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Acupuncture for type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Acupuncture has been used to treat type 2 diabetes (T2DM) for 2000 years and there are emerging clinical evidence and animal studies for its efficacy. However, we are unable to conclude the effectiveness and safety on this issue yet.
Objectives: To assess the effects and safety of acupuncture for T2DM.
Methods: We systematically searched 5 databases and 2 clinical registry platforms from inception to 2018-6-4. RCTs for acupuncture or its variants compared with sham acupuncture or no acupuncture controls for T2DM were included. The primary outcomes were glycemic control and adverse events.
Results: A total of 21 studies, which comprised a total of 1943 participants, were included in the final meta-analysis. Compared with sham acupuncture or no acupuncture plus baseline treatments, acupuncture plus baseline treatments yield reduction in FBG(MD 1.21 mmol/l, 95%CI 1.56 to 0.87), 2 h BG(MD 2.13 mmol/l, 95%CI 2.79 to 1.46), HA1c (MD 1.12%, 95%CI 1.62 to 0.62). Our results also show acupuncture can improve blood lipids and blood pressure control, and reduce weight.
Conclusions: As one type of multifactorial intervention, acupuncture could be recommended as a supplementary treatment in the management of T2DM, especially in those with obesity or metabolic disorders. However, due to the small sample size, poor methodological quality of trials reviewed, the amount of evidence is not fully convincing. There is a need for well-planned, long-term studies.
Registration: International Prospective Register of Systematic Reviews (Number CRD42018094573).

1. Introduction

T2DM is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs [1]. According to the 8th edition of IDF(International Diabetes Federation) diabetes atlas, 8.8%(424.9 million) people live with diabetes, and it is expected to grow to 628.6 million by 2045 [2]. Diabetes is also one of the leading cause of death. According to the report from WHO, 43% of deaths before the age of 70 (around 2.2 million) are caused by hyperglycemia [3]. Although new drugs and new therapies emerged, the growth population of diabetes grow faster than expected [3,4]. The attainment of glycaemic targets is also compromised by the limitation of available treatment [5]. Therefore, searching for new effective therapies is in demand.

Acupuncture originated in China more than 2500 years ago and is one of the oldest medical procedures in the world, which refers to a family of procedures used to stimulate anatomical points on the skin [6]. Acupuncture has been used to treat diabetes mellitus for more than two thousand years. The earliest existing record (about 215-140 B.C.) can be found in the Han Dynasty at “Records of the Historian”, written by Sima Qian. The modern literature on the topic has been published in China since the 1950s, and most of them concluded that acupuncture is effective [7]. A review summarized the mechanism and limited clinical evidence of acupuncture for insulin resistance [8], which is the main characteristic of T2DM [9]. The potential mechanism of animal experiments include improve insulin sensitivity [10], suppress appetite to reduce food intake [11], lower the blood glucose [12] and regulate the blood lipids metabolism [13], etc. There are increasing clinical trials reported the efficacy of acupuncture for T2DM. Due to the small sample size and methodological flaws, we are unable to conclude the

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effectiveness and safety on this issue, which suggests the need for studies that synthesizes existing research. The goal of the review is to assess the effects and safety of acupuncture for T2DM.

2. Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14].

2.1. Selection criteria

We regarded studies as eligible for inclusion if it were randomized controlled trials done in T2DM patients (as diagnosed using any recognized diagnostic criteria, such as WHO 1999 [15] or ADA 2018 [16]), comparing the efficacy of acupuncture to sham acupuncture or no acupuncture control. Acupuncture refers to a set of treatments that stimulate certain points on the body. We do not limit the source of stimulation. The stimulation could be the hand, needle, electrical, laser, moxibustion etc. However, acupuncture in those studies involved with certain drugs, such as acupoint injection, would be excluded, for which might interfere the outcome. Sham acupuncture is defined as any intervention designed to prevent the patients from knowing whether he or she has received real acupuncture, but which is thought to have minimal activity against diabetes [17]. This includes that superficial needling, needling at non-acupuncture points, or use placebo needles such as Streitberger needle [18]. Baseline treatment, which includes lifestyle intervention, education, anti-diabetic drugs or herbal medicine, etc., should be the same in the intervention group and control group.

Quasi-randomized trials and retrospective trials were excluded. For those trials of duplicated publications, the latest publication was selected whereas all others were excluded.

The primary outcomes assessed are glycemic control (FBG, 2 h BG, HA1c) and adverse events. The priori adverse events we consider is incidence of hypoglycemia and infection. Pain, injury or other events related acupuncture are also considered. Secondary outcomes included body mass index (BMI), blood lipids levels (triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)), fasting insulin level, HOMA-IR (Homeostasis model assessment), blood pressure (systolic blood pressure, diastolic blood pressure).

2.2. Search strategy

We searched the following electronic databases from inception to July 4th, 2018: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, China National Knowledge Infrastructure (CNKI), and Chinese Biomedicine Literature Database (CBM). Ongoing trials were searched in United States clinical trials registry (ClinicalTrials.gov) and WHO International Trials Registry Platform (ICTRP) on August 6th, 2018. Languages were limited to English and Chinese. Free text and subject terms (MeSH terms in Pubmed, EMTREE in Embase, and the CMeSH terms in CBM database) were both used in search strategy. Randomized trials were identified by using Cochrane sensitivity and precision-maximizing version strategies [19]. The search strategy for each databases is listed in appendix. If relevant systematic reviews were identified by the strategy, additional trials would be hand screened by the reference lists. All the references were managed by Endnote X7.8.

2.3. Study selection and data extraction

One author (CC) screened the studies by scanning the titles and/or abstracts. If the study satisfied the inclusion criteria, then a full-text assessment would be conduct. All the excluded studies were classified with certain reasons in Endnote. One author (JL) checked all the data.

We created a data entry form set by epidata manager (version: 4.4.1). The terms of the form includes: the first author, publishing contact details, affiliation, country, trial registration, characteristics of trial participants (including age, sex, disease course, diagnosis criteria), duration and details of intervention, outcomes and other data required in meta-analysis. For studies that fulfilled inclusion criteria, two authors (CC, MS) extracted the data from the paper and input the data by EpiData Entry Client (Version: 4.4.1). The third author (JL) checked the data. The disagreements were resolved by consensus.

We attempted to contact authors of the included studies that reported outcome data were inadequate for meta-analysis and the related registered trials by electronic mail, but all the authors did not respond.

2.4. Statistical analysis

We calculated pooled estimates of the mean difference before and after the treatment in FBG, 2 h BG, HA1c, blood lipids levels, fasting insulin level, HOMA-IR (Homeostasis model assessment), blood pressure between groups by using a random-effects model (DerSimonian–Laird method) to adequately account for the additional uncertainty associated with inter-study variability.

We used the Cochran Q test to assess heterogeneity between studies [20]. I [2] testing was used to assess the magnitude of the heterogeneity between studies, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity [21]. METANINF is a module in Stata that evaluates the impact of individual study in meta-analysis estimation [22].If the pooled outcomes contained sufficient numbers of inclusion studies ($n >= 10$), the likelyhood publication bias would be assessed by the funnel plot. We used the Egger test to assess the asymmetry of the funnel plots and defined a significant publication bias as a p-value < 0.1 [23]. If the publication bias were detected, the trim-and-fill computation would be used to correct for funnel plot asymmetry and estimate the effect of publication bias [24]. We performed all statistical analysis using Stata (version 12.0) and Review Manager [25] (version 5.3).

As different acupuncture modalities will contribute to considerable clinical heterogeneity, the subgroup analysis would be conducted according to the different acupuncture therapies. We also conducted 3 sensitivity analysis. As some studies have shown that sham acupuncture is superior to no treatment or routine care [26,27], sensitivity analyses would be done based on the type of control. We predefined the timing of outcome measurement as short term, medium term and long-term. Only 2 trials [28,29] intervention treatment are longer than 3 months. Therefore, we redefined the long-term (more than 3 months) and short term (3 months or less than 3 months) on which sensitivity analyses was based. The preplanned sensitivity analysis also included different diagnosis criteria.

We followed the GRADE system [30](The Grading of Recommendations Assessment, Development and Evaluation) to evaluate the quality of final evidence and form the recommendation and its strength. We used GRADEpro GDT (Available from gradepro.org.) to generate the summary of finding (SoF) table of primary outcomes.

3. Results

We identified 2541 studies, of which 25 met our inclusion criteria. The process is summarized in Fig. 1.

The included studies were all published between 2001 and 2018, and 21 of them were published after 2010. 6 trials were published in English whereas the others were Chinese. 23 of them implemented in China, and rest 2 of them in India [31] and Indonesia [32]. The characteristics of trials are listed in Table 1.

Note: TENS: transcutaneous electrical nerve stimulation; FINS: Fasting Insulin; HOMA: homeostatic model assessment; TCM: Traditional Chinese Medicine; EA: Electro-Acupuncture; NA: No

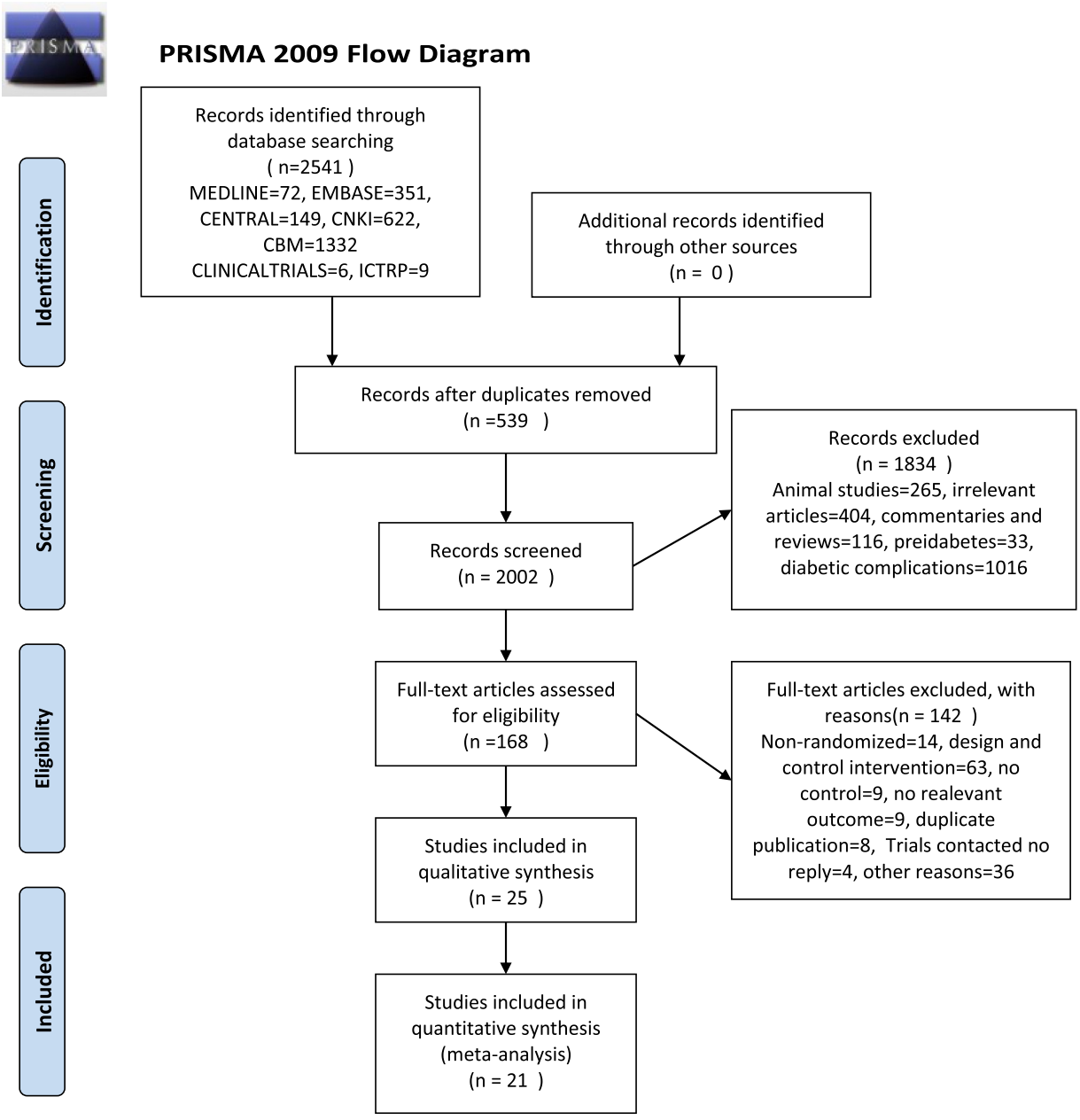


Fig. 1. PRISMA flow diagram.

acupuncture; SA: Sham Acupuncture.

3.1. Risk of bias in included studies

Risk of bias assessment was conducted by 2 independent authors (CC and JL) using the Cochrane Collaboration risk of bias tool [54]. Disagreements were resolved by discussion with involvement of the third review author (HW).Fig. 2 shows the assessment of risk of bias in the trials.

Seven of trials reported random sequence generation, and only 1 trial reported adequate allocation concealment. It has been demonstrated that unconcealed allocation is the most important source of bias in randomized trials [55]. Inadequate allocation concealment can lead to exaggerated estimates of treatment effect [56,57].

Six trials used sham acupuncture control. It is confusing 3 of them [32,46,49] did not mention blinding in the studies. Three trials blinded the participants, and the rest were all in high risk of performance bias. The magnitude of bias associated with inadequate blinding of participants is likely to be greater for more subjective outcomes [58]. Considering all the outcomes assessed are objective outcomes in this paper, we judge the outcome measurement is not likely to be influenced by lack of blinding.

Four trials reported that no one lost in the trials and 2 trials reported the number of drop outs in the trial, and the missing data was not included in the final analysis. One trial has the similar reasons for missing data across the groups whereas the other is not. Therefore, only 5 trials are at low risk of attrition bias. Two trials reported the registration number, yet both are retrospective registration. The original protocol of the rest of the trials are not available. Therefore, all trials were at unclear risk of selective reporting. Four trials might have unbalanced baseline treatments in baseline both groups, which mentioned the hypoglycemic agents can be adjust according the blood glucose. One trial terminated the trials in advance because of recruitment and 1 trial showed that the baseline data for participants might not equivalent. Therefore, 7 trials have high risk of other bias while the rest have at unclear risk of other bias.

Table 1
Characteristics of included studies.

Author	Year	Number	Mean age	Mean duration of diabetes	Duration of Interventions	Baseline treatment in both groups	Acupuncture treatment in experimental group	Control type	Relevant Outcomes
Bao et al. [33]	2014	60	–	–	1 month	Metformin	TCM Acupuncture	NA	FBG, HA1c, BMI
Bi et al. [34]	2014	100	55.8 years	4.9 years	12 weeks	Lifestyle instructions, relevant antidiabeteic drugs(not specified)	Ear acupuncture	NA	HA1c, weight, TC, TG, LDL, FBG, 2 h BG
Chen et al. [35]	2002	102	51.8 years	–	20–30 days	Glipzide or Metformin, or both	TCM acupuncture	NA	FBG
Ding et al. [36]	2013	202	52.5 years	–	39 days	Lifestyle instructions, relevant antidiabeteic drugs(not specified)	TCM acupuncture	NA	FBG, 2 h BG, HA1c, BMI, HOMA, Leptin
Dong et al. [37]	2002	62	57.3 years	3.6 years	2 months	Glibenclamide	Acupoints catgut embedding	NA	FBG, TC, TG, LDL, HDL
Firouzjaei et al. [38]	2016	39	41.3 years	–	3 weeks	Metformin	EA, ear acupuncture	SA	Weight, BMI, FINS, HOMA, TC, TG, LDL, HDL, Leptin
He et al. [28]	2012	100	49.0 years	–	2 years	Lifestyle education, community	TCM acupuncture	NA	FBG, HA1c
Jin et al. [29]	2018	80(16 quit)	53.8 years	11.4 years	3 years	Oral drugs, Lifestyle education	Acupressure	NA	TC, TG, LDL, HDL
Kumar et al. [31]	2017	40	56.2 years	–	1 session	No	TCM acupuncture	SA	Random BG
Lin et al. [39]	2013	31	49.0 years	–	1 session	Rosiglitazone	EA	SA	FBG, FINS, HOMA
Liu et al. [40]	2018	156	43.8 years	12.2 years	3 months	Metformin	TCM acupuncture, ear acupuncture	NA	FBG, TC, TG, LDL, HDL, FINS, HOMA
Qian et al. [41]	2017	60	52.5 years	63.2 months	3 months	Maintain original lifestyle and medications	Ear acupuncture	NA	FBG, 2 h BG, HA1c
Tang et al. [42]	2013	100	52 years	–	1 month	Metformin, Simvastatin	TCM acupuncture	NA	FBG, 2 h BG, HA1c
Tang et al. [43]	2016	40	52.4 years	2.6 years	8 weeks	Lifestyle intervention	TCM acupuncture	NA	FBG, 2 h BG, HA1c
Tjipto et al. [32]	2014	43(9 quit)	-(distribution)	-(distribution)	10 days	Metformin	EA	SA	FBG, 2 h BG, FINS
Wang et al. [44]	2012	127	51.1 years	3.0 years	14 days	Insulin, Education, Lifestyle intervention	Acupressure	NA	FBG, 2 h BG
Wang [45]	2014	146	59.8 years	7.4 years	2 months	Glimepiride, Lifestyle intervention	TCM acupuncture	NA	FBG, 2 h BG, HA1c
Wu et al. [46]	2015	60	63.6 years	–	2 months	Lifestyle intervention	TENS	SA	BMI, 2 h BG, HA1c, FINS, TC, TG
Wu et al. [47]	2017	120	44.2 years	–	3 months	Metformin, Lifestyle instruction	Acupoints catgut embedding	NA	FBG, BMI, SBP, DBP, TG, TC, LDL
Xiong et al. [48]	2001	65	64.9 years	3.6 years	30 days	Diet control	TCM acupuncture	NA	FBG, FINS
Xiong et al. [49]	2015	44	61.0 years	9.2 years	15 days	Diet education, oral drugs	Laser acupuncture	SA	2 h BG, HA1c, BMI
Yang et al. [50]	2015a	160	70.6 years	12.0 years	3 weeks	Herbal medicines, maintain original drugs, lifestyle intervention	TCM acupuncture	NA	FBG, 2 h BG, HA1c, FINS, HOMA
Yang et al. [51]	2015b	60	48 years	46.2 months	3 weeks	Maintain original drugs	Abdomen acupuncture	NA	FBG, 2 h BG, HA1c, SBP, DBP, weight, FINS, TC, TG, LDL, HDL, HOMA
Yao et al. [52]	2004	60	58.6 years	–	30 days	Herbal medicines	Ear acupuncture	NA	FBG
Zhou et al. [53]	2013	76	41.6 years	–	90 days	Lifestyle Intervention, Maintain original drugs	TCM acupuncture	NA	FBG, HA1c, FINS, BMI, HOMA, SBP, DBP

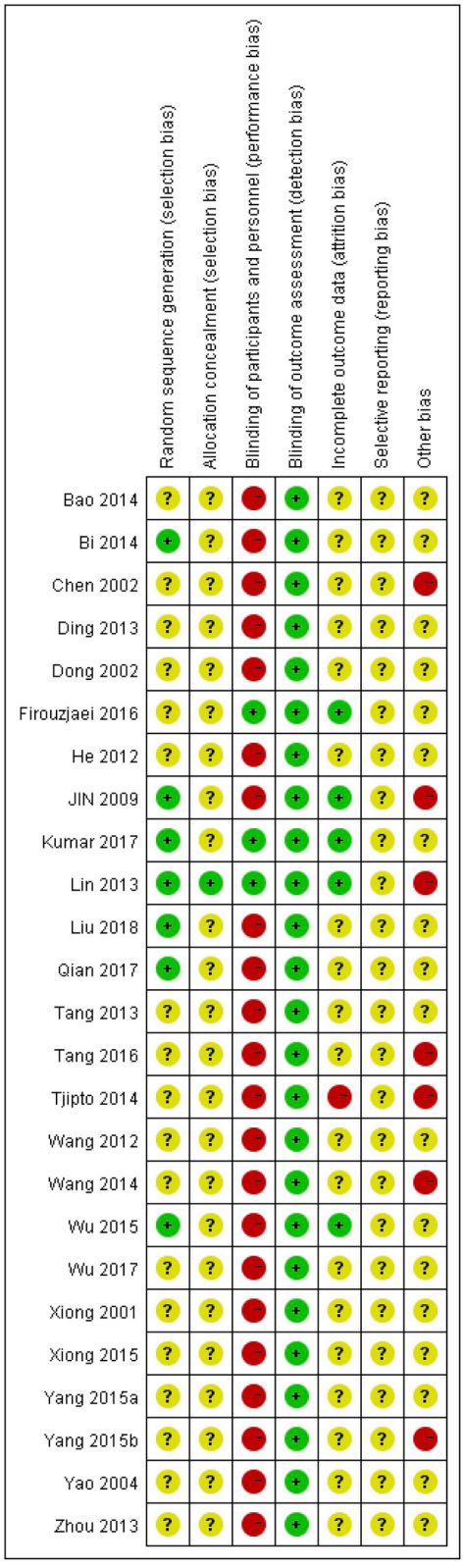


Fig. 2. Risk of bias summary.

We thought the blinding issues are acceptable considering blinding can be a challenge [59] and it's impossible to blind the acupuncturists in acupuncture trials. We regard the overall risk of a trials are acceptable if the trial have low risk in randomization and allocation concealment and no high risk in last 3 domains. None of the studies meets the criteria of overall high quality.

3.2. Effects of interventions

Three studies [32,39,46] reported the box plot in the papers, but did not report the standard deviation. We attempted to contact the authors, but none of them responded. One study [31] only reported random blood glucose change before and after the treatment. Therefore, 21 studies were included in the final quantitative synthesis. A total of 1943 people were included in the 21 studies, including 1000 patients in the treatment group and 943 patients in the control group. Only 1 trial [38] used a placebo control and the rest were no acupuncture controls design in the final meta-analysis.

3.3. Primary outcomes

We categorized acupuncture therapies as 6 subgroups according to the included studies: TCM acupuncture, ear acupuncture, acupressure, acupoint catgut embedding, the combined therapies (ear acupuncture and acupuncture) and transcutaneous electrical nerve stimulation (TENS).

Compared with sham acupuncture or no acupuncture plus baseline treatments, acupuncture plus baseline treatments showed a mean reduction in FBG for 1.21 mmol/l with statistically significant between the study heterogeneity in a pooled analysis of 19 trials (Fig. 3). Egger test shows no evident publish bias was detected (P = 0.450). METANINF analysis shows that no single trial had greater influence in the outcome.

In a pooled analysis of 10 trials, compared with no acupuncture plus baseline treatments, acupuncture plus baseline treatments showed a mean reduction in 2 h BG for about 2.13 mmol/l with statistically significant between the study heterogeneity (Fig. 4). Egger test shows no evident publish bias was detected (P = 0.359). METANINF analysis indicates that no individual trial have great influence on the overall outcome.

In a pooled analysis of 10 trials, compared with no acupuncture plus baseline treatments, acupuncture plus baseline treatments showed a mean reduction of 1.12% in HA1c with statistically significant between the study heterogeneity (Fig. 5). Egger test shows no evident publish bias was detected (P = 0.464). METANINF analysis indicates no individual trial have great influence on the overall outcome.

Only two trials [39,50] reported no significant adverse effects in acupuncture combined therapies. The safety of acupuncture for T2DM cannot be assessed due to the insufficient information.

We generated the SoF table (in Appendix 2) for the primary outcomes. Because of very serious risk of bias and serious inconsistency, the quality of the evidence of three primary outcomes are very low.

3.4. Secondary outcomes

Meta-analysis of secondary outcomes are listed in Table 2. All the results are synthesized in mean difference by random model.

Six trials reported HOMA-IR, and six trials reported FINS. The mean values are too different to synthesize the data. This may be resulted from the different measure methods, as none of them reported the details of measurements and two of the trials did not report the calculation methods of HOMA-IR.

3.5. Subgroup analysis and sensitivity analysis

Subgroup analysis shows that all the subgroups are effective than the control. However, several subgroups fail to reach the statistical significance, which may be caused by insufficient simple size. In the most subgroups with 2 or more studies included, there are substantial heterogeneity found ($I^2 > 75\%$).

The preplanned sensitivity analysis shows that a decreased estimates of HA1c in the long-term (95%CI, [-0.59, −0.41]) compared to short-term (95%CI, [-1.70, −0.69]). The different type of control group

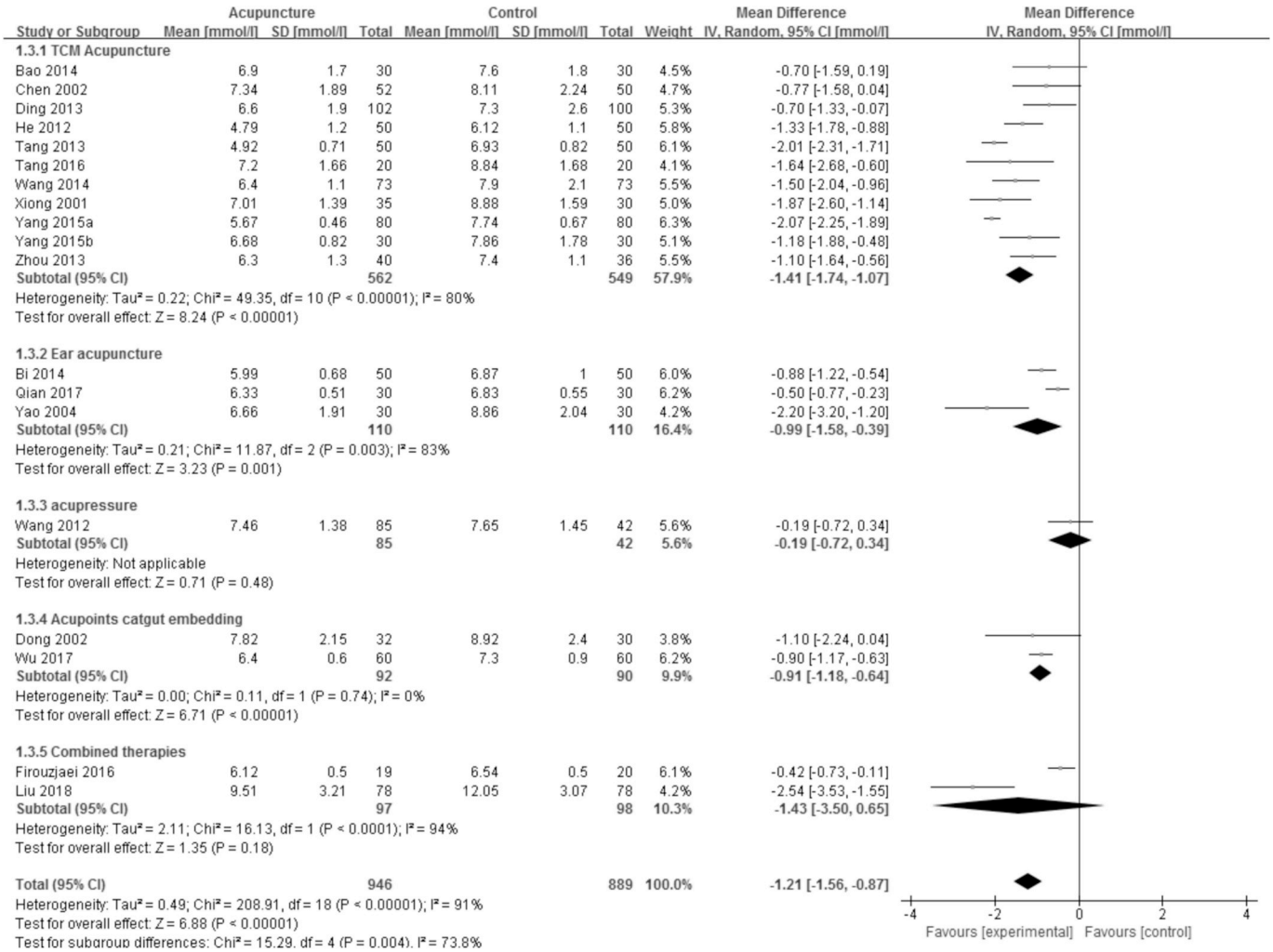


Fig. 3. Acupuncture plus baseline treatments versus sham acupuncture or no acupuncture plus baseline treatments, Outcome Fasting Blood Glucose, Units mmol/l.

shows decreased estimates of FBG, TG, LDL, BMI and weight in sham acupuncture group. Other sensitivity analysis related of different diagnosis criteria and different application sites show that the results are robust. No sensitivity analysis could be performed according to the results of quality assessment.

4. Discussion

Our results show that compared with sham acupuncture or no acupuncture plus baseline treatments, acupuncture plus baseline treatments can improve glycemic control, blood lipids levels, blood pressure levels (diastolic blood pressure may not clinically significant), and lose weight. The information is insufficient to assess the safety of acupuncture for T2DM.

A review of reviews [60] reporting that three relevant reviews exist. One review reported herbal acupuncture [61] for T2DM. The herbal acupuncture, which also called acupoints injection, might involve the effects of herbal injection. One review reported moxibustion [62] for T2DM, which is narrative review. The other one published in Chinese, which compares acupuncture with hypoglycemic agents for T2DM. Reviews reported acupuncture for diabetic peripheral neuropathy [63,64] are also available. Therefore, there is no research report the specific effects of acupuncture for T2DM.

From the GRADE approach, the strength of the recommendation is not only determined by the quality of evidence, but also the balance of desirable and undesirable consequences, variability in values and preferences, and resource use [65]. These aspects are described as follows.

Our results show desirable consequences include improved glycemic control, blood lipids, blood pressure and weight loss in acupuncture group. Some studies have shown that the control the blood pressure and blood lipids in the management of T2DM can reduce the risk of microvascular and macrovascular diseases [66,67]. Multiple combined intervention on these outcomes have sustained beneficial effects with respect to vascular complications and on mortality on any cause [68]. The philosophy of acupuncture in treating diseases is the holistic concept. For diabetes, the purpose of acupuncture is not to control blood glucose, but maintain the balance in the whole body. Acupuncture may be one type of multifactorial intervention and might be beneficial in the vascular complications and mortality.

Some trials included show that acupuncture plus hypoglycemic agents can achieve better glycemic control compared with hypoglycemic agents alone. Several animal studies have explored the potential mechanism with certain drugs, such as Rosiglitazone [69], metformin [70], glimepiride [71] could be enhanced by acupuncture. Also, certain hypoglycemic drugs can lead to weight gain (such as thiazolidinediones, sulfonylureas, insulin), which is strongly associated with T2DM [72]. Our results show the weight loss in the acupuncture group. One systematic review also concluded that acupuncture may be an effective treatment for obesity [73]. Modest weight loss can improve glycemic control and reduce the need for hypoglycemic agents [74,75], which suggests that acupuncture in combination with hypoglycemic drugs can

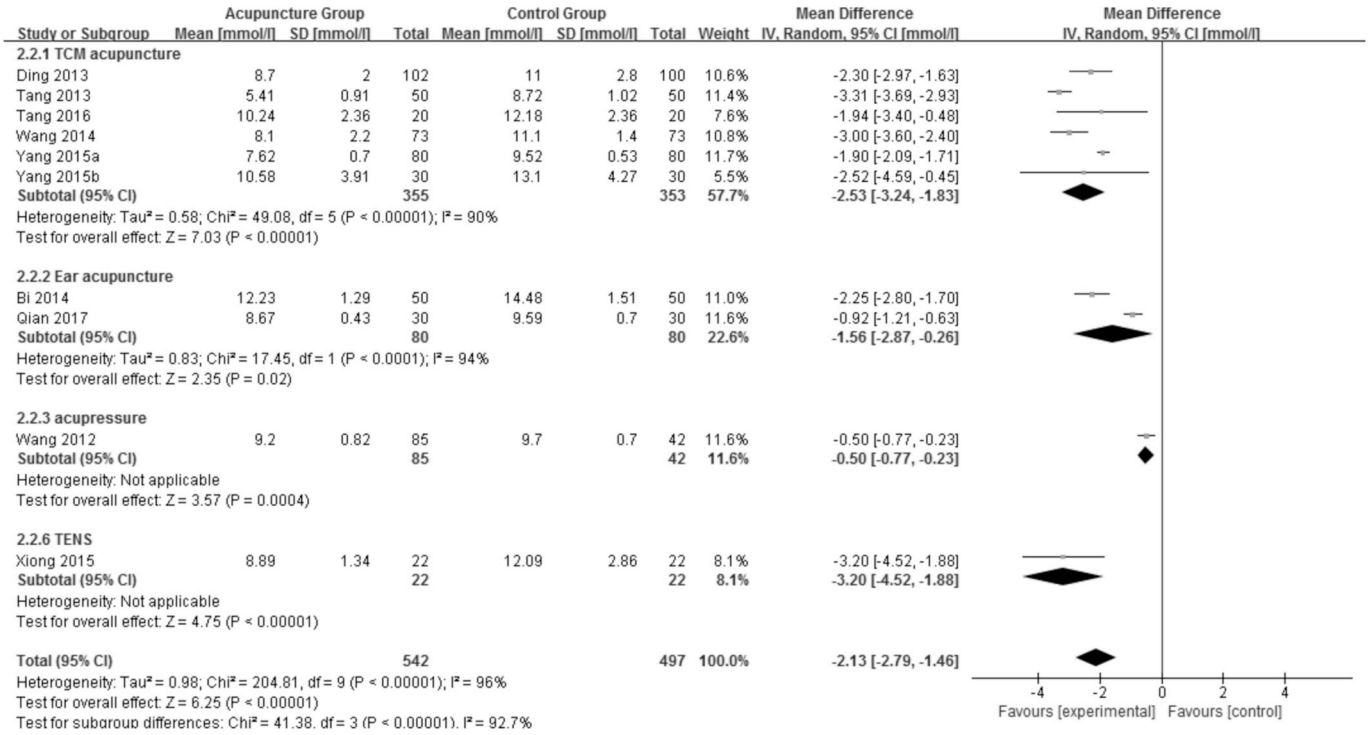


Fig. 4. Acupuncture plus baseline treatments versus no acupuncture plus baseline treatments, Outcome 2 h BG, Units mmol/l.

lead to better glycemic control or reduced dose of drugs.

Adverse events are quite rare. In this study, we could not draw inclusion on safety of acupuncture for diabetes due to insufficient data. However, acupuncture is generally considered safe in the hands of competent practitioners [76]. The main adverse events of acupuncture are needling pain, hematoma, bleeding [77]. The risk of serious events associated with acupuncture is very low (0.05 per 10,000 treatments), below that of many common medical treatments [78]. However, how the acupuncture affect the incidence of hypoglycemia and infection is unknown. Every healthcare intervention comes with the risk, especially in those with diabetes which susceptible to infection. Without assessing the adverse effects may cause an imbalance evaluation and may make the intervention look more favorable than it should [19]. Future researches should attach more importance to the reporting of adverse events.

No studies addressed the resource use of acupuncture for T2DM. As

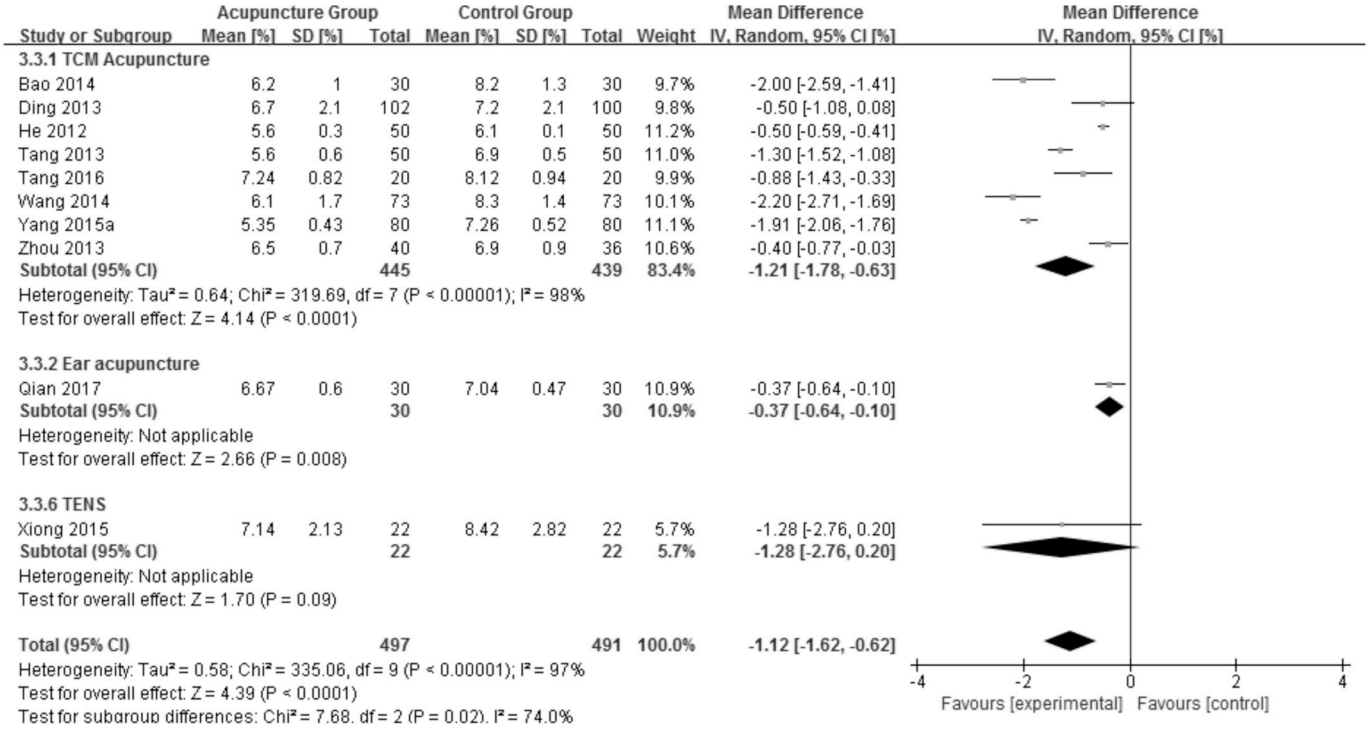


Fig. 5. Acupuncture plus baseline treatments versus no acupuncture plus baseline treatments, Outcome HA1c, Units %.

Table 2
Acupuncture plus baseline treatments versus sham acupuncture or no acupuncture plus baseline treatments, Secondary outcome.

Outcome or Subgroup	Studies	Participants	Effect Estimate(95% CI)	Units	Heterogeneity
1.1 TG	7	596	−0.49 [-0.74, −0.24]	mmol/l	(P < 0.00001); I^2 = 84%
1.2 HDL	5	397	0.25 [0.06, 0.45]	mmol/l	(P < 0.00001); I^2 = 94%
1.3 LDL	7	637	−0.49 [-0.76, −0.21]	mmol/l	(P < 0.00001); I^2 = 91%
1.4 TC	6	578	−0.47 [-0.65, −0.30]	mmol/l	(P = 0.25); I^2 = 24%
2.1 BMI	7	601	−1.75 [-2.56, −0.94]	kg/m^2	(P = 0.001); I^2 = 73%
2.2 wt	2	139	−4.01 [-6.34, −1.68]	kg	(P = 0.75); I^2 = 0%
3.1 Systolic Blood Pressure	3	256	−8.51 [-12.94, −4.09]	mmHg	(P = 0.25); I^2 = 29%
3.2 Diastolic Blood Pressure	3	256	−1.71 [-3.99, 0.56]	mmHg	(P = 0.56); I^2 = 0%

health resources are relatively scarce now, the decision-making is closely related to health costs for the health policymakers, clinician and patients. Some studies have found acupuncture is relatively cost-effective in some diseases [79–81]. Acupuncture treatment only needs acupuncture needles, which costs less health resources but needs more human resources. Considering long-term use of acupuncture, self-service acupuncture, such as TENS or self-cupping, might be more cost-effective and more executable.

The values and preferences are closely related to the desirable and undesirable consequences, and the cost. Our results show overall beneficial effects on endocrine system and rare adverse events. Probably no important uncertainty or variability would be found.

Overall, acupuncture plus baseline treatments can improve glycemic control, blood lipids levels, blood pressure levels and lose weight without significant adverse events. Caution should be taken that the results are of limited value due to the substantial clinical heterogeneity, poor methodological quality of the included studies.

4.1. This review has several limitations

Firstly, many important outcomes are not addressed, and the long-term or follow up effects of acupuncture is unknown. All the outcomes we assessed are surrogate outcomes, and end point outcomes are not investigated in the trials, such as the incidence of diabetic complications, all-cause mortality, cost-effective and quality of life. Without the information, we cannot comprehensively evaluate the value and significance of acupuncture treatment for diabetes. At present, there is no cure for diabetes. The purpose of treatment is not only to control blood glucose, but attention should also be paid to preventing or delaying the occurrence of diabetes complications, improving the quality of life, reducing all cause of mortality. Only two trials are longer than 3 months and no trials reported follow-up effects. T2DM is lifetime disease, which requires long-term treatment. One study shows acupoint irradiation with a semiconductor laser can inhibit islet beta-cell apoptosis in rats with T2DM [82], which may indicate potential long-term effect for acupuncture.

Secondly, there are substantial heterogeneity in most of the pooled estimates. We tried to include more trials by the relative relatively broaden inclusion criteria, which made the baseline treatments are quite different in every trials. The differences of intervention, also the poor quality of the trials, may be a source of heterogeneity. Acupuncture is one kind of manipulation technique clinical practice; different acupuncturists cannot perform the same as robot. For instance, the different acupoints selection, the manipulation techniques, the depth of insertion, the duration and the time of the treatments, will all infect the eventual outcomes. That is the reason we identified substantial heterogeneity in most subgroup analysis. As a therapy that stimulates the body surface, acupuncture refers to many different forms of medical procedures. The main purpose of this study is to explore the effectiveness of acupuncture. Given the heterogeneity of the research, the interpretation of the effect estimates should be cautious.

Thirdly, there is concern about the bias in the trials. Most of the trials were conduct in China. There are concerns that most Chinese trials reported unusually high proportions of positive results [83], also with the inadequacy randomization issues [84]. Sensitivity analysis shows an exaggerate estimates in the sham acupuncture group. While there are good explanations why sham controls might be active in pain, this seems less plausible in diabetes. This might indicates that there is bias in other trials.

5. Conclusions

The current available evidence shows that compared to sham acupuncture or no acupuncture control, acupuncture is beneficial for improving glycemic control, blood lipids and blood pressure control, helping losing weight in the management of T2DM.

Based on the GRADE, the quality of evidence we have reached are of very low. Because acupuncture plus hypoglycemic agents can achieve better effects than hypoglycemic agents alone, considering its overall potential benefits on the endocrine system, acupuncture could be recommended as a supplementary therapy in T2DM patients with metabolic disorders or obesity patients. More research and well-designed, long-term clinical trials are needed. Future studies need to focus on the issues which include whether long-term acupuncture treatment can reduce the risk of diabetic complications, improve the quality of life and the cost effectiveness of acupuncture.

Role of the funding source

The study is part of PhD research program of one author (CC), with no commercial entity involved. The funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Declaration of interests

All authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.04.004.

Appendix

MEDLINE

Search	Query	Items found	Time
#1	acupuncture[MeSH Terms]	21903	6:31:26
#2	acupuncture therapy[MeSH Terms]	21203	6:31:39
#3	acupuncture, ear[MeSH Terms]	357	6:33:18
#4	acupuncture points[MeSH Terms]	5494	6:33:27
#5	electroacupuncture[MeSH Terms]	3299	6:33:39
#6	((((Pharmacopuncture[Title/Abstract]) OR Pharmacopuncture treatment*[Title/Abstract]) OR Pharmacopuncture therapy[Title/Abstract]) OR acpuncture treatment*[Title/Abstract])	156	6:33:48
#7	acupotom*[Title/Abstract]	53	6:34:02
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	22029	6:34:47
#9	Diabetes Mellitus[MeSH Terms]	382455	6:35:02
#10	Diabetes mellitus, type 2[MeSH Terms]	114121	6:35:10
#11	(((Noninsulin Dependent Diabetes Mellitus[Title/Abstract]) OR Non Insulin Dependent Diabetes Mellitus, [Title/Abstract]) OR Ketosis-Resistant Diabetes Mellitus[Title/Abstract])	1190	6:35:17
#12	((NIDDM[Title/Abstract]) OR MODY[Title/Abstract])	7929	6:35:25
#13	((Maturity Onset Diabetes[Title/Abstract] OR (Slow-Onset[All Fields] OR Diabetes Mellitus[Title/Abstract])) OR Adult-Onset Diabetes Mellitus [Title/Abstract])	182449	6:35:32
#14	((Type 2 Diabetes[Title/Abstract]) OR Type II Diabetes[Title/Abstract])	110649	6:35:39
#15	Stable Diabetes Mellitus[Title/Abstract]	16	6:35:47
#16	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	467756	6:37:08
#17	randomized controlled trial[Publication Type]	461599	6:37:31
#18	controlled clinical trial[Publication Type]	549176	6:37:40
#19	randomized[Title/Abstract]	444582	6:37:49
#20	placebo[Title/Abstract]	194237	6:37:56
#21	clinical trials as topic [mesh: noexp]	183684	6:38:03
#22	randomly[Title/Abstract]	291547	6:38:12
#23	trial[Title]	182397	6:38:21
#24	(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)	1160202	6:39:16
#25	((animals [mh] NOT humans [mh]))	4460022	6:39:34
#26	(#24 not #25)	1068718	6:40:10
#27	(#8 AND #16 AND #26)	72	6:46:07

EMBASE

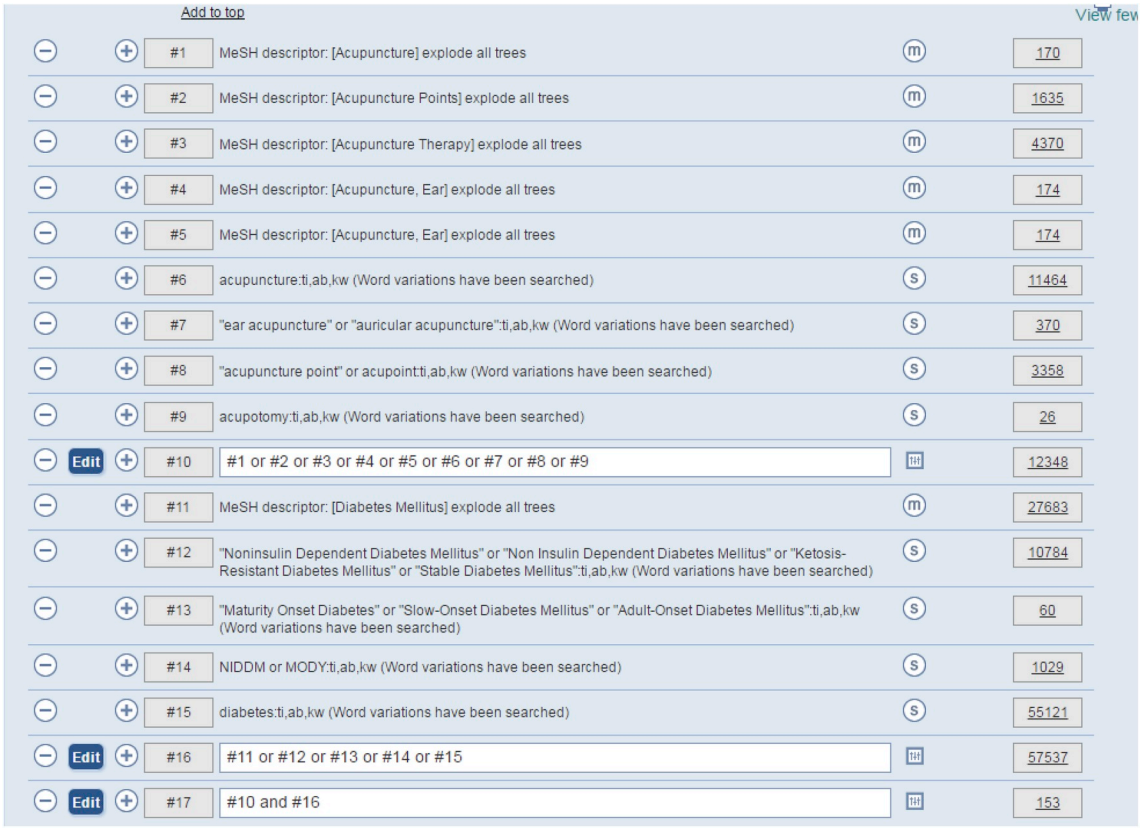
No. Query Results Results Date.

#29. #13 AND #27 AND #28 351 4 Jun 2018
#28. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti 2,240,744 4 Jun 2018
#27. #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 883,880 4 Jun 2018
#26. 'type ii diabetes mellitus':ab,ti 3668 4 Jun 2018
#25. 'type 2 diabetes mellitus':ab,ti 50,174 4 Jun 2018
#24. 'mody':ab,ti 1839 4 Jun 2018
#23. 'niddm':ab,ti 7912 4 Jun 2018
#22. 'adult-onset diabetes mellitus':ab,ti 178 4 Jun 2018
#21. 'slow-onset diabetes mellitus':ab,ti 4 Jun 2018
#20. 'maturity onset diabetes':ab,ti 2236 4 Jun 2018
#19. 'stable diabetes mellitus':ab,ti 24 4 Jun 2018
#18. 'ketosis-resistant diabetes mellitus':ab,ti 1 4 Jun 2018
#17. 'non insulin dependent diabetes mellitus':ab,ti 7677 4 Jun 2018
#16. 'noninsulin dependent diabetes mellitus':ab,ti 1017 4 Jun 2018
#15. 'diabetes mellitus':ab,ti 236,761 4 Jun 2018
#14. 'diabetes mellitus'/exp 857,812 4 Jun 2018
#13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 44,174 4 Jun 2018
#12. 'acupoint*':ab,ti 5277 4 Jun 2018
#11. 'acupuncture point*':ab,ti 2387 4 Jun 2018
#10. 'auricular acupuncture*':ab,ti 470 4 Jun 2018
#9. 'ear acupuncture*':ab,ti 281 4 Jun 2018
#8. 'acupotom*':ab,ti 65 4 Jun 2018
#7. 'acupuncture':ab,ti 27,611 4 Jun 2018
#6. 'acupressure':ab,ti 1175 4 Jun 2018
#5. 'auricular acupuncture':ab,ti 469 4 Jun 2018
#4. 'electroacupuncture':ab,ti 4518 4 Jun 2018

#3. 'acupuncture point'/exp 283 4 Jun 2018
#2. 'acupuncture needle'/exp 867 4 Jun 2018
#1. 'acupuncture'/exp 41,864 4 Jun 2018

CENTRAL

#1 MeSH descriptor: [Acupuncture] explode all trees
#2 MeSH descriptor: [Acupuncture Points] explode all trees
#3 MeSH descriptor: [Acupuncture Therapy] explode all trees
#4 MeSH descriptor: [Acupuncture, Ear] explode all trees
#5 MeSH descriptor: [Acupuncture, Ear] explode all trees
#6 acupuncture:ti,ab,kw (Word variations have been searched)
#7 ″ear acupuncture" or "auricular acupuncture":ti,ab,kw (Word variations have been searched)
#8 ″acupuncture point" or acupoint:ti,ab,kw (Word variations have been searched)
#9 acupotomy:ti,ab,kw (Word variations have been searched)
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Diabetes Mellitus] explode all trees
#12 ″Noninsulin Dependent Diabetes Mellitus" or "Non Insulin Dependent Diabetes Mellitus" or "Ketosis-Resistant Diabetes Mellitus" or "Stable Diabetes Mellitus":ti,ab,kw (Word variations have been searched)
#13 ″Maturity Onset Diabetes" or "Slow-Onset Diabetes Mellitus" or "Adult-Onset Diabetes Mellitus":ti,ab,kw (Word variations have been searched)
#14 NIDDM or MODY:ti,ab,kw (Word variations have been searched)
#15 diabetes:ti,ab,kw (Word variations have been searched)
#16 #11 or #12 or #13 or #14 or #15
#17 #10 and #16



CNKI:

（ SU=’二型糖尿病’ OR SU=’2 型糖尿病’ OR SU=’Ⅱ型糖尿病’ OR SU=’II 型糖尿病’ OR SU=’消渴’ OR SU=’糖尿病’ OR SU=’非胰岛素依赖性糖尿病’ OR SU=’非胰岛素依赖型糖尿病’）AND （ SU=’针灸’ OR SU=’针刺’ OR SU=’体针’ OR SU= ’头针’ OR SU=’耳针’ OR SU=’电针’）AND （ SU=’随机’ OR SU=’对照’ OR SU=’盲法’ OR SU=’单盲’ OR SU=’双盲’）

Results:622

CBM：

#1 (((((((("糖尿病"[不加权:扩展]) OR "二型糖尿病"[常用字段:智能]) OR "2 型糖尿病"[常用字段:智能]) OR "Ⅱ型糖尿病"[常用字段:智能]) OR "II 型糖尿病"[常用字段:智能]) OR "消渴"[常用字段:智能]) OR "糖尿病"[常用字段:智能]) OR "非胰岛素依赖性糖尿病"[常用字段:智能]) OR "非胰岛素依赖型糖尿病"[常用字段:智能]

369582

#2 ((((((("针灸"[常用字段:智能]) OR "针刺"[常用字段:智能]) OR "体针"[常用字段:智能]) OR "头针"[常用字段:智能]) OR "耳针"[常用字段:智能]) OR "电针"[常用字段:智能]) OR "针刺疗法"[不加权:扩展]

171118

#3 ((((("随机"[常用字段:智能]) OR "对照"[常用字段:智能]) OR "盲法"[常用字段:智能]) OR "单盲"[常用字段:智能]) OR "双盲"[常用字段:智能]

2039542

#4 #1 AND #2 AND #3

1332

Acupuncture plus baseline treatment compared to sham acupuncture or no acupuncture plus baseline treatment for type 2 diabetes

Patient or population: type 2 diabetes
Setting: Inpatient/Outpatient
Intervention: Acupuncture plus baseline treatment
Comparison: sham acupuncture or no acupuncture plus baseline treatment

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham acupuncture or no acupuncture plus baseline treatment	Risk difference with Acupuncture plus baseline treatment
Fasting Blood Glucose (FBG)	1835 (19 RCTs)	⨁◯◯◯ VERY LOW [a,b]	-	The mean fasting Blood Glucose ranged from **4.79~9.51** mmol/l	MD **1.21 mmol/l lower** (1.56 lower to 0.87 lower)
2h Blood Glucose (2h BG)	1039 (10 RCTs)	⨁◯◯◯ VERY LOW [b,c]	-	The mean 2h Blood Glucose ranged from **7.62~12.23** mmol/l	MD **2.13 mmol/l lower** (2.79 lower to 1.46 lower)
HA1c	988 (10 RCTs)	⨁◯◯◯ VERY LOW [b,c]	-	The mean hA1c ranged from **5.6~7.24** %	MD **1.12 % lower** (1.62 lower to 0.62 lower)
Adverse Events	(2 RCTs)	-	2 trials reported no adverse events in acupuncture group.		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. only 3 of the trial reported adequate random sequence generation, none of them used adequate allocation concealment, only 1 blinding of participants or researchers. Also, all of them were at risk of attrition bias and other risks.
b. due to substantial heterogeneity.
c. only 2 of the trials reported adequate random sequence generation, none of the trials used adequate allocation concealment and blinding of participants or researchers. Also, all of them were at high or unclear risk of attrition bias or other bias.

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