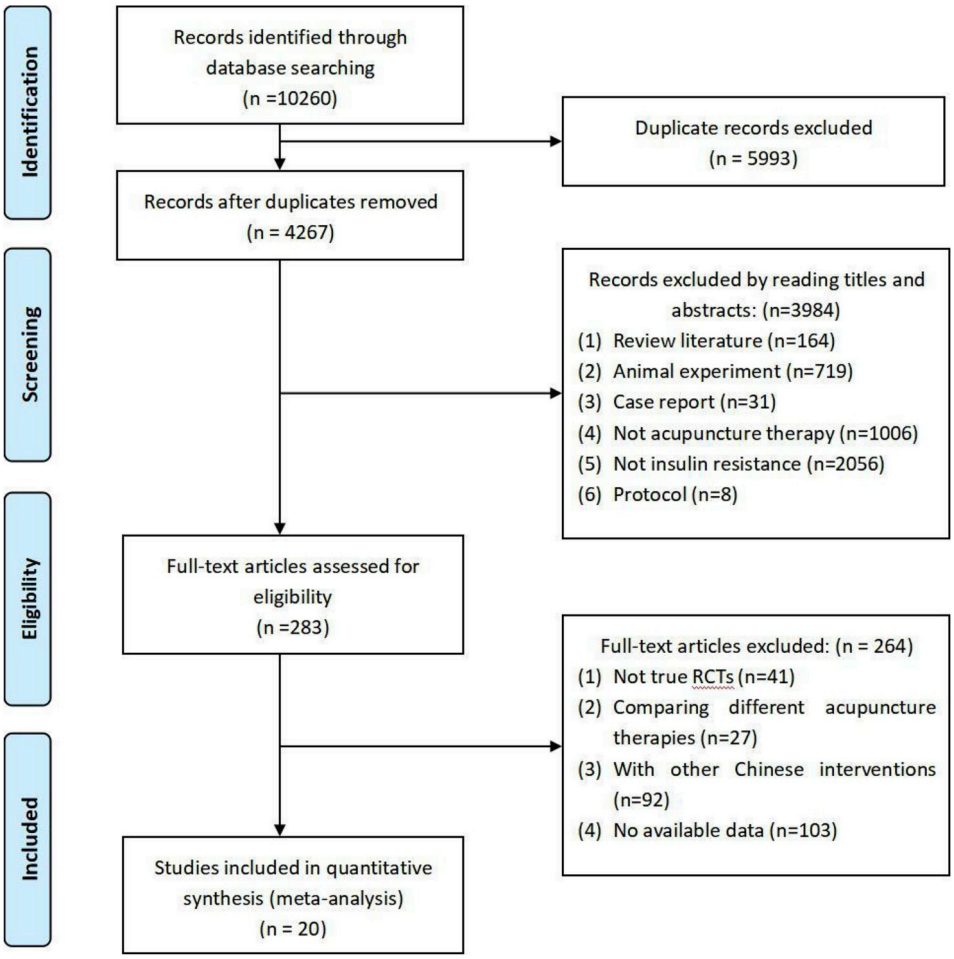

Fig. 1. Literature screening process and results.

because they had compared alternative acupuncture therapies; and 92 were excluded because their experimental groups had combined acupuncture with other TCM interventions; 103 were excluded because the complete texts were not available. Ultimately, 20 studies covering 1639 patients were included in this review.

3.2. Description of studies

Table 1 summarizes the characteristics of the included RCTs. All of the studies were conducted in China, with one exception which was done in Egypt. 4 studies (20%)[31−32 35 47] were published in English databases, and the other 16 (80%) [29,30,33,34,36–46,48] were published in Chinese databases.

3.2.1. Participants

In the 20 included studies, participants had been diagnosed with IR-related diseases, including 8 (40%) patients with T2DM [29,30,33,34,36–46,48], 8 (40%) with PCOS [31,34,36,37,39,43,45,47], 2 (10%) with metabolic syndrome [35,38], 1(5%) with essential hypertension [33] and 1 (5%) with abdominal obesity [39].

3.2.2. Interventions

3 studies (15%) [31,36,39] evaluated the effects of acupuncture compared to sham acupuncture. 12 studies (60%) [29,30,32,35,37,40–45,48] evaluated the effects of acupuncture combined with Western medical treatments compared to Western treatments alone. 5 studies (25%) [33,34,38,46,47] evaluated the effects of acupuncture alone compared to those of Western medical treatments such as glyburide, metformin, enalapril maleate, or lifestyle modifications.

3.2.3. Outcomes

18 studies (90%) [29–32,34–37,39–48] reported homa-IR, 3 (15%) [33,38,46] reported ISI, 17 (85%) [17–29,29,30,30,31,31,32,32,40–48] reported FBG, 8 (40%) [29,30,33–35,40,41,43,44,47] reported 2hPG, 14 (70%) [32–37,41–48] reported FINS, and 5 (25%) [34,36,37,41,42] reported adverse effects.

3.3. Assessment of risk of bias

The assessment of risk of bias is summarized in Fig. 2. All studies were described as “randomized” and 16 [31–33,35–38,40–48] described appropriate methods for sequence generation. The remaining RCTs did not report specific random methods. 3 studies [31,32,47] conducted allocation concealment. As for the blinding of participants and personnel, 4 studies [29,31,32,36] were ranked as “low risk”, and the others were ranked as “unclear risk”. The outcome assessments of 2 of the studies [31,32] were blinded. 4 studies [35,40,42,47] reported dropouts, but did not state the reasons. Study protocols could be found for 2 of the studies [32,48]. Furthermore, studies with other biases (e.g., drug company sponsorship) were ranked as having “unclear risk” due to the lack of available evidence. In total, 3 studies [31,32,47] (15%) were assessed as “low risk”, while the others [29,30,33–46,48] (85%) were assessed as “high risk”.

3.4. Meta-analysis of outcomes

3.4.1. Effects of acupuncture on homa-IR

According to the meta-analysis, the results of the primary outcome measure, homa-IR, are shown in Figs. 3–5, respectively. 18 studies

Table 1
Characteristics of included studies.

Study ID	P	SS	Intervention		Outcomes	Mean age		Sex				DOI
	Diseases	(EG/CG)	EG	CG		EG	CG	EG		CG		
								M	F	M	F	
Chen 2013 [13], China	T2DM coupled with obesity	29/27	MO and A	MO	①③④	54 ± 6	56 ± 6	12	20	10	21	3 m
Ding 2013 [14], China	T2DM	102/100	HT and A	HT	①③④	52 ± 8.2	53 ± 9.4	48	54	47	53	63 d
Fayiz 2018 [15], Egypt	PCOS	11/10	A	SA	①	20 ± 1.2	20 ± 1.2	0	13	0	12	12 w
Firouzjaei 2016 [16], China	T2DM with obesity	19/20	MO and A	MO	①③⑤	42.2	40.5	8	11	8	12	3 w
Guo 2009′ [17], China	essential	30/30	A	EMO	②④⑤	32–64	29–65	16	14	17	13	4 w
Lai 2012′ [18], China	PCOS	60/60	A	MO	①③④⑤⑥	26.72 ± 2.65	26.46 ± 2.72	0	60	0	60	4 m
Li,Q 2014 [19], China	metabolism syndrome	37/39	G&FO and A	G&FO	①③④⑤	46.1 ± 6.6	45.9 ± 6.3	18	19	19	20	40 d
Li 2014 [20], China	obesity-type PCOS	53/51	MO and A	MO and SA	①③⑤⑥	26.2 ± 2.1	25.2 ± 1.8	0	49	0	51	6 m
Liang 2015 [21], China	PCOS	30/30	CO and A	CO	①③⑤⑥	28.64 ± 3.07	27.53 ± 3.18	0	30	0	30	4 consecutive menstrual cycles
Ma 2012 [22], China	metabolism syndrome	34/37	A	MO	②	50.24 ± 10.21	49.03 ± 9.87	28	9	24	10	12 w
Peng 2017 [23], China	PCOS	50/50	A	SA	①	28.58 ± 3.82	28.68 ± 3.33	0	50	0	50	3 m
Wang 2016 [24], China	T2DM	43/43	RO and A	RO	①③④	46.8 ± 7. 0	46.5 ± 7.5	25	18	26	17	12 w
Yang 2015 [25], China	T2DM with obesity	30/30	HT and A	HT	①④⑤⑥	47 ± 8	49 ± 13	15	15	10	20	3 w
Yang 2017 [26], China	abdominal obesity	28/26	BT and A	BT	①③⑤⑥	58.6 ± 6.1	58.8 ± 6.1	9	21	8	22	12 w
Yin 2016 [27], China	PCOS	30/30	MO and A	MO	①③④⑤	27.54 ± 2. 03	27.56 ± 2. 01	0	30	0	30	3 m
Zhang 2014 [28], China	elderly T2DM	50/50	HT and A	HT	①③④⑤	69.85 ± 10.57	71.39 ± 12.14	22	28	24	26	4 w
Zhang 2017 [29], China	obesity-type PCOS	64/64	MO and A	MO	①③⑤	28.3 ± 4.2	27.9 ± 4.3	0	64	0	64	90 d
Zhao 2011 [30], China	T2DM	40/40	A	GO	①②③⑤	50.25 ± 7.07	51.40 ± 8.30	15	25	23	17	12 w
Zheng 2013 [31], China	obesity-type PCOS	43/43	A	MO	①③④⑤⑥	26.5 ± 3.0	24.9 ± 4.9	0	43	0	43	6 m
Zhou 2013 [32], China	T2DM with new-onset obesity	40/36	LM and A	LM	①③⑤	40.6 ± 9.7	42.6 ± 9.4	17	23	15	21	3 m

P: participants; SS: sample size; A: acupuncture; SA: sham acupuncture; LM: lifestyle modification; MO: metformin hydrochloride orally; GO: glyburide orally; RO: rosuvastatin orally; CO: clomiphene orally; G&FO: glucotrol XL and felodipine orally; EMO: enalapril maleate orally; HT: hypoglycaemic therapy; BT: basic treatment; E: experimental groups; C: control groups; M: male; F: female; DOI: duration of intervention; m: months; d: days; w:weeks. ① homa-IR; ② ISI; ③ FBG; ④ 2hPG; ⑤ FINS; ⑥ adverse events.

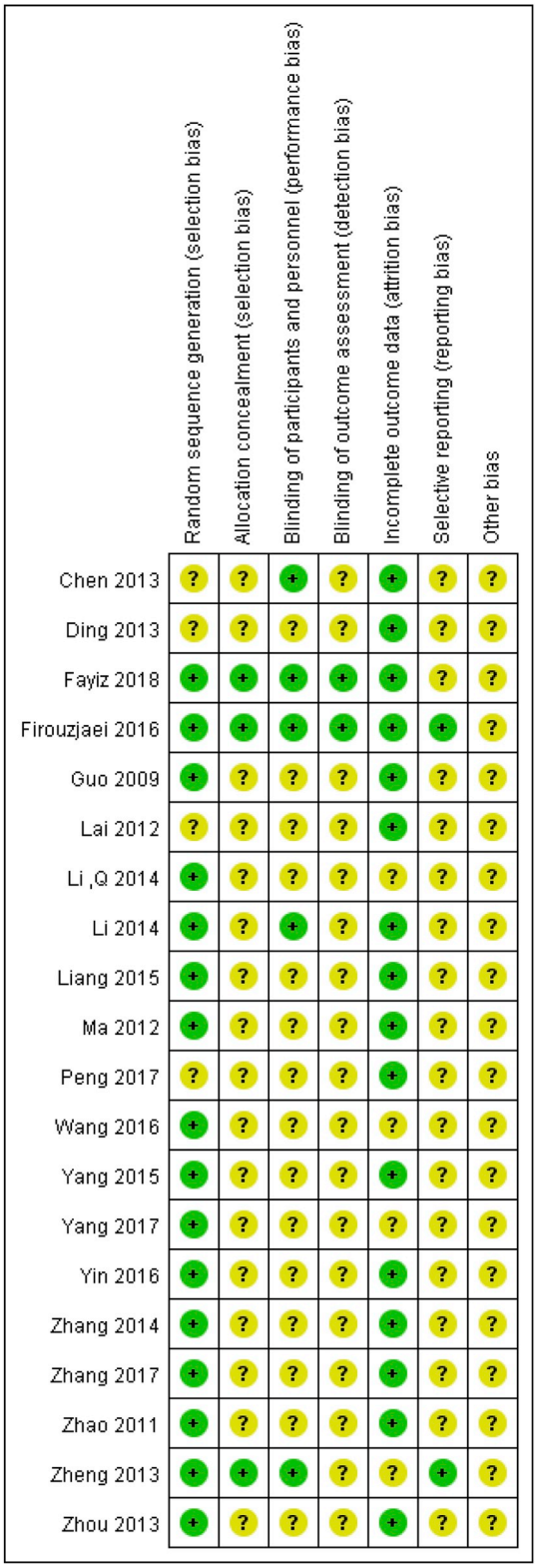

Fig. 2. Risk of bias assessment.

(90%) [29–32,34–37,39–48] with 1508 patients reported homa-IR. Significant heterogeneity was discovered among the RCTs (I^2 = 95%; $P < 0.00001$). Using a random-effects model, the results indicated that acupuncture treatment was of significant benefit in decreasing homa-IR (MD = −1.04, 95% CI -1.37 to −0.71; $P < 0.00001$). Due to the high heterogeneity among the RCTs, subgroup analyses were conducted with consideration of RCT quality (Fig. 3), different types of interventions (Fig. 4), and diseases (Fig. 5). In RCTs with high risk, the experimental group was significantly more effective than the control group in decreasing homa-IR (MD = −1.12, 95% CI: −1.47 to −0.76; $P < 0.00001$; I^2 = 96%), while no difference was found for those with low risk (MD = −0.62, 95% CI: −1.58 to 0.35; P = 0.21; I^2 = 86%). Pooled data revealed that acupuncture alone exerted better effects in decreasing homa-IR levels than sham acupuncture (MD = −0.41, 95% CI: −0.73 to −0.09; P = 0.01; I^2 = 0%). Furthermore, the effects of acupuncture with Western medicine were superior to Western medicine monotherapy (MD = −1.21, 95% CI: −1.62 to −0.79; $P < 0.00001$; I^2 = 96%). However, there was no significant difference in decreasing homa-IR levels between acupuncture alone and Western medicine monotherapy [34,46,47] (MD = −1.36, 95% CI: −3.01 to 0.29; P = 0.11; I^2 = 94%). Pooled analysis also showed that patients with T2DM receiving acupuncture with or without Western medicine experienced more reduction in homa-IR than those adopting other therapies (MD = −1.63, 95% CI: −2.38 to −0.87; $P < 0.0001$; I^2 = 98%), and those with PCOS (MD = −0.56, 95% CI: −0.89 to −0.23; P = 0.0008; I^2 = 91%). However, acupuncture did not significantly reduce homa-IR in patients with other diseases (MD = −2.38, 95% CI: −5.31 to 0.54; P = 0.11; I^2 = 83%).

3.4.2. Effects of acupuncture on ISI

The results of the another outcome, ISI, are shown in Fig. 6. Data from 3 studies [33,46,48], all with high risk, showed that ISI increased significantly in the experimental group, compared to that of the control group (MD = 0.36, 95% CI 0.18 to 0.53; $P < 0.0001$). However, once again, heterogeneity was high (I^2 = 84%; P = 0.002).

3.4.3 Effects of acupuncture on FBG and 2hPG. Figs. 7 and 8 show that acupuncture therapies had an advantage in decreasing FBG (MD = −0.56, 95% CI -0.88 to −0.25; P = 0.0005) with statistical heterogeneity (I^2 = 96%; $P < 0.00001$), and 2hPG (MD = −0.91, 95% CI -1.62 to −0.20; P = 0.01), with equal heterogeneity (I^2 = 96%; $P < 0.00001$). To explore the sources of the high heterogeneity, subgroup analyses of the quality scores were conducted on FBG (Fig. 9) and 2hPG (Fig. 10), respectively. Pooled analysis of high-risk RCTs indicated that acupuncture with or without Western medicine decreased FBG (MD = −0.50, 95% CI: −0.81 to −0.18; P = 0.0008) and 2hPG (MD = −1.03, 95% CI: −1.84 to −0.22; P = 0.01) more than did Western medicine monotherapy or Western medicine; for sham acupuncture, the FGB heterogeneity (I [2] = 91%; $P < 0.00001$), 2hPG (I [2] = 97%; $P < 0.00001$), did not significantly decrease. Nevertheless, according to the pooled analysis of low-risk RCTs, FBG did not significantly increase in the experimental group, compared to that of the control group (MD = −0.30, 95% CI: −0.67 to −0.06; P = 0.10). However, the heterogeneity was lower (I^2 = 26%; $P < 0.00001$).

3.4.3. Effects of acupuncture on FINS

As shown in Fig. 11, a significant reduction in FINS was observed in the experimental group (MD = −3.23, 95% CI -4.14 to −2.31; $P < 0.00001$), with high heterogeneity (I^2 = 90%; $P < 0.00001$). Subgroup analysis was conducted on the RCT quality scores (Fig. 12). Though the pooled analysis of the high-risk subgroup still showed that acupuncture treatment was of significant benefit in decreasing FINS (MD = −3.53, 95% CI: −4.62 to −2.45; $P < 0.00001$), the FINS heterogeneity decreased slightly (I [2] = 89%; $P < 0.00001$). Additionally, the pooled analysis of low-risk RCTs manifested that FINS did not significantly increase in the experimental group, compared to that of the control group (MD = −1.89, 95% CI: −5.60 to 1.82; P = 0.32), with no significant change in heterogeneity (I [2] = 94%; $P < 0.0001$).

3.4.4. Effects of acupuncture on adverse events

Table 2 displays reported adverse events. 6 studies [34,36,37,41,42,47] mentioned adverse effects. 1 [34] reported 20 cases of nausea, emesis, diarrhoea and loss of appetite in the control

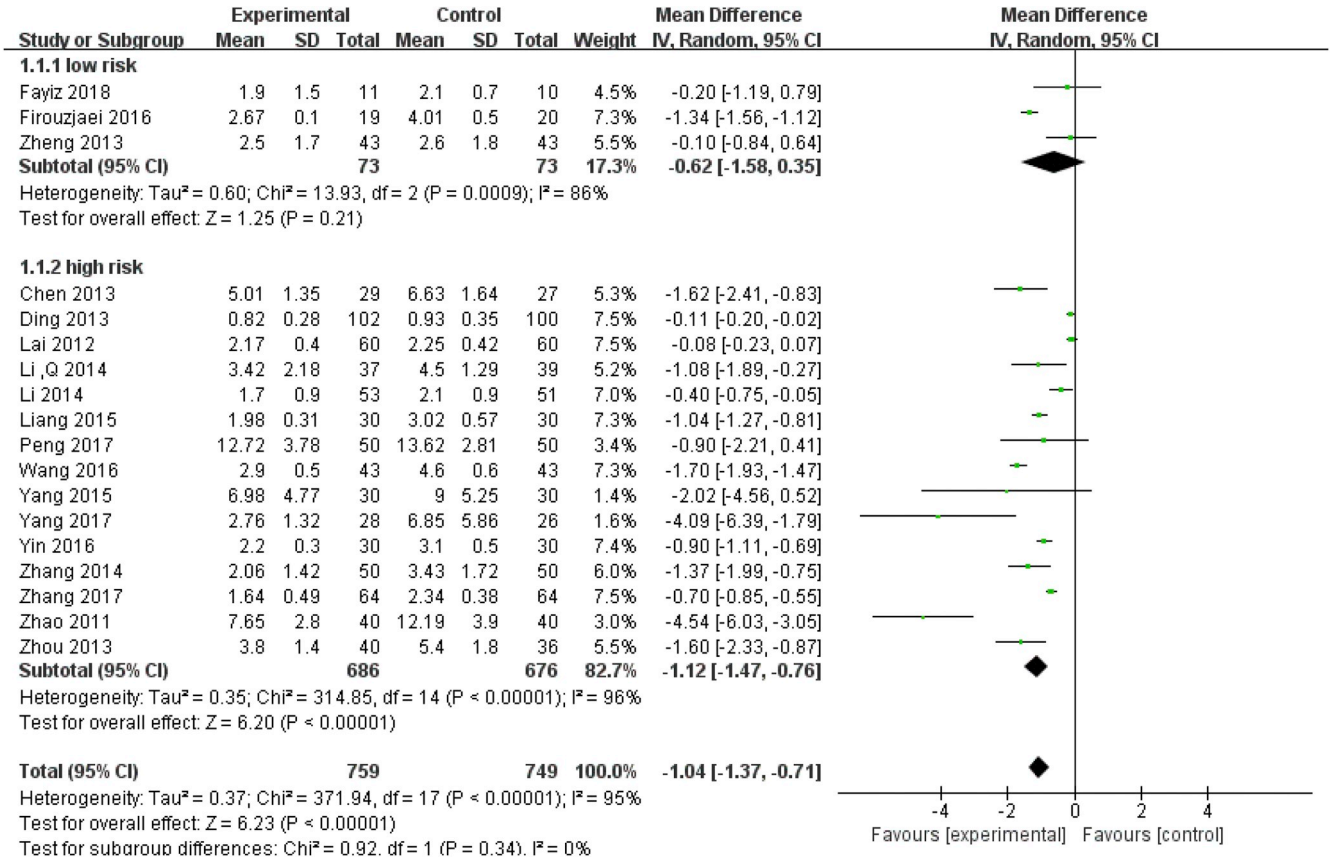

Fig. 3. Forest plot of homa-IR changes between the experimental and control groups, respectively, for low-risk and high-risk RCTs.

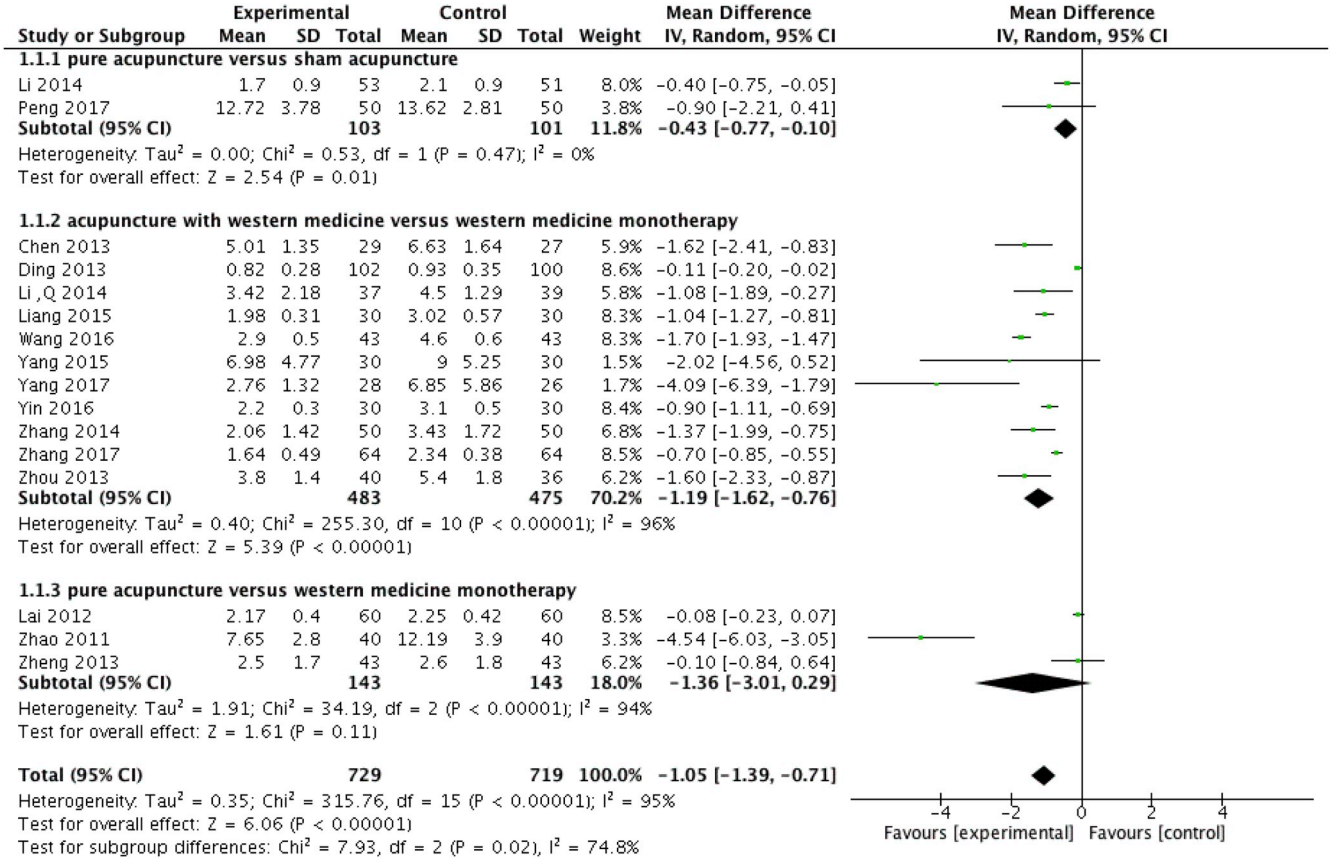

Fig. 4. Forest plot of homa-IR changes between the experimental and control groups, respectively, for different interventions.

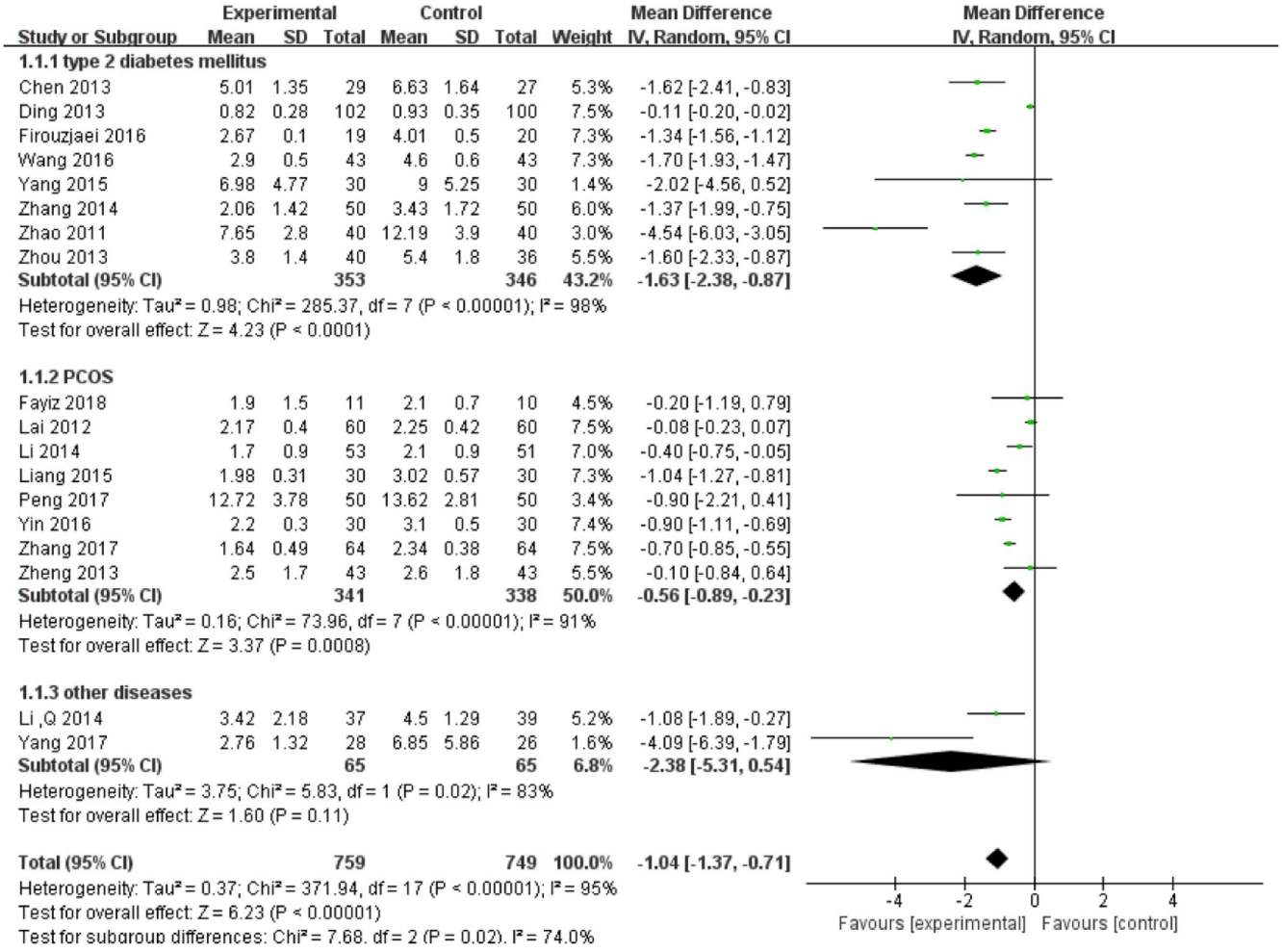

Fig. 5. Forest plot of homa-IR changes between the experimental and control groups, respectively, for different diseases.

group, while the experimental group had no adverse events. 1[36] reported 22 cases of nausea, emesis, diarrhoea and loss of appetite in the control group and 18 cases in the experimental group. 1[37] reported no obvious abnormalities in the blood, urine or stool on routine examination with no allergic reaction or other adverse events. 1[41] reported 30 cases of mild pain due to the insertion of the needle in the experimental group and no other adverse events in either groups. 1[42] reported 2 cases of subcutaneous haematoma due to needling in the experimental group. The other [47] reported neither uncomfortable symptoms nor liver or kidney injury. Overall, although some adverse events occurred, most were digestive tract reactions, mild pain, or subcutaneous haematoma, which resolved quickly.

4. Discussion

20 RCTs were analysed in this review to evaluate the effectiveness of acupuncture in treating insulin resistance. Previous studies [20–25] have limited the inclusive criteria to patients of certain diseases, and have not included all IR-related diseases. Additionally, these studies did not compare acupuncture alone with sham acupuncture, which could have led to overestimation of the effect, given the placebo effect. As far as we know, our review is the first meta-analysis to systematically examine the efficacy of acupuncture for patients with IR. In 2017, one systematic review of 7 trials with 628 patients evaluated the efficacy of herbal acupuncture for type 2 diabetes [49]. Since herbal acupuncture is a combination of needling and herbal medicine, this study could not limit the control group to acupuncture alone and separate its effect from other treatments. In our review, the effects of acupuncture treatments were estimated using pooled analysis, given the types of interventions and the RCT quality. This minimized the possibility of overestimation. We also examined the effects of acupuncture, not only on one disease, but on all diseases related to IR.

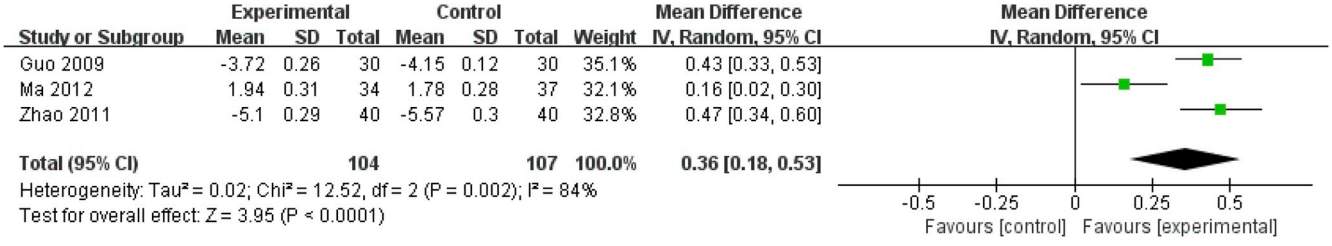

Fig. 6. Forest plot of ISI changes between the experimental and control groups.

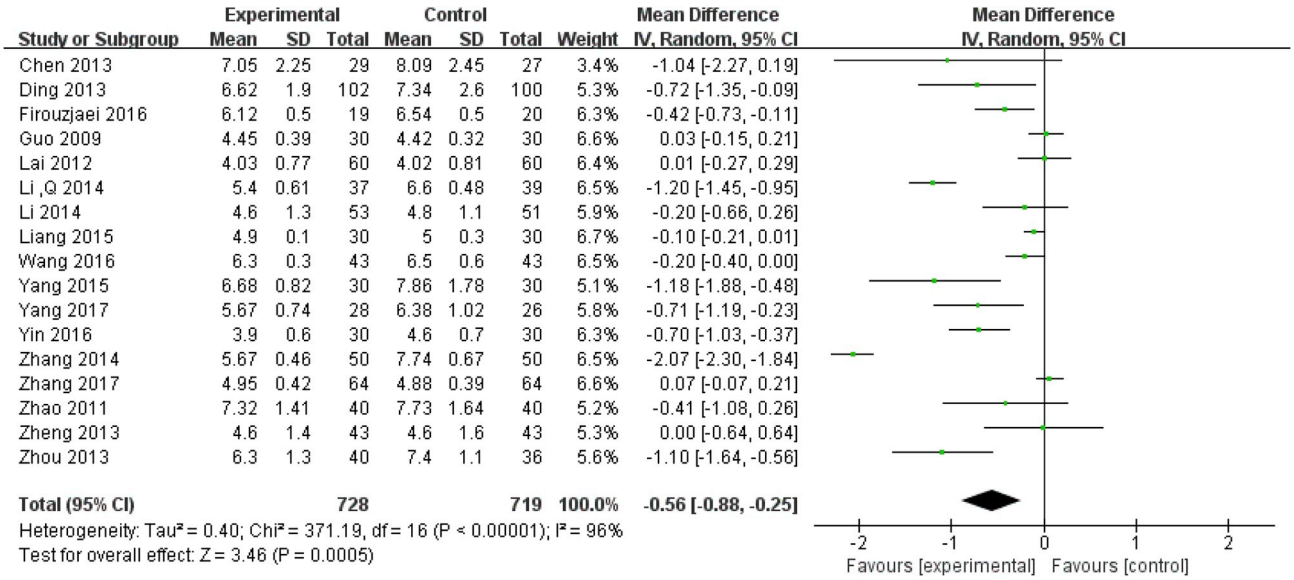

Fig. 7. Forest plot of FBG changes between the experimental and control groups.

One of the main findings was that acupuncture alone was more effective than sham acupuncture at decreasing homa-IR levels. Several systematic reviews of sham-controlled RCTs of acupuncture have reported that not only legitimate acupuncture, but also sham acupuncture, have significant effects in T2DM treatment. In other words, they suggest that there is no difference between the two groups respective effects [50,51]. Considering the small sample size of included RCTs and the overall high risk of bias, these results remain to be discussed.

Our subgroup analysis of different interventions also found that the effectiveness of acupuncture in decreasing homa-IR improved significantly, whether it had been combined with Western medicine or not. Meanwhile, the effect size of acupuncture alone in reducing homa-IR was low when compared with Western medicine monotherapy. This indicates that acupuncture is better as an adjuvant therapy for IR management than as a replacement. Hence, individualized drug therapy is still the most fundamental therapy for insulin resistance. The other subgroup analysis also demonstrated significant benefits of acupuncture treatment for different diseases, including T2DM and PCOS. However, the effectiveness for other diseases, such as abdominal obesity and essential hypertension, remained unknown. Many diseases are potentially related to IR, but not all RCTs of these diseases that used acupuncture have focused on IR and reported IR-related outcomes. Thus, additional RCTs using acupuncture that report IR-related

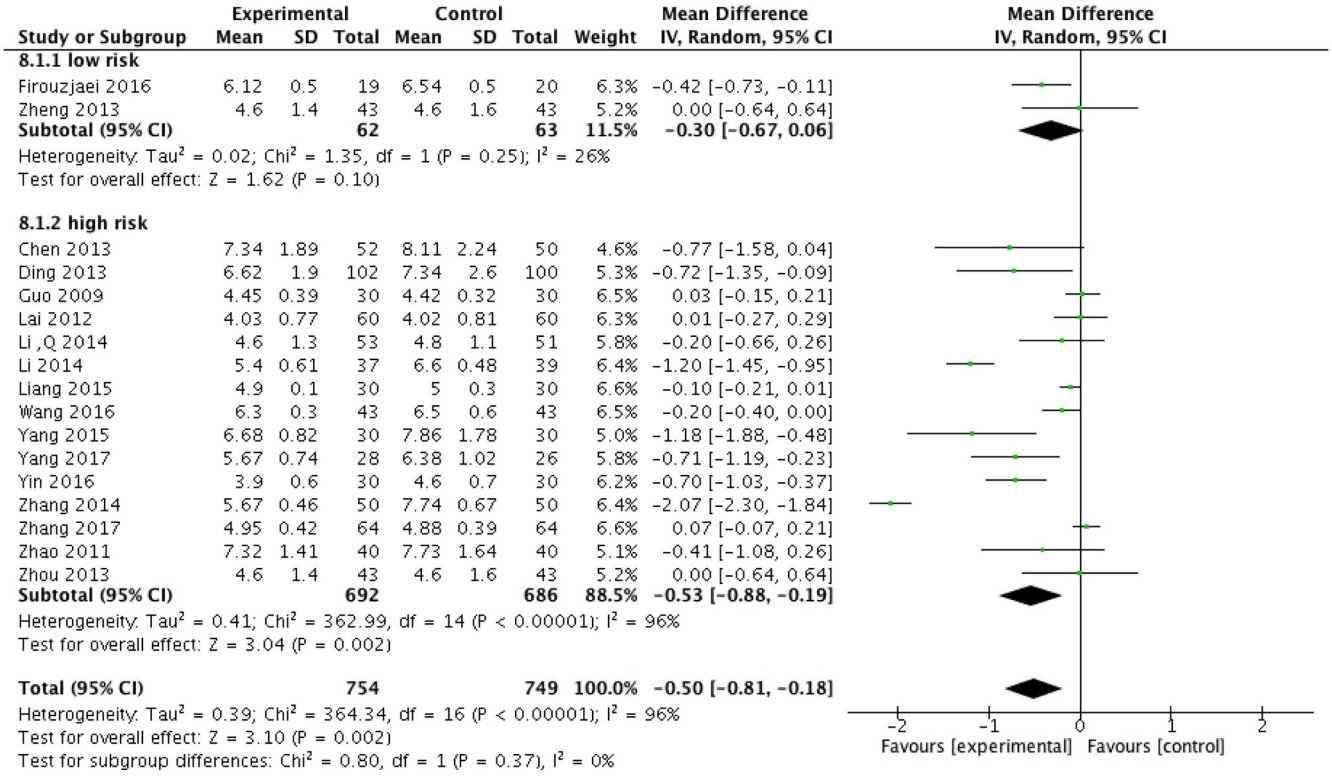

Fig. 8. Forest plot of FBG changes between the experimental and control groups, respectively, for low- and high-risk RCTs.

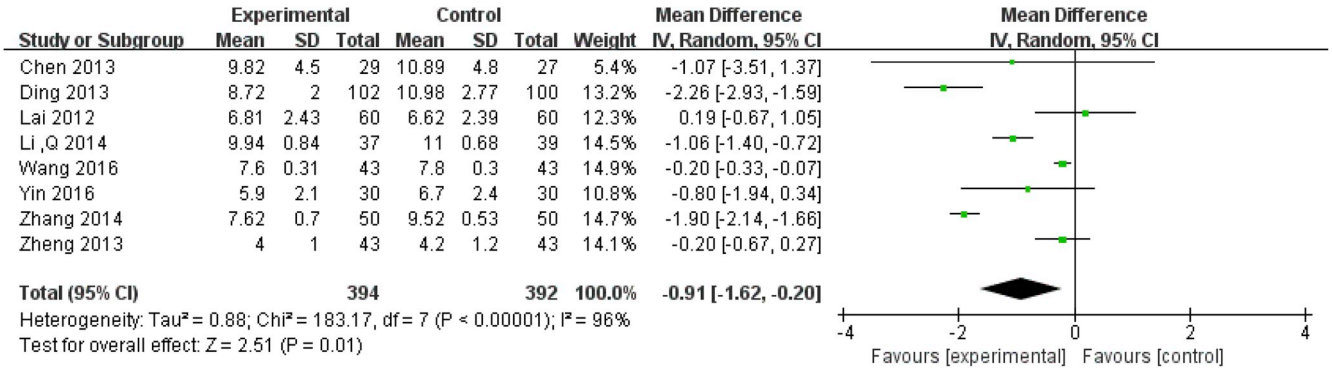

Fig. 9. Forest plot of 2hPG changes between the experimental and control groups.

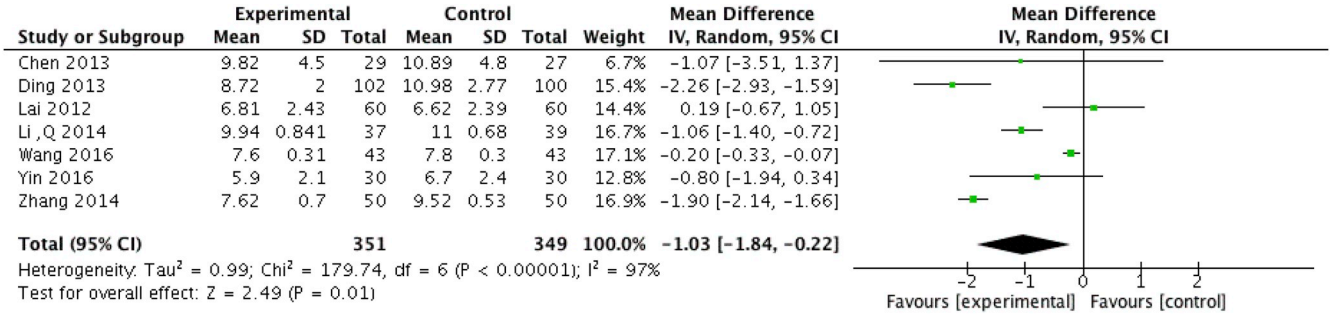

Fig. 10. Forest plot of 2hPG changes between the experimental and control groups in high-risk RCTs.

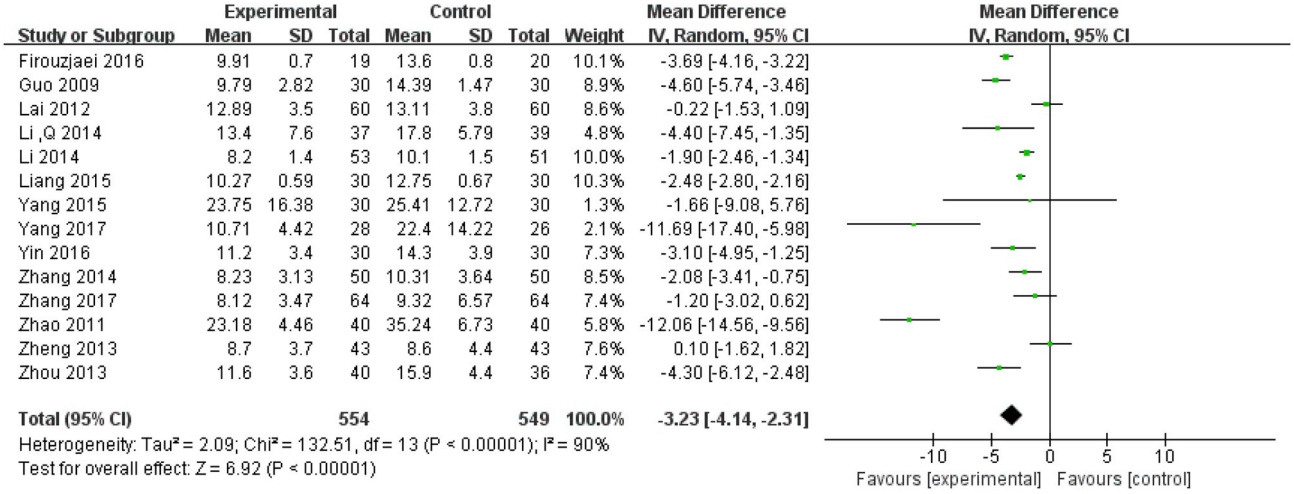

Fig. 11. Forest plot of FINS changes between the experimental and control groups.

outcomes on abdominal obesity and essential hypertension and other diseases are needed to confirm the clinical efficacy of acupuncture.

Our study also showed that acupuncture had an advantage over control groups in decreasing FBG, 2hPG and FINS levels, though the heterogeneity was high. After conducting subgroup analyses according to the quality scores, the pooled analysis of the high-risk RCTs still showed positive effects for FBG, 2hPG and FINS, while the pooled analysis of low-risk RCTs showed significance in decreasing neither FBG nor FINS. Considering that the sample size of the low-risk RCTs was too small and the heterogeneity was still high, these results remain to be confirmed.

In terms of the adverse effects, acupuncture was well tolerated by patients with fewer mild and transient side effects, and no withdrawals were reported due to serious adverse events. In line with previous literature, acupuncture is safe when administered by qualified practitioners [52].

Our review has included the latest evidence and has provided subgroup analyses based on interventions and quality scores which may produce most of the heterogeneity. Nonetheless, several limitations were unavoidable. First, the quality of most of the included RCTs was unsatisfactory. The details of the stochastic method, the allocation concealment, and blinding strategies were rarely described, and most of the selective reporting was unclear. Second, because of the lack of generally accepted criteria for recommended acupuncture treatment, the effectiveness may have varied when acupuncture techniques and acupoint selections were applied by varying doctors and to different patients. This could have caused the high heterogeneity. Third, four studies were published in English, and one was conducted in Egypt. The rest were conducted in China. Thus, it remains unclear whether these results can be extrapolated to individuals outside of China. Therefore,

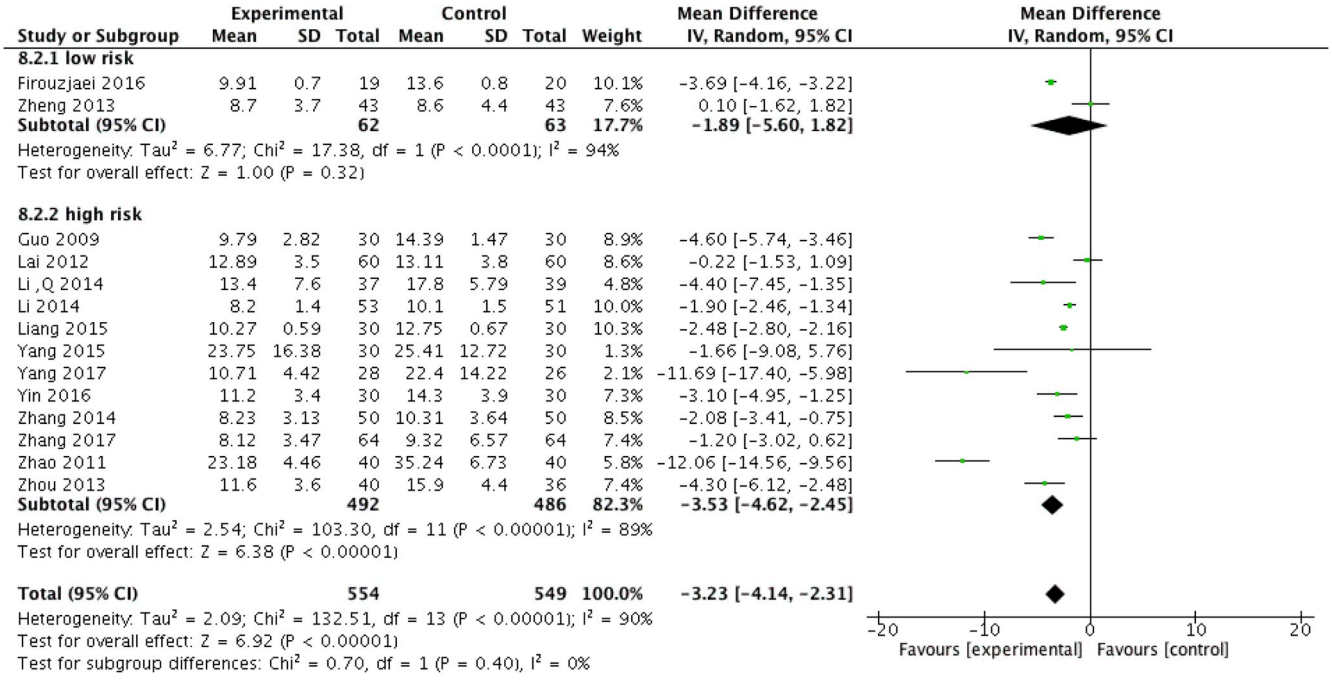

Fig. 12. Forest plot of FINS changes between the experimental and control groups in low-risk and high-risk RCTs.

Table 2
Reported adverse events in the RCTs.

Studies	Nausea, emesis, diarrhoea and loss of appetite		Mild pain due to the needling		Subcutaneous haematoma due to the needling		Sample		Total
	EG	CG	EG	CG	EG	CG	EG	CG	
Lai 2012 [34]	0	20	-	-	-	-	60	60	120
Li 2014 [36]	18	22	-	-	-	-	53	51	104
Liang 2015 [37]	-	-	-	-	-	-	30	30	60
Yang 2015 [41]	-	-	30	0	-	-	30	30	60
Yang 2017 [42]	-	-	-	-	2	0	28	26	54

EG: experimental groups; CG: control groups.

there may be publication bias.

5. Conclusion

This systematic review suggests that acupuncture may be of therapeutic value in the treatment of insulin resistance by improving homa-IR, ISI, FBG, 2hPG and FINS, with fewer adverse events. However, the conclusions are limited by flaws in the methodologies of the included RCTs. In the future, we look forward to further multi-centre and rigorous blinded studies for more solid evidence. Hopefully, this will enable researchers to determine an optimal acupuncture approach for insulin resistance.

Author contributions

Conception and design of the meta-analysis: Liming Lu and Wei Yi. Study selection, data extraction and quality assessment of the included studies: Jiao Lan, Chunxiao Wu and Zhixing Li. Analysis of study data and composition of the paper: Liqun Wu, Xiaokun Chen and Yun Liu. All authors read and approved the final version of the manuscript.

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Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.08.002.

Appendix 1. Search strategies

1. The Cochrane Library, Medline, and Embase (via OVID) 1144
   1 exp Glucose Tolerance Test/or exp Glucose Intolerance/
   2 exp Diabetes Mellitus, Type 2/pc [Prevention & Control]
   3 exp Insulin Resistance/

4 exp Metabolic Syndrome X/
5 exp Prediabetic State/
6 (glucose adj3 (intolerance or tolerance test*)).tw,ot.
7 (impaired fasting adj3 (glucose or glyc?emia*)).tw,ot.
8 (impaired glucose adj3 (toleran* or stat* or respons* or control* or regul* or metab* or homeost*)).tw,ot.
9 (reduced glucose adj3 (metab* or toleran*)).tw,ot.
10 (pr?ediabet* or pr?e diabet*).tw,ot.
11 (metabolic syndrom* or syndrome X).tw,ot.
12 ((borderline or mild) adj3 diabet*).tw,ot.
13 insulin resistan*.tw,ot.
14 ((impaired or reduced) adj3 insulin secret*).tw,ot.
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 exp Acupuncture/
17 exp Acupuncture Therapy/
18 exp Medicine, Chinese Traditional/
19 acupunctur*.tw.
20 (meridian* or moxi*).tw.
21 (electrostimulat* or electroacupunctur*).tw.
22 (electro* adj1 (stimulat* or acupunctur*)).tw.
23 acupoint*.tw.
24 exp Bloodletting/
25 body needl*.tw.
26 bloodletting.tw.
27 ((chinese adj3 medicin*) or TCM).tw.
28 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 exp Randomized Controlled Trial/or exp Crossover-procedur/or exp Double-blind Procedure/
30 Controlled Clinical Trial.pt.
31 (randomized or randomized).ab,ti.
32 placebo.ab,ti.
33 drug therapy.fs.
34 randomly.ab,ti.
35 trial.ab,ti.
36 groups.ab,ti.
37 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38 15 and 28 and 37

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SU/AB =('Insulin resistance' + 'glucose tolerance test' + 'glucose intolerance' + 'diabetes' + 'metabolic syndrome' + 'pre-diabetes' + 'hyperglycemic ' + 'loss of fasting blood glucose ') AND SU/AB =('needle'+' acupuncture' + 'acupuncture' + 'electric needle' + 'warm needle' + 'fire needle' + 'abdominal needle' + 'floating needle' + ' plum blossom needle ' + ' meridian ' + 'shu Acupoint '+' Acupoint '+' Moxibustion' + 'Moxibustion' + 'Moxibustion' + 'Cotton' + 'cupping ' + 'Acupoint embedding line ' + 'embedded line ' + ' acupoint sticking ' + 'point injection ' + 'Auricular Needle' + 'Auricular Point' + 'Auricular Point Press Bean') AND SU/AB =('Randomized Controlled Trial '+' Randomized Control' + 'Random' + 'Test '+ 'Clinical Control Trial '+ 'RCT')

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Subject/Abstract: ("Insulin resistance" + "glucose tolerance test" + "glucose intolerance" + "diabetes" + "metabolic syndrome" + "pre-diabetes" + "excessive blood sugar" + "fasting blood glucose damage")* Theme: ("needle" + "needle" + "acupuncture" + "electric needle" + "warm needle" + "fire needle" + "abdominal needle" + "floating needle" + " plum needle" + "meridian" + "shu "+" acupoint "+" moxibustion "+" moxibustion "+" moxibustion method "+" cupping" + "cupping" + "acupoint embedding line" + "buried line" + "acupoint sticking" + "acupoint injection" + "Auricular Needle" + "Auricular Point" + "Auricular Point Pressed Bean") * Subject: ("Randomized Controlled Trial" + "Randomized Control" + "Random" + "Test" + "Clinical Control Trial" + "RCT")

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(R/M = insulin resistance OR R/M = glucose tolerance test OR R/M = glucose intolerance OR R/M = diabetes OR R/M = metabolic syndrome OR R/M = pre-diabetes OR R/M = hyperglycemia OR R/M = impaired fasting glucose) AND (R/M = needle OR R/M = acupuncture OR R/M = acupuncture OR R/M = electroacupuncture OR R/M = warm needle OR R/M = fire needle OR R/M = abdominal needle OR R/M = floating needle OR R/M = plum needle OR R/M = meridian OR R/M = acupoint OR R/M = Acupoint OR R/M = moxibustion OR R/M = moxibustion OR R/M = moxibustion OR R/M = cupping OR R/M = cupping OR R/M = acupoint embedding OR R/M = embedding OR R/M = acupoint sticking OR R/M = acupoint injection OR R/M = ear hole OR R/M = auricular OR R/M = auricular pressure bean) AND (R/M = randomized controlled trial OR R/M = randomized control OR R/M = random OR R/M = trial OR R/M = clinical controlled trial OR R/M = RCT).

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