ORIGINAL ARTICLE

Effects of yoga in adults with type 2 diabetes mellitus: A meta-analysis

Jie Cui[1,2], Jun-Hong Yan[3], Li-Ming Yan[4], Lei Pan[5], Jia-Jin Le[1], Yong-Zhong Guo[6]*

[1]Glorious Sun School of Business and Management, Donghua University, [2]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, Departments of [3]Clinical Medical Technology, [4]Clinical Outpatient, [5]Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, and [6]Department of Respiratory Medicine, Xuzhou Central Hospital, The Affiliated Xuzhou Center Hospital of Nanjing University of Chinese Medicine, Xuzhou, China

ABSTRACT

Aims/Introduction: A meta-analysis was carried out to evaluate the efficacy of yoga in adults with type 2 diabetes mellitus.

Materials and Methods: The PubMed, EMBASE and Cochrane databases were searched to obtain eligible randomized controlled trials. The primary outcome was fasting blood glucose, and the secondary outcomes included glycosylated hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and postprandial blood glucose. Weighted mean differences and 95% confidence intervals (CIs) were calculated. The I^2 statistic represented heterogeneity.

Results: A total of 12 randomized controlled trials with a total of 864 patients met the inclusion criteria. The pooled weighted mean differences were −23.72 mg/dL (95% CI −37.78 to −9.65; $P = 0.001$; $I^2 = 82\%$) for fasting blood glucose and −0.47% (95% CI −0.87 to −0.07; $P = 0.02$; $I^2 = 82\%$) for hemoglobin A1c. The weighted mean differences were −17.38 mg/dL (95% CI −27.88 to −6.89; $P = 0.001$; $I^2 = 0\%$) for postprandial blood glucose, −18.50 mg/dL (95% CI −29.88 to −7.11; $P = 0.001$; $I^2 = 75\%$) for total cholesterol, 4.30 mg/dL (95% CI 3.25 to 5.36; $P < 0.00001$; $I^2 = 10\%$) for high-density lipoprotein cholesterol, −12.95 mg/dL (95% CI −18.84 to −7.06; $P < 0.0001$; $I^2 = 37\%$) for low-density lipoprotein cholesterol and −12.57 mg/dL (95% CI −29.91 to 4.76; $P = 0.16$; $I^2 = 48\%$) for triglycerides.

Conclusions: The available evidence suggests that yoga benefits adult patients with type 2 diabetes mellitus. However, considering the limited methodology and the potential heterogeneity, further studies are necessary to support our findings and investigate the long-term effects of yoga in type 2 diabetes mellitus patients.

INTRODUCTION

Type 2 diabetes mellitus is one of the most frequently encountered metabolic syndromes worldwide[1]. The most recent meta-analysis showed that the overall prevalence (9.1%) has been increasing among inland residents in China since the 1970s, and it increased rapidly with age[2]. Effective control of blood glucose to reduce the risk of various complications, including diabetic foot, diabetic neuropathy, cataract and cardiovascular disease, is especially important for type 2 diabetes mellitus management[3,4]. Medication, diet and physical activity or exercise are the major components of diabetes management. Training exercises have been recommended by recent evidence-based clinical studies as a cardinal non-pharmacotherapy[5]. Numerous training programs, such as jogging, walking, swimming, housework and other outdoor exercises, have been developed. However, taking into account the increasing prevalence of obesity, and the disabilities and complications associated with a sedentary lifestyle[6,7], few patients participate in conventional physical exercise.

Yoga originated in India over 4,000 years ago as a traditional form of mind–body training that seeks to unite the individual self with the transcendental self[8]. Yoga *asanas* (postures) and *pranayama* (breath control) have recently become very popular, and the role of yoga in several chronic diseases, such as hypertension, asthma, chronic obstructive pulmonary disease and diabetes, has been studied[8–10]. Several trials have

shown that yoga can reduce fasting blood glucose (FBG) and glycosylated hemoglobin A1c (HbA1c), as well as improve the lipid levels and quality of life of type 2 diabetes mellitus patients[11–18]. However, these studies present wide variations in sample size and even inconclusive results. Other studies applied a non-randomized study design that could affect the final outcomes[11–13]. Thus, in the present study, we carried out a meta-analysis of randomized controlled trials (RCTs) to determine the effectiveness of yoga in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS
The current meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[19], and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[20].

Data sources and searches
The PubMed, Embase and Cochrane databases were searched (until April 2016) for eligible RCTs using the key words 'yoga' and 'diabetes'. Eligible trials were limited to adult human subjects, and only trials published with the full text and written in English were included in this work. To ensure literature saturation, the bibliographies of all potentially eligible studies, including reference lists, citation searches and relevant systematic reviews, were searched by hand.

The available trials followed the PICOS criteria, including: (i) (P) patients: adult type 2 diabetes mellitus patients with or without chronicity and diabetes-associated complications; (ii) (I) intervention: yoga with or without other treatments; (iii) (C) control: any type of control including usual care or standard treatment; (iv) (O) outcomes: the primary outcome was FBG and the secondary outcomes included HbA1c, postprandial blood glucose (PPBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride; and (v) (S) study design: RCT.

Data extraction
Two investigators (JC and JHY) independently extracted all of the data, including the first author, publication year, country, study population and grouping (sample size per group), age, form or style of two groups, yoga protocol, duration, outcomes, study design, and Jadad scale, from the eligible RCTs. Disagreements were resolved by a third investigator (LP).

Quality and risk of bias assessment
The quality of each trial was evaluated according to the Jadad scale[21]. Randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point) were identified in the scale. A trial with a score ≤2 indicates low quality, whereas a score of ≥3 indicates high quality[22]. The risk of bias was assessed by the Cochrane Risk of Bias Assessment tool[19].

Statistical analysis
All of the data were combined using Revman 5.3 (The Cochrane Collaboration, Oxford, UK). Weighted mean differences (WMDs) with 95% confidence intervals (CIs) for continuous variables were calculated and pooled using the random effects model[23]. Heterogeneity was tested using Cochrane's Q-test and the I^2 statistic, and I^2 values >50% were considered to show significant heterogeneity[24]. If I^2 >50%, sensitivity analyses was carried out to explore potential sources of heterogeneity and investigate the influence of a single study on the overall pooled estimate. Combined with the demographic data of study participants included in the present study, as well as to minimize the risk of bias as a result of grouping criteria, subgroup analyses were carried out to explore potential heterogeneity and examine the influence of various exclusion criteria on the basis of sample size (>60 *vs* ≤60), Jadad score (>2 *vs* ≤2), duration (>3 months *vs* ≤3 months) and region (India *vs* non-India). Publication bias was assessed using Stata version 12.0 (Stata Corporation LP, College Station, TX, USA), and results were analyzed using Begg's and Egger's test[25]. Finally, two-sided *P*-values <0.05 were considered to show statistical significance.

RESULTS
Search results and study characteristics
Initially, 189 potential studies were retrieved from the electronic databases. After reviewing their titles and abstracts, 164 studies were excluded because they were unrelated to the aims of the present study. Another 13 candidate studies were excluded for various reasons (Figure 1). Finally, 12 RCTs were selected for the present meta-analysis[14–18,26–32].

The main characteristics of 12 RCTs involving 864 patients are summarized in Table 1. All RCTs were made available in English between 1992 and 2014. The total sample size ranged from 20 to 277. A total of 11 RCTs were carried out in four countries, including the UK[15,27], India[14,16,28–32], Cuba[17,18] and Iran[26]. Two RCTs were carried out by Gordon *et al.*[17,18] on the same study population, and another two RCTs were carried out by Shantakumari *et al.*[16,30], also on the same study population. Follow-up periods varied from 15 days to 9 months. All RCTs applied different yoga protocols with different exercise times and times per session. Furthermore, Table S1 shows additional information reported in all the randomized controlled trials.

Quality and risk of bias assessment
Two investigators (JC and JHY) agreed on each item of the Jadad score and Cochrane Risk of Bias Assessment tool. The mean Jadad score of the 12 RCTs was 2.8 (SD = 0.8). Risk-of-bias assessment showed that all RCTs generated low risk in terms of random sequence generation. None of the trials was double-blinded, and just three RCTs were single-blinded[17,18,28]. Details of the quality and risk-of-bias assessment of all of the RCTs are shown in Table 1 and Figure S1, respectively.
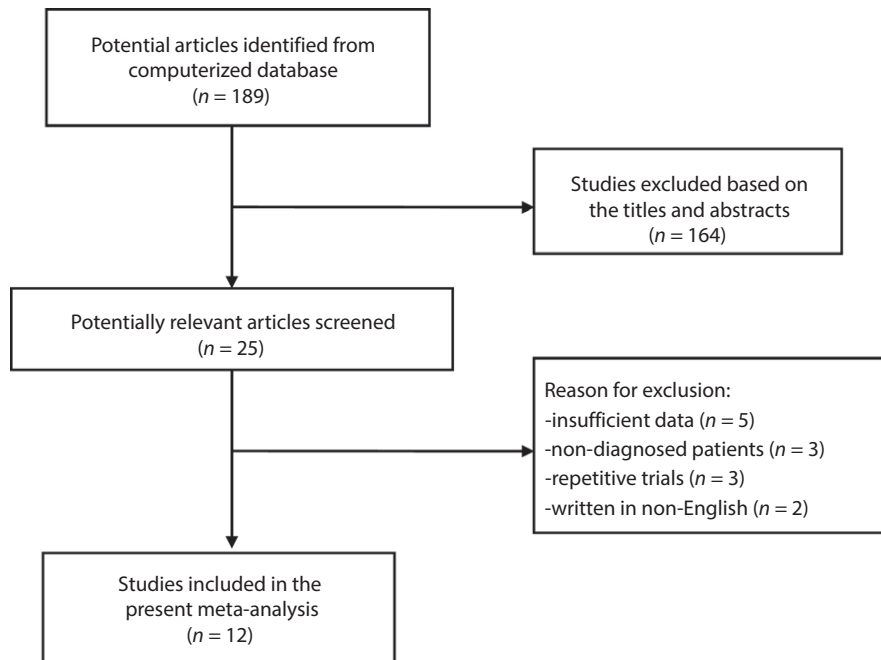
Figure 1 | Search strategy and flow chart for this meta-analysis.

Meta-analyses of primary outcome

Nine RCTs reported FBG as a primary outcome[14,17,26–32]. The pooled WMDs were −23.72 mg/dL (95% CI −37.78 to −9.65; $P = 0.001$; P for heterogeneity <0.00001; $I^2 = 82\%$) for FBG (Figure 2). Heterogeneity was clearly significant for the primary end-point. We carried out sensitivity analyses to investigate the potential sources of heterogeneity. However, regardless of which study was excluded from our analysis, the source of heterogeneity was not observed and the overall combined WMDs, which ranged from −27.90 mg/dL (95% CI −41.84 to −13.96; $P < 0.0001$) to −20.61 mg/dL (95% CI −33.99 to −7.23; $P = 0.003$), were not significantly altered. Next, we carried out subgroup analyses to examine the influence of various exclusion criteria with respect to FBG according to sample size (>60 vs ≤ 60), Jadad score (>2 vs ≤2), duration (>3 months vs ≤3 months) and region (India vs non-India). The detailed results are shown in Table 2. We found that the overall combined effects of the trials, regardless of their quality, sample size or follow-up period, were poor. Furthermore, non-Indian patients might benefit from yoga more than Indian patients.

Meta-analyses of secondary outcomes

The aggregated results suggested that the WMDs were −0.47% (95% CI −0.87 to −0.07; $P = 0.02$; P for heterogeneity <0.00001; $I^2 = 82\%$) for HbA1c (Figure 3a), −17.38 mg/dL (95% CI −27.88 to −6.89; $P = 0.001$; P for heterogeneity = 0.73; $I^2 = 0\%$) for PPBG (Figure 3b), −18.50 mg/dL (95% CI −29.88 to −7.11; $P = 0.001$; P for heterogeneity = 0.003; $I^2 = 75\%$) for TC (Figure 4), −12.95 mg/dL (95% CI −18.84 to −7.06;

$P < 0.0001$; P for heterogeneity = 0.18; $I^2 = 37\%$) for LDL-C (Figure 4), −12.57 mg/dL (95% CI −29.91 to 4.76; $P = 0.16$; P for heterogeneity = 0.12; $I^2 = 48\%$) for triglycerides (Figure 4) and 4.30 mg/dL (95% CI 3.25 to 5.36; $P < 0.00001$; P for heterogeneity = 0.34; $I^2 = 10\%$) for HDL-C (Figure 5).

Publication bias

Publication bias is shown in Figure 6. The results of the Begg's and Egger's tests suggested that no evidence of publication bias was found from funnel plots and associated statistics for FBG ($P_{Begg} = 0.917$; $P_{Egger} = 0.328$).

DISCUSSION

The aim of the present meta-analysis of the existing data is to quantitatively assess the role of yoga in patients with type 2 diabetes mellitus. The available evidence from 12 RCTs with a total of 864 patients suggested that yoga can significantly decrease patient FBG, PPBG, HbA1c, TC and LDL-C levels, and increase their HDL-C.

Several systematic reviews focusing on yoga for adult patients with type 2 diabetes mellitus have been published[33–36]. Although differences between our meta-analysis and these previous studies can be noted, our principal findings are consistent with the published results. Three studies carried out by Innes et al.[33–35] were mainly narrative reviews. Although a recent systematic review[34] also meta-analyzed several clinical endpoints, including glucose control, lipid levels and body composition, only studies reporting significant changes were included in that work. We believe that pooled results are not suitable for

Table 1 | Characteristics of randomized controlled trials included in the meta-analysis

First author, year and country	Study population	Study group (sample size)	Mean age, years (I/C)	Form or style (I/C) Intervention group	Control group	Yoga protocol	Duration	Outcomes	Study design/ Jadad score
Gordon, 2008, 2008, Cuba	154 patients without complications or malnutrition, trained for T2DM self-care; 81% F	Yoga (77); Control (77)	64.0/63.6	Hatha yoga (pranayamas, dynamic warm-up exercises, asanas, and savasana)	Usual care (a treatment plan as per their doctors, no active exercise)	1 class/week, 2-h class	6 months	FBG, Lipid, HbA1c	RCT/4
Habibi, 2013, Iran	26 female patients without taking insulin	Yoga (16); Control (10)	Age range: 45-60	Asana and pranayama exercise	Standard care	3 sessions/week, 75 min/session	3 months	FBG	RCT/2
Jyotsna, 2014, India	120 patients with lifestyle modification and oral antidiabetic medication	Yoga (64); Control (56)	49.92/47.25	Sudarshan Kriya Yoga + standard treatment	Standard treatment	3-day group training followed by classes 1x/week and daily home practice with a total of 25-35 min	6 months	FBS, PPBG, HbA1c	RCT/3
Monro, 1992, UK	21 patients taking medication (13) or on diet control alone (8)	Yoga (11); Control (10)	Age range: 45-67	Yoga classes (pranayama, shavasana and asanas) + standard care	Standard care (continuing on medication, diet)	1-2 classes/wk + 90 min, 1-5 times/ wk at home	3 months	FBG, HbA1c	RCT/2
Nagarathna, 2012, India	277 patients with stable dose of oral hypoglycemic agents or insulin for at least 3 wks; 31% F	Yoga (141); Control (136)	53.46/51.38	Integrated yoga (yogasanas, pranayama, meditation and lectures on yogic life style)	Physical exercises and life style education.	1 h/day, 5 days/week for 12 weeks, and then one 2 h class/week and 1 h daily home practice	9 months	Lipid, FBG, PPBG, HbA1c	RCT/4
Pardasany, 2010, India	30 patients taking hypoglycemic medications; 38% F	Yoga (15); Control (15)	Age range: 40-60	Hatha yoga (asanas and pranayamas)	Oral hypoglycemic medications	3 times/week	3 months	FBG, PPBG, Lipid, HbA1c	RCT/2
Shantakumari, 2013,2012, India	100 patients with hypertension and dyslipidemia; 48% F	Yoga (50); Control (50)	45.51/44.46	Asana, pranayama and meditation + standard treatment	Standard treatment (oral hypoglycemic drugs)	Daily for 1 h duration	3 months	FBG, PPBG, Lipid,	RCT/2
Subramaniyan, 2012, India	20 adult males patients	Yoga (10); Control (10)	Age range of 55% patients: 31-40	Yogic exercises	Brisk walking + routine medicines	60 min daily between 6AM and 7AM for 15 consecutive days	15 days	FBG	RCT/3

Table 1 (Continued)

First author, year and country	Study population	Study group (sample size)	Mean age, years (I/C)	Form or style (I/C) Intervention group	Control group	Yoga protocol	Duration	Outcomes	Study design/ Jadad score
Skoro-Kondza, 2009, UK	59 patients without taking insulin but receiving advice and leaflets on healthy lifestyle and exercise; 61% F	Yoga (29); Control (30)	Total mean age: 60	Yoga classes (pranayama, gentle stretching and asanas)	Wait list	Twice-weekly, 90-min class	3 months	HbA1c	RCT/3
Vaishali, 2012, India	57 elderly patients; 36.8% F	Yoga (27); Control (30)	65.8/64.4	Individualized yoga asanas and pranayama + educational intervention	Educational Intervention (general healthy lifestyle and exercise)	6 days a week, 45–60 min/session	3 months	FBG, Lipid, HbA1c	RCT/3

F, female; FBG, fasting blood glucose; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin A1c; I/C, intervention/control; RCT, randomized controlled trial; PPBG, postprandial blood glucose; T2DM, type 2 diabetes mellitus.

inclusion in the present study because, they can lead to selection bias, and affect the objectivity and authenticity of our findings. Additionally, another previous systematic review enrolling just five RCTs with a total of 362 participants was published in 2008[36]. In comparison with that review, the present meta-analysis included 12 RCTs with a total of 864 patients. Considering the limited data on the topic, we combined existing RCTs to increase the sample size, strengthen our analyses and produce more robust results.

The present results showed that yoga significantly decreased FBG, PPBG, HbA1c, TC and LDL-C levels, and increased HDL-C in patients with type 2 diabetes mellitus. Significant heterogeneity was noted during our analyses of FBG and HbA1c. Given that we specified the primary end-point was FBG, sensitivity and subgroup analyses were carried out to explore the potential sources of heterogeneity for FBG. We found that exclusion of each of the RCTs considered in this work did not resolve the heterogeneity issue or materially alter the overall combined FBG. We thus believe that the heterogeneity observed across trials could be viewed as a result of clinical and methodological differences. Subgroup analyses were carried out to investigate the impact of various exclusion criteria according to sample size, Jadad score, duration and region. The overall combined effects of the trials, regardless of their quality, sample size or follow-up period, were poor. Furthermore, non-Indian patients might benefit from yoga more than Indian patients. The exact reason is still unknown, and it might be related to racial differences, and different diet and lifestyle habit, and also might be derived from the limited data or other related bias, such as the existing heterogeneity. Thus, we believe that robust, well-designed and larger-scale trials should be carried out to substantiate the long-term effects of yoga in type 2 diabetes mellitus patients, especially those who are not from India.

Combining the present results with those reported in the related literature, the following considerations might help direct future clinical research on the effects of yoga on type 2 diabetes mellitus management. First, exercise is a key factor for diabetes management. As the optimal exercise form and appropriate exercise parameters for type 2 diabetes mellitus patients are unknown, the development of exercise regimens for these patients seems to be warranted. Second, the aspects of yoga that benefit patients with type 2 diabetes mellitus remain unknown, and objective outcome measurements, such as peripheral nerve modulation, quality of life, blood pressure, overall survival, inflammatory mediators and immune cell function, especially at the cellular and molecular levels, are not carried out in most studies. Therefore, further research should focus on improving measurement modalities to better address potential mechanisms and obtain more reliable evidence of the role of yoga-based training in type 2 diabetes mellitus patients. Third, the follow-up periods of the RCTs included in the present study ranged from 15 days to 9 months, and the long-term effects of yoga remain unknown. Most of the RCTs included in the present
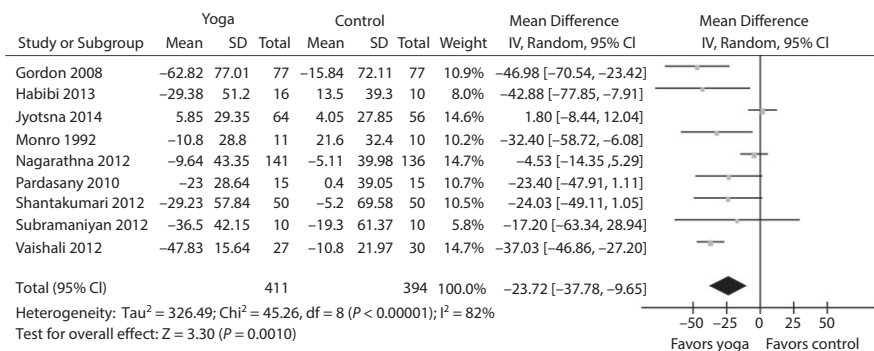
Figure 2 | Forest plots of evaluating the effect of yoga on fasting blood glucose.

Table 2 | Subgroup analyses based on various exclusion criteria for fasting blood glucose

Various exclusion criteria	n (N)	WMDs, mg/dL (95% CI)	P-value	I^2 (%)	$P_{heterogeneity}$
All included trials[38–46]	805 (9)	−23.72 (−37.78 to −9.65)	0.001	82	<0.00001
Jadad scores ≥3	628 (5)	−19.96 (−40.02 to 0.09)	0.05	90	<0.00001
Jadad scores ≤2	177 (4)	−28.82 (−42.29 to −15.36)	<0.0001	0	0.80
Sample sizes >60	651 (4)	−15.16 (−32.37 to 2.04)	0.08	81	0.001
Sample sizes ≤60	154 (5)	−34.73 (−42.97 to −26.50)	<0.00001	0	0.77
Duration >3 months	551 (3)	−13.19 (−32.99 to 6.60)	0.19	86	0.001
Duration ≤3 months	254 (6)	−33.69 (−41.51 to −25.87)	<0.00001	0	0.78
Region (India)	604 (6)	−16.70 (−33.15 to −0.25)	0.05	86	<0.00001
Region (non-India)	201 (3)	−40.97 (−56.66 to −25.28)	<0.00001	0	0.72

CIs, confidence intervals; n, number of patients; N, number of trials; WMDs, weighted mean differences.
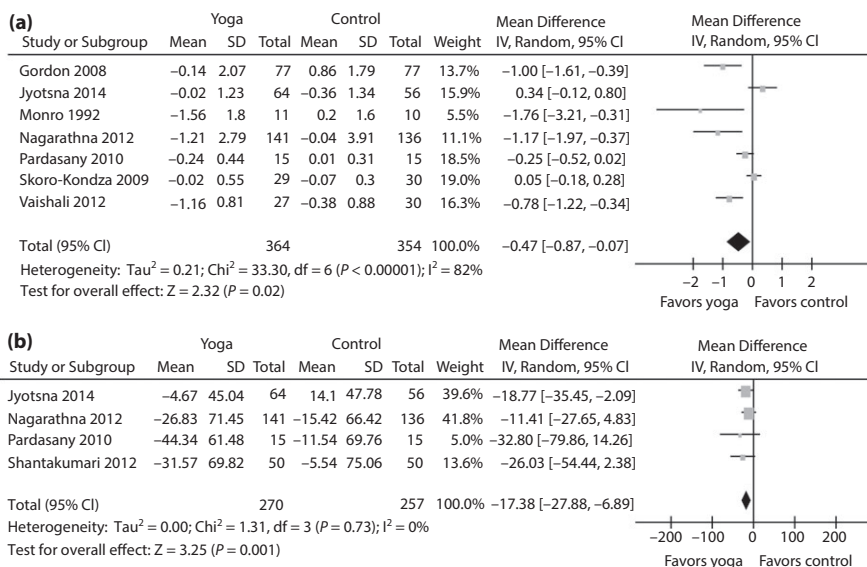

Figure 3 | Forest plots of evaluating the effect of yoga on (a) glycosylated hemoglobin A1c and (b) postprandial blood glucose.

study were not blinded. Considering that blinding prevents bias and protects the sequence after allocation[37], appropriate blinding, such as blind-outcome assessments, should be carried out.

Compared with previous reviews, our meta-analysis was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the
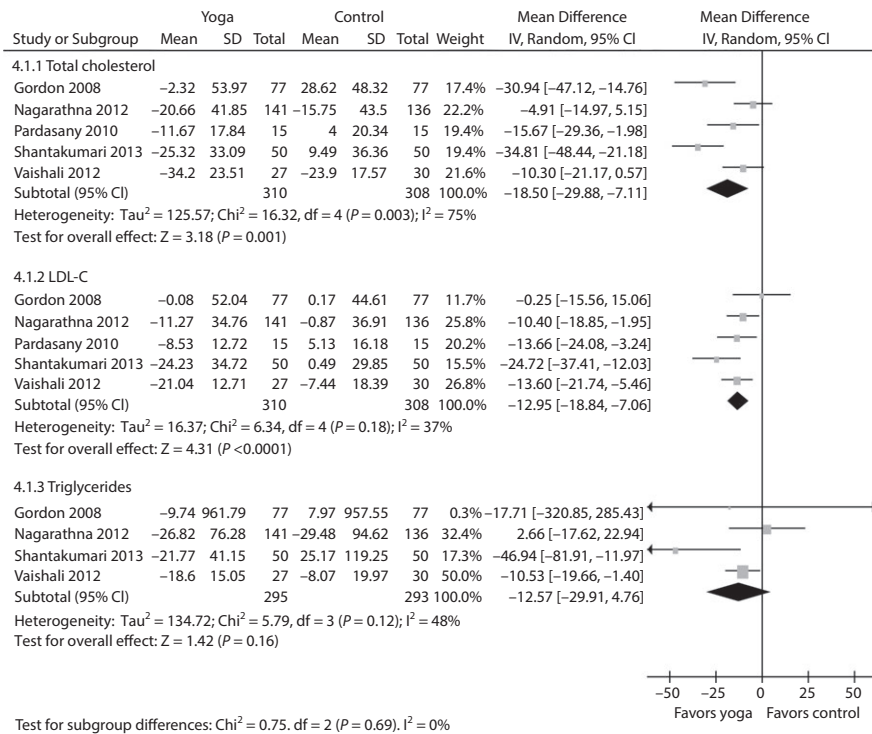
Figure 4 | Forest plots of evaluating the effect of yoga on total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride.
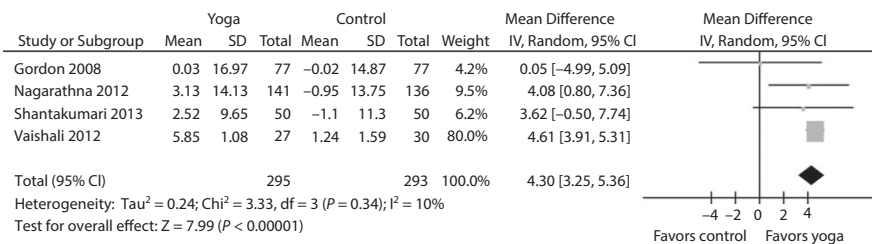

Figure 5 | Meta-analysis of evaluating the effect of yoga on high-density lipoprotein cholesterol.
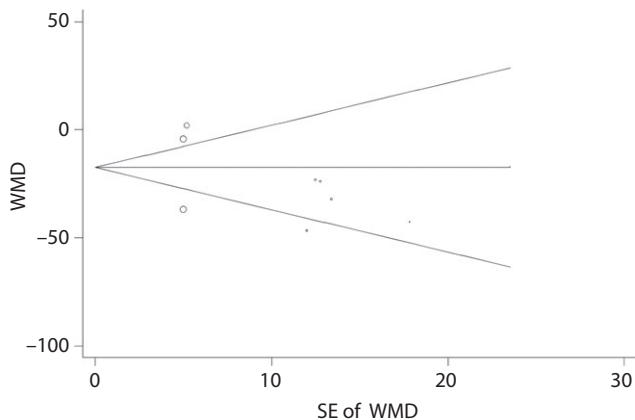

Figure 6 | Publication bias. Begg's funnel plot of pseudo 95% confidence intervals. SE, standard error; WMD, weighted mean differences.

Cochrane Collaboration, which is one of its main strengths. Another major strength is that we enrolled well-designed RCTs with relatively large sample sizes and performed subgroup analyses according to various exclusion criteria, including sample size, Jadad score, duration and region, thereby improving the critical significance of the present findings for clinical practice.

When interpreting the results, several limitations should be taken into account: (i) different characteristics of study participants, yoga forms and protocols, and exercise durations are the most crucial confounders of the RCTs, and could result in risk of bias and heterogeneity; (ii) except for three RCTs[17,18,28], all other RCTs surveyed were not blinded, which could result in performance and detection bias; (iii) considering that 12 RCTs with a wide variation in sample size were incorporated into our analysis, the effects of overestimation of treatment efficiency may be significant; and (iv) missing and unpublished data, as

well as the exclusion of non-English language studies, could result in effect size bias.

In sum, based on the evidence, yoga significantly reduces FBG levels and alters other significant clinical outcomes in patients with type 2 diabetes mellitus. These results support the idea that yoga-based training is a possible alternative exercise for type 2 diabetes mellitus management. However, given the aforementioned limitations and potential bias of our analyses, more large-scale and robust RCTs must be carried out to verify our current findings and substantiate the long-term effects of yoga in type 2 diabetes mellitus patients.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1| Additional information reported in all the randomized controlled trials.

Figure S1| Risk-of-bias analysis. (a) Risk-of-bias graph: the authors' judgments about each risk-of-bias item presented as percentages across all included studies. (b) Risk-of-bias summary: the authors' judgments about each risk-of-bias item for the each included studies.