Systematic Review and Meta-Analysis

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The efficacy and safety of cupping as complementary and alternative therapy for metabolic syndrome

A systematic review and meta-analysis

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Abstract

Introduction: This systematic review and meta-analysis aimed to assess the efficacy and safety of cupping therapy in patients with metabolic syndrome (MetS).

Methods: This systematic review focused on patients with MetS and included randomized controlled trials (RCTs) that compared the effects of cupping therapy with control groups. A total of 12 electronic databases were searched from inception until February 03, 2023. The main outcome after the meta-analysis was waist circumference; the others included anthropometric variables, blood pressure, lipid profile, fasting blood glucose level, and high-sensitivity C-reactive protein level. The incidence of adverse events and the follow-up courses were also evaluated. Risk of bias (ROB) was evaluated using ROB 2.0 from the Cochrane Handbook.

Results: This systematic review included five studies involving 489 patients. Some risks of bias were also identified. The meta-analysis revealed a statistically significance in waist circumference (MD = –6.07, 95% CI: –8.44 to –3.71, $P < .001$, $I^2 = 61\%$, $\tau 2 = 3.4$), body weight (MD = –2.46, 95% CI: –4.25 to –0.68, $P = .007$, $I^2 = 0\%$, $\tau 2 = 0$) and body mass index (MD = –1.26, 95% CI: –2.11 to –0.40, $P = .004$, $I^2 = 0\%$, $\tau 2 = 0$) between the cupping therapy and control groups. However, there were no significant results in total fat percentage and blood pressure values. Regarding biochemical markers, cupping significantly lowered the concentration of low-density lipoprotein cholesterol (MD = –3.98, 95% CI: –6.99 to –0.96, $P = .010$, $I^2 = 0\%$, $\tau 2 = 0$) but had no significant effect on total cholesterol, triglyceride, high-density lipoprotein cholesterol, fasting blood glucose, and high-sensitivity C-reactive protein. 3 RCTs reported no adverse events.

Conclusions: Despite some ROB and low to substantial heterogeneity of the included studies, cupping therapy can be considered a safe and effective complementary intervention for reducing waist circumference, body weight, body mass index, and low-density lipoprotein cholesterol in patients with MetS. In the future, well-designed, high-quality, rigorous methodology, and long-term RCTs in this population are required to assess the efficacy and safety of cupping therapy.

Abbreviations: AEs = adverse events, BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, MD = mean difference, MetS = metabolic syndrome, RCTs = randomized controlled trials, ROB = risk of bias, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WHO = World Health Organization.

Keywords: adverse events, cup, cupping, dysmetabolic syndrome, Hijama, insulin resistance, metabolic syndrome, obesity, safety, syndrome X

L-KW and Y-CC contributed equally to this work.

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1. Introduction

Metabolic syndrome (MetS), also known as dysmetabolic syndrome, or syndrome X, is defined by the World Health Organization (WHO) as a pathological disorder characterized by abdominal obesity, insulin resistance, hypertension, hyperglycemia, and atherogenic dyslipidemia.[1,2] In recent years, the prevalence of MetS has been reported to be 34.7% in the United States and 24.5% in mainland China.[3,4] MetS is associated with an increased risk of diabetes, cardiovascular disease, cerebrovascular diseases, and all-cause mortality, making it a serious public health concern.[3] Although there is some variation in the definition by different authoritative academic institutions, the diagnosis is based on waist circumference, body mass index (BMI), insulin resistance, blood glucose, blood pressure, and lipid profile.[5] Although its pathophysiology is not completely understood, obesity is believed to be at the core of MetS progression.[6] The development of MetS seems to be largely attributable to insulin resistance, excessive fatty acid flux, and proinflammatory states.[7] Insulin resistance is a pathogenic link between different metabolic abnormalities in MetS. It can be induced by different environmental factors such as diet and habits.[8] Lipotoxicity is caused by exposure to toxic levels of fatty acids, which leads to cell damage, and is involved in the pathogenesis of MetS. Adipokines are inflammatory cytokines secreted by adipose tissue. Adipokines are associated with low-grade state of inflammation that may contribute to the development of MetS and obesity-associated diseases.[2,9]

However, the 5 weight loss drugs approved by the Food and Drug Administration of the United States are highly limited in clinical use for MetS because of moderate to severe adverse reactions.[10] As there are insufficient treatments for obesity, complementary and alternative medicines are urgently required.

Cupping therapy is a technique that uses cups placed over the skin to create negative pressure through suction and has been widely used in clinical situations in Asian countries.[11] Cupping therapy was proved to have significant effect on low back pain, ankylosing spondylitis, knee osteoarthritis, neck pain, herpes zoster, migraine, plaque psoriasis, and chronic urticaria by the evidence of systematic review.[12] However, the efficacy of cupping therapy for metabolic syndrome still lacks sufficient evidence. A clinical trial showed cupping combined with diet control had significant effect on lowering BMI, body weight, waist circumference, hip circumference, total cholesterol (TC), triglycerides (TG), and high-sensitivity C-reactive protein (hs-CRP) in obese adult.[13] A randomized controlled trial from China also reported cupping could reduce waist circumference and BMI and lower the level of TC and TG in obese patient.[14] A network meta-analysis from Korea showed cupping plus acupressure was optimal for BMI reduction compared with non-treatment in childhood simple obesity.[15]

The mechanism how cupping can treat obesity is mainly by regulating the expression of pro-inflammatory factors such as hs-CRP, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) to improve insulin resistance and regulate metabolism of the body.[16] Cupping could increase the level of anti-inflammatory factors secreted by adipocytes, such as adiponectin, interleukin-10 (IL-10), and secreted frizzled related protein 5 (SFRP5).[16] Ahmed et al[17] investigated the effects of wet cupping therapy on inflammatory and immunological parameters in patients with rheumatoid arthritis. A significant reduction in the erythrocyte sedimentation rate and hs-CRP level was observed in the wet cupping group. Current research showed cupping intervention might benefit simple obesity by increasing blood circulation, regulating immune system, and reducing inflammation.[16] Recently, randomized controlled trials (RCTs) evaluated the efficacy of cupping for MetS. However, the results of different trials are controversial. Therefore, our study aimed to assess the efficacy of cupping for MetS using a systematic review and meta-analysis.

2. Materials and methods

This systematic review and meta-analysis was registered with PROSPERO (ID: CRD42022352216) on August 19, 2022, without amendments between the registration and the final article. The study was conducted in accordance with the PRISMA guidelines but without a published protocol. This study focused on RCTs examining the efficacy of cupping therapy in patients with MetS.

2.1. Search strategy

Nine English databases (PubMed, Embase, Cochrane, Alt HealthWatch, CINAHL, Medline, Health Source, Web of Science, Health and Psychosocial Instruments), 3 clinical trials repository (Clinical Trials.gov, World Health Organization International Clinical Trials Registry Platform, International Standard Randomised Controlled Trial Number) and 3 Chinese databases (CNKI, WanFang, and AiritiLibrary) were searched for RCTs published from database inception through February 03, 2023. The search strategy consisted of 2 components: Metabolic Syndrome (Metabolic Syndrome OR Plurimetabolic syndrome OR Dysmetabolic syndrome OR syndrome X OR insulin resistance) and Cupping (Cupping or Cups or Hijama or Al-Hijamah) (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/I690, which illustrates the search strategy carried out in each database). To establish the eligibility of the studies, 2 reviewers (L.-K.W. and C.-Y.Y.) independently screened the records of the comprehensive searches by titles and abstracts or full text, as needed. If there is a disagreement, a third reviewer (Y.-C.C.) will help resolve this controversy.

2.2. Inclusion criteria

1) Only randomized controlled trials (RCTs) reporting clinical efficacy comparing cupping intervention to non-cupping control group in Mets were included.
2) The included population was diagnosed with metabolic syndrome by a physician clinically, or met the diagnostic criteria for metabolic syndrome by international authoritative academic institutions, including WHO, National Cholesterol Education Program, American Heart Association, International Diabetes Federation, European Group for the Study of Insulin Resistance, American Association of Clinical Endocrinology, Chinese Society of Cardiology, and Chinese Diabetes Society.
3) Participants for inclusion should be primary MetS rather than comorbidity.
4) Eligible interventions comprise various cupping therapy (cupping, dry cupping, wet cupping, bleeding cupping, fire cupping, herbal cupping, moving cupping, needling cupping, Hijama or Al-Hijamah) with or without standard treatment for MetS.
5) Eligible control groups were sham cupping, blank control group, waiting group or standard treatment of MetS.
6) For outcome measurement, studies had to assess the resolution of metabolic syndrome. Primary outcome was the anthropometric parameter after the cupping intervention such as waist circumference, body weight, body mass index, or total fat percentage. Secondary outcomes could be metabolic parameters such as blood pressure values, lipid profile values, or biochemical markers.

2.3. Exclusion criteria

1) MetS belong to secondary metabolic diseases, such as hypothalamic lesions, hypothyroidism, polycystic ovary syndrome and Cushing syndrome.

2) Intervention group comprising more than Cupping therapy or standard care of MetS.

2.4. Data extraction and quality assessment

Two reviewers (L.-K.W. and C.-Y.Y) independently extracted the data, and a third reviewer (Y.-C.C.) was consulted if there was any disagreement. We recorded the first author, year of publication, type of study, location, sample size, age, sex, course of disease, diagnosis for inclusion, details of the intervention and control groups, treatment duration, outcome measures, adverse events (AEs), and follow-up (Table 1). Where data were missing or unclear, the corresponding authors were contacted via email to request for missing data. Extracted data were converted to the same unit, for example, from mmol/L to mg/dL, when measuring triglycerides. We assumed that the units of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) should be mg/dL rather than mmol/L in the study by Farahmand et al[18] because of the normal range of laboratory values.

For critical appraisal, the methodological quality of the included studies was evaluated by 2 reviewers (L.-K.W. and C-Y. Y) independently using the assessment tool for Risk of Bias 2.0, from the Cochrane Handbook for Systematic Reviews of Interventions.[23,24] In addition, the level of evidence was analyzed using the GRADEpro Guideline Development tool (developed by Evidence Prime Inc.).[25] Any assessment discrepancies between reviewers were resolved via discussion or by a third reviewer (Y.-C. C).

2.5. Data synthesis and analysis

The population size, mean, and standard deviation values at the end of treatment for cupping-induced changes in anthropometric parameters and biochemical markers were subjected to meta-analyses. The primary outcome was the mean difference (MD) in waist circumference with a 95% confidence interval (CI). Other outcome measures included anthropometric variables (weight, body mass index, and total fat percentage), blood pressure (systolic and diastolic blood pressures), lipid profile (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein), fasting blood glucose, and high-sensitivity C-reactive protein (hs-CRP). The incidence of AEs and follow-up course were also investigated. A random-effects model was employed to pool the MDs using the R software (version 4.2.1; 2022, Vienna, Austria).[26] Heterogeneity between trials was determined using the tau square (τ^2) and I square (I^2) test, I^2 values > 50% indicating high heterogeneity. If considerable heterogeneity was observed, meta-regression and subgroup analyses were performed. Funnel plots and Egger's tests were used to examine potential publication bias. Statistical significance was set at $P < .05$. Sensitivity analysis was performed by reanalyzing with omitting any of the included studies to determine the robustness of the observed outcomes.

Table 1

Main characteristics of the included studies.

1st author, year	Sample size (I/C)	Age ranges (I/C)	Mean ages (I/C)	M:F	Course of disease (I/C)	Diagnosis for inclusion	Intervention	Control	Outcome measures	Adverse event (I/C)	Follow up	Location
Farahmand (2012)[18]	126 (63/63)	18–65	45.1/47.1	NM	NM	Physician diagnosed	Wet Cupping + dietary advice	Dietary advice	1) Anthropometric: weight, BMI, WC, HC, W: Hip, SBP, DBP 2) Laboratory: FBG, TC, TG, HDL-C, LDL-C, Fat %, total body fat mass	No Adverse event	6 wk	Iran
Farahmand (2014)[19]	126 (63/63)	18–65	NM	NM	NM	Physician diagnosed	Wet Cupping + dietary advice	Dietary advice	hs-CRP, Hsp 27 antibody	No Adverse event	6 wk	Iran
Wang (2015)[20]	60 (30/30)	19–46	31.5/30.6	52:8	1–10 yr	CSC Criteria 2007	Fire Cupping + needle cupping + manipulation + herb	Herb	1) Anthropometric: weight, BMI, WC, W:H, Fat %, SBP, DBP 2) Laboratory: FBG, TC, TG, HDL-C, LDL-C, hs-CRP, HOMA-IR, Chemerin, LP, Ob-R, TNF-α, ER	No Adverse event	4 wk	China
Liang (2019)[21]	75 (25/25/25)	25–70	47.9/51.8/51.2	16:59	NM	CDS Criteria 2013	1. Fire Cupping + moving cupping with ointment 2. Acup	Waiting group	WC, SBP, DBP, FBG, 2hBG, TG, HDL-C, Subcutaneous fat thickness, MetS prevalence	NM	Nil	China
Zhou (2021)[22]	102 (51/51)	Nil	45.6/44.9	60:42	3.4/3.4 yr	IDF Criteria	Moving Cupping + Acup	Acup	Weight, BMI, WC, W: Hip, AFT, VAI	NM	Nil	China

2hBG = 2 hours postprandial blood glucose, Acup = acupuncture, AFT = abdominal fat thickness, BMI = body mass index, CDS = Chinese Diabetes Society, CSC = Chinese Society of Cardiology, DBP = diastolic blood pressure, ER = effective rate, Fat% = Body Total Fat percentage, FBG = fasting blood glucose, HDL-C = high density lipoprotein cholesterol, herb = Traditional Chinese herbal medicine, HOMA-IR = Homeostasis Model Assessment-Insulin Resistance index, hs-CRP = high sensitivity C-reactive protein, IDF = International Diabetes Federation, LDL-C = low density lipoprotein cholesterol, LP = leptin, MetS = metabolic syndrome, NM = not mentioned, Ob-R = obese gene receptor, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, TNF-α = tumor necrosis factor-alpha, VAI = visceral adiposity index, W:H = waist:height, W:Hip = waist:hip circumference ratio, WC = waist circumference.

3. Results

3.1. Study search and characteristics

We retrieved 1323 non-duplicate citations and excluded 943 records based on their titles and abstracts. We included five studies after eliminating the remaining 375 articles that did not meet the inclusion criteria (Fig. 1). In total, 116 studies that did not include RCTs were excluded.[27] A total of 259 articles were excluded due to an irrelevant study design.[28]

Three of the included articles were published in journals with a science citation index,[18,19,21] while another article was a doctoral dissertation.[20] 2 trials were conducted in Iran, and 3 in China.[18–22] Table 1 summarizes the study characteristics and details of the methodology used in the five included studies.

3.2. Risk of bias in the included studies

The risk of bias (ROB) assessment is shown in Figure 2. Five of the included RCTs were associated with some concerns. The main reason was the lack of reporting allocation sequence concealment during the randomization process. 3 RCTs assessed some concerns regarding bias due to missing outcome data domains. These 3 RCTs had several participants lost to follow-up and failed to complete the intention-to-treat analysis.

3.3. Outcome of interventions

3.3.1. Anthropometrics. Our primary outcome was the MD and 95% CI of waist circumference after the cupping intervention. Compared to the control group, the cupping therapy group displayed a significantly lower waist circumference after treatment (MD = −6.07, 95% CI: −8.44 to −3.71, $P < .001$, $I^2 = 61\%$, $\tau^2 = 3.4$). Four studies addressing the meta-analysis of primary outcomes were all with some concerns risk of bias. Secondary outcomes such as body weight (kg) (MD = −2.46, 95% CI: −4.25 to −0.68, $P = .007$, $I^2 = 0\%$, $\tau^2 = 0$) and Body Mass Index (MD = −1.26, 95% CI: −2.11 to −0.40, $P = .004$, $I^2 = 0\%$, $\tau^2 = 0$) also showed significant results between cupping therapy group and control group. After meta-analysis, total fat percentage showed non-significant results (MD = −1.49, 95% CI: −4.51 to 1.54, $P = .336$, $I^2 = 63\%$, $\tau^2 = 3.1$), but tended to favor cupping (Fig. 3).

3.3.2. Blood pressure. Meta-analyses revealed no significant evidence of the effects of cupping compared with the control group on systolic blood pressure (SBP) (MD = −1.97, 95% CI: −4.85 to 0.92, P = .181, $I^2 = 0\%$, $\tau^2 = 0$) and diastolic blood pressure (DBP) (MD = 0.05, 95% CI: −2.58 to 2.68, P = .969, $I^2 = 0\%$, $\tau^2 = 0$) (Fig. 4).

3.3.3. Lipid profile. For LDL-C, cupping therapy had a significant effect on lowering the LDL-C blood concentration (MD = −3.98, 95% CI: −6.99 to −0.96, $P = .010$, $I^2 = 0\%$, $\tau^2 = 0$). It showed non-significant results about the effect of cupping on TC, TG, and HDL-C (Fig. 5).

3.3.4. Blood sugar. The MD and 95% CI of fasting blood glucose (FBG) after the meta-analysis showed non-significance with high heterogeneity (MD = −9.18, 95% CI: −25.46 to 7.10, $P = .269$, $I^2 = 90\%$, $\tau^2 = 173.4$) (Fig. 6).

3.3.5. hs-CRP. There was a non-significant result, but with a tendency to favor the cupping group for hs-CRP (MD = −0.10, 95% CI: −0.23 to 0.03, $P = .131$, $I^2 = 0\%$, $\tau^2 = 0$) (Fig. 6).

3.4. Adverse events

Three of the 5 RCTs reported no AEs during the research period,[18–20] while Liang et al and Zhou did not mention safety-related data during trials.[21,22] Wang[20] reported that there were no abnormalities in the blood test, urine test, stool test, or

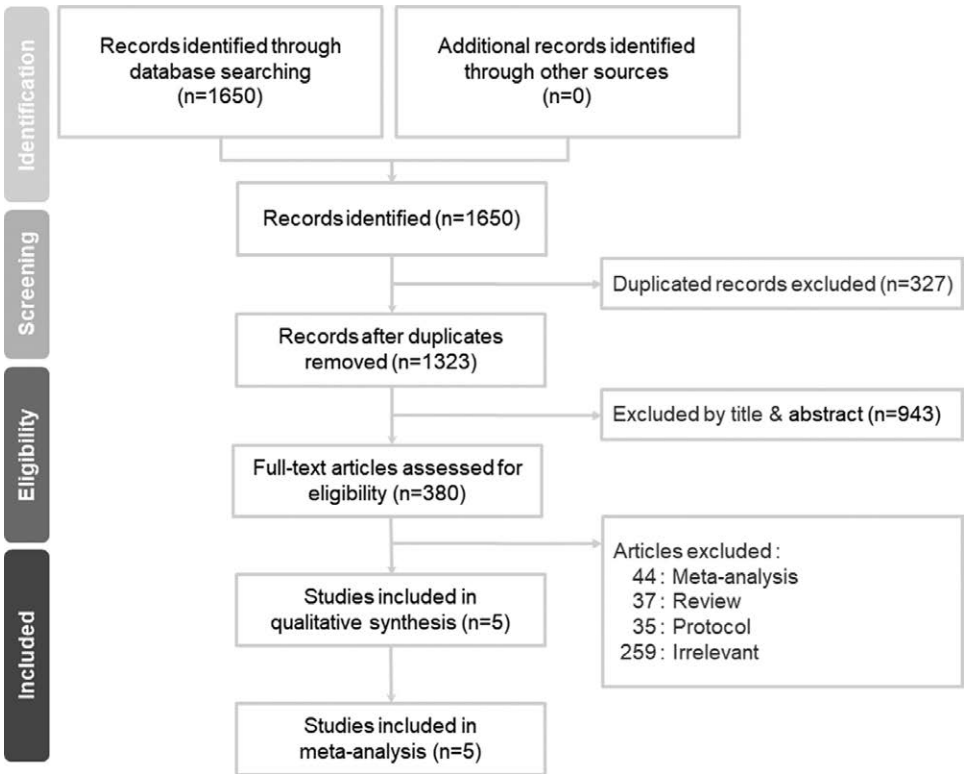

Figure 1. PRISMA flow diagram for the searching and identification of included studies.

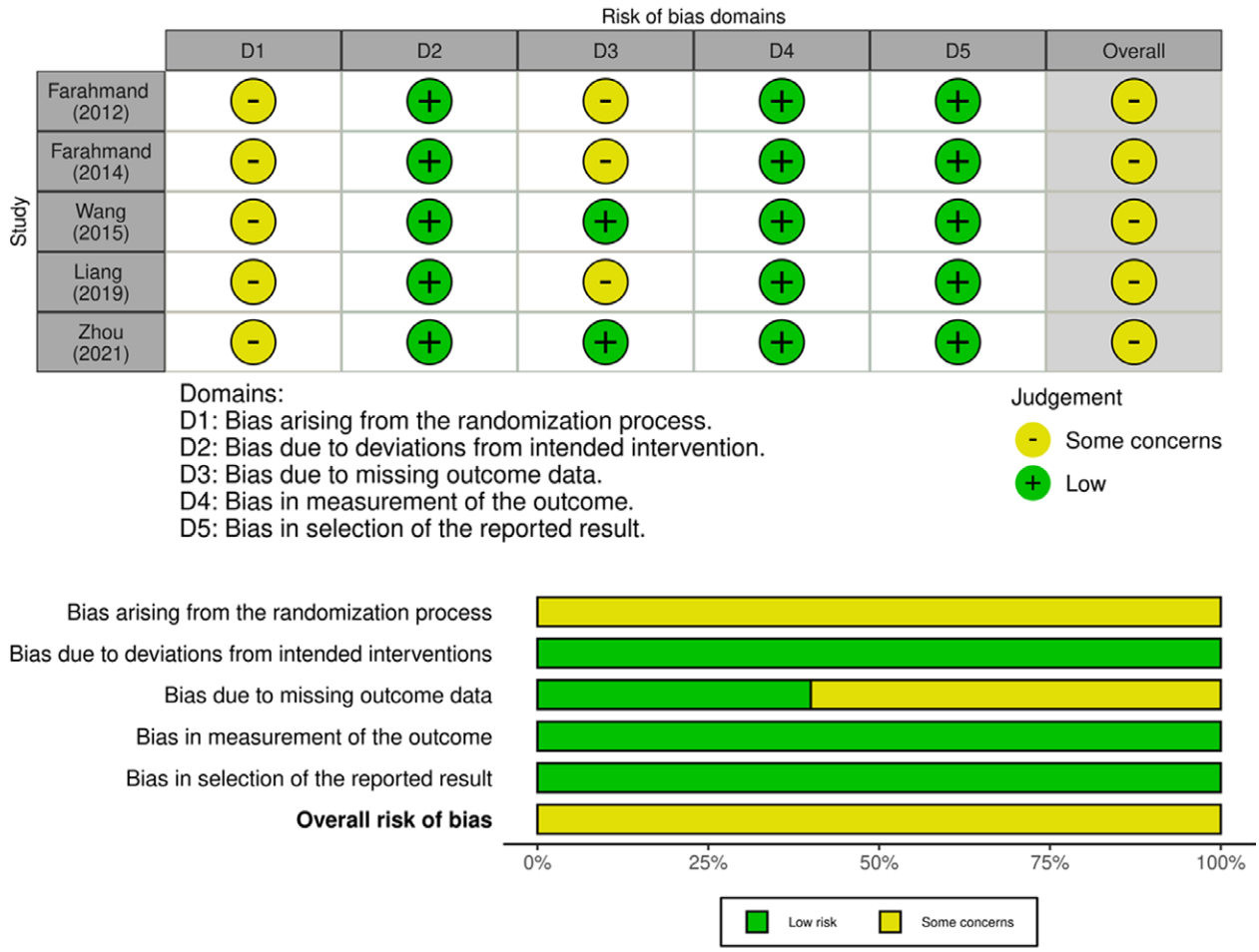

Figure 2. Cochran Risk of Bias 2.0 assessment for included studies.

function of the heart, liver, and kidney. No local skin injuries, infections, scalding, or allergies were observed.[20]

3.5. Follow-up

Wang[20] reported that the Traditional Chinese medicine symptom score of MetS still made a significant difference after 4 weeks of follow-up (cupping: control = 16.4 ± 2.1: 26.1 ± 3.4, $P < .05$). This indicates that cupping therapy has long-term effects on MetS.

3.6. Cupping parameters

The details of the cupping procedures, including the treatment period, total number of treatments, frequency of treatment, cupping retention time, number of cupping points, and cupping point selection, are summarized in Table 2. The most common selected point was the Zhongwan (Ren-12) in the conception vessel and the trapezius muscle between the 2 scapulae.

3.7. Heterogeneity analysis

Substantial heterogeneity was found after meta-analysis of the waist circumference of the cupping therapy group compared with that of the control group ($I^2 = 61\%$, $\tau^2 = 3.4$). Heterogeneity was still severe in the results for total fat percentage and TC, TG, HDL-C, and FBG levels. Low to moderate heterogeneity was observed in the results of weight, BMI, SBP, DBP, LDL-C, and hs-CRP levels. After meta-regression, heterogeneity came from the variable "Location" (see Graph S2, Supplemental Digital Content, http://links.lww.com/MD/I691, which illustrates the result of meta-regression of the mean difference in waist circumference). Thus, subgroup analysis by "Location" was performed, and the residual heterogeneity of I^2 decreased to 0.0% (see Graph S3, Supplemental Digital Content, http://links.lww.com/MD/I692, which illustrates subgroup analysis by location of waist circumference in the meta-analysis).

3.8. Sensitivity analysis

We performed sensitivity analyses for each of the parameters by omitting any of the included studies. For example, regarding the outcome of waist circumference, the meta-analysis results remained significant (MD = −6.33, 95% CI: −10.59 to −2.07, $P < .01$, $I^2 = 72\%$, $\tau^2 = 10.6$) after omitting the study by Zhou.[22] We confirmed that the results obtained from these sensitivity analyses were consistent with those without omitting studies (see Graph S4, Supplemental Digital Content, http://links.lww.com/MD/I693, which illustrates the sensitivity analyses for each of the parameters by omitting any of the included studies), which showed the robustness of our assessment.

3.9. GRADE certainty of evidence

The level of evidence, as assessed by GRADEpro,[25] is shown in Table 3. The quality of evidence was moderate for the waist circumference assessment because of the inconsistency caused by considerable heterogeneity ($I^2 = 61\%$, $\tau^2 = 3.4$). For weight, BMI, LDL-C, the quality of evidence was high because of the

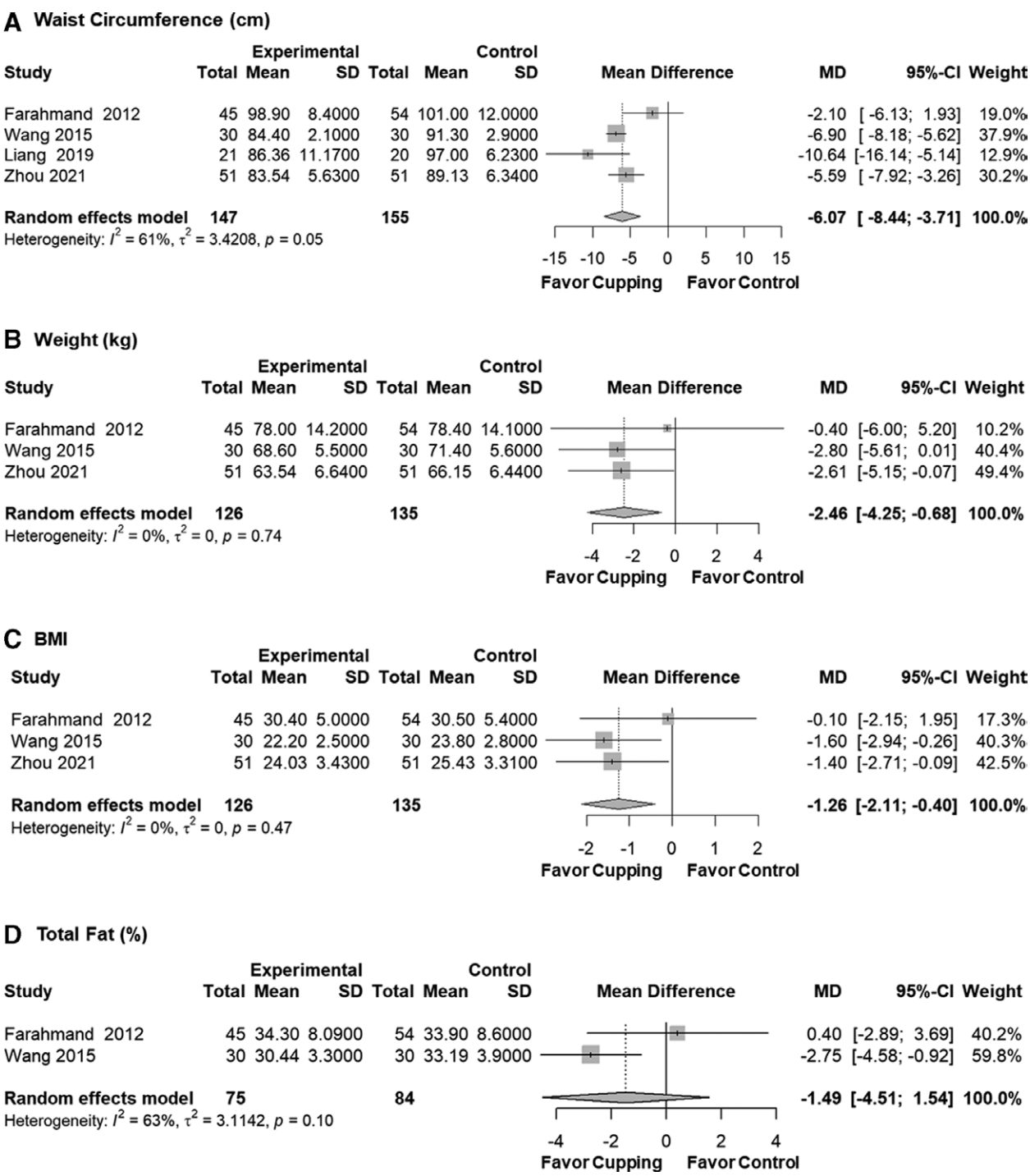

Figure 3. Anthropometric results after meta-analysis by mean difference. BMI = body mass index, CI = confidence interval, MD = mean difference.

low heterogeneity without study limitations, inconsistency, indirectness, imprecision, or publication bias.

4. Discussion

4.1. Summary of evidence

To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the efficacy of cupping therapy for MetS. Five RCTs, involving 489 participants, were included in this study. The pooled metabolic parameter data showed that cupping had a significant effect on waist circumference, body weight, and BMI, but not significant on total fat percentage and blood pressure. As for biochemical markers, cupping significantly lowered the concentration of LDL-C, but had no effect on total cholesterol, triglyceride, HDL-C, fasting blood glucose, and hs-CRP. In addition, cupping therapy had a long-term effect on follow-up, without AEs. In evidence-based medicine, there is very little evidence of cupping therapy for metabolic indices. In previous study, wet cupping was shown to improve fatty liver severity and homeostatic model assessment for insulin resistance in patients with nonalcoholic fatty liver disease.[29] By reducing insulin resistance, wet cupping can potentially relieve MetS. A few small and poor methodological studies have suggested that wet cupping alone significantly reduces blood pressure compared with antihypertensive medication.[30] In a randomized controlled

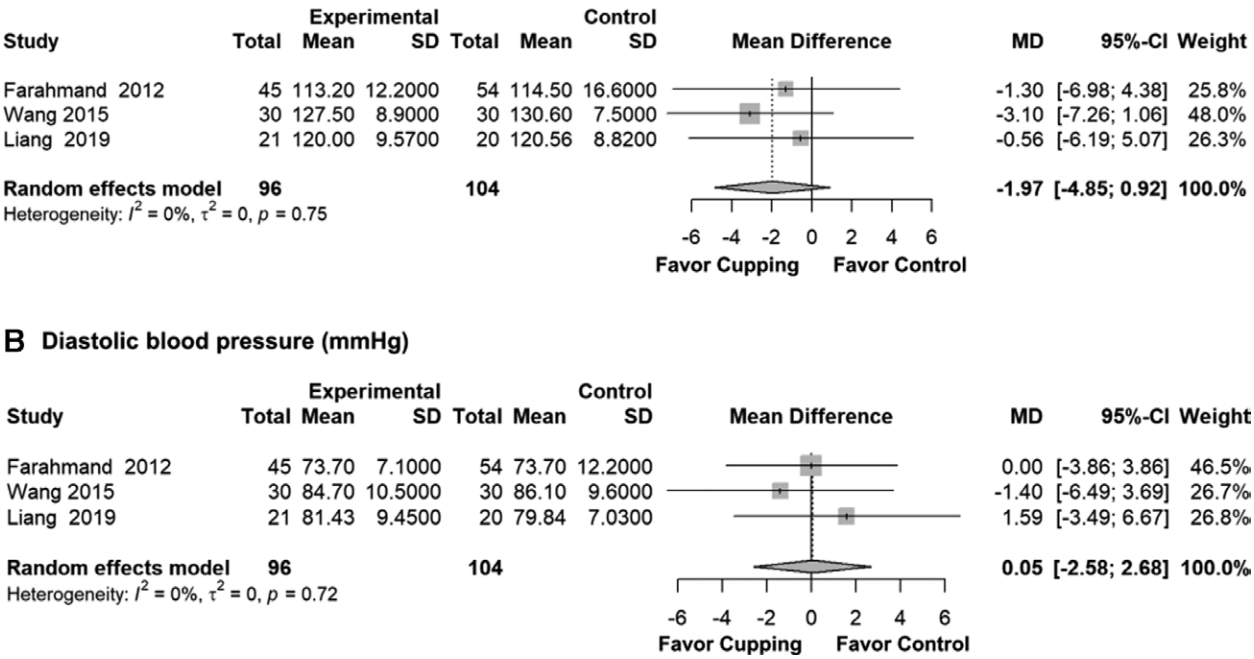

Figure 4. Blood pressure results after meta-analysis by mean difference. CI = confidence interval, MD = mean difference.

clinical trial, the cupping and acupoint catgut embedding group had significant differences compared with the acupoint catgut embedding group alone in the weight, waist circumference, hip circumference, leptin and leptin-adiponectin ratio of simple obesity patients.[31] Based on the results of our meta-analysis, cupping therapy can be considered a safe and effective complementary intervention for reducing waist circumference, body weight, BMI, and LDL-C levels in patients with MetS.

4.2. Pathophysiology and mechanism

Although the mechanism by which cupping influences MetS remains unclear, there are 3 deductions based on evidence-based medicine. First, a previous randomized clinical trial suggested that wet cupping might be an effective method for reducing LDL-C levels in healthy young men.[32] Farahmand et al and Wang revealed that cupping tended to lower LDL-C levels in patients with MetS,[18,20] but these results were not statistically significant. After our meta-analysis, cupping significantly reduced the LDL-C concentration in Mets. By lowering blood LDL-C levels, cupping may have a protective effect against atherosclerosis and the progression of MetS. Second, an increasing number of studies have demonstrated that obesity and MetS are related to chronic inflammation and oxidative status.[33] In a mice study, the anti-inflammatory lipids such as Prostaglandin E1 (PGE1) and 5,6 epoxyeicosatrienoic acid (5,6-EET) were significantly increased while pro-inflammatory lipids such as hydroxyeicosatetraenoic acid (12-HETE) and Thromboxane B2 (TXB2) were deceased after cupping treatment. A significant reduction in the erythrocyte sedimentation rate and hs-CRP level was observed in the wet cupping group compared to control group of Ahmed et al[17] study in patients with rheumatoid arthritis. By reducing inflammation, wet cupping may have the potential to treat chronic inflammatory diseases such as MetS. Third, adipokines play crucial roles in the regulation of metabolism. In humans, "chemerin" is a newly discovered adipokine that is involved in inflammation, adipogenesis, angiogenesis, and energy metabolism.[34] Wang[20] showed that fire cupping and needle cupping can significantly reduce the level of chemerin in patients with MetS compared with the control group. Cupping might regulate body metabolism by lowering chemerin concentration.[20]

Our systematic review and meta-analysis showed cupping therapy significantly decrease waist circumference, body weight, body mass index, and LDL-C level. The extract mechanisms underlying the beneficial effects of cupping therapy remain unclear. However, previous investigators have postulated theories to explain the clinical benefits of cupping therapy in this study. These theories include the "activation of immune system," which lead to immunological effects and hormonal adjustments and "blood detoxification," which results in releasing of toxins and removal of wastes.[35] The investigators also suggested the notion that these theories may overlap or work interchangeably to produce various therapeutic effects in specific diseases.[35]

Previous findings regarding the therapeutic effects of cupping therapy are mostly positive in population with metabolic syndrome, but are controversial in healthy population. A randomized controlled trial in obese patient reported cupping could reduce waist circumference, BMI, and the level of TC and TG.[14] However, the improvements of other anthropometric or metabolic parameters were not observed. In a randomized controlled trial of healthy young men population, it was found that a substantial decrease in LDL-C and in the LDL-C/HDL-C ratio in the wet cupping group compared to the control, whereas no statistically significant effects were noted in TG, TC, and HDL-C.[32] Thus, the differences in the population studied, sampling size, follow-up time, treatment time and heterogeneity of the cupping method may all contribute to the differences in the therapeutic effects of cupping therapy.

4.3. Heterogeneity

Substantial heterogeneity was found among the included RCTs in the meta-analysis result of waist circumference. After meta-regression, heterogeneity came from the variable "Location." Subgroup analysis by variable "Location" was performed, and

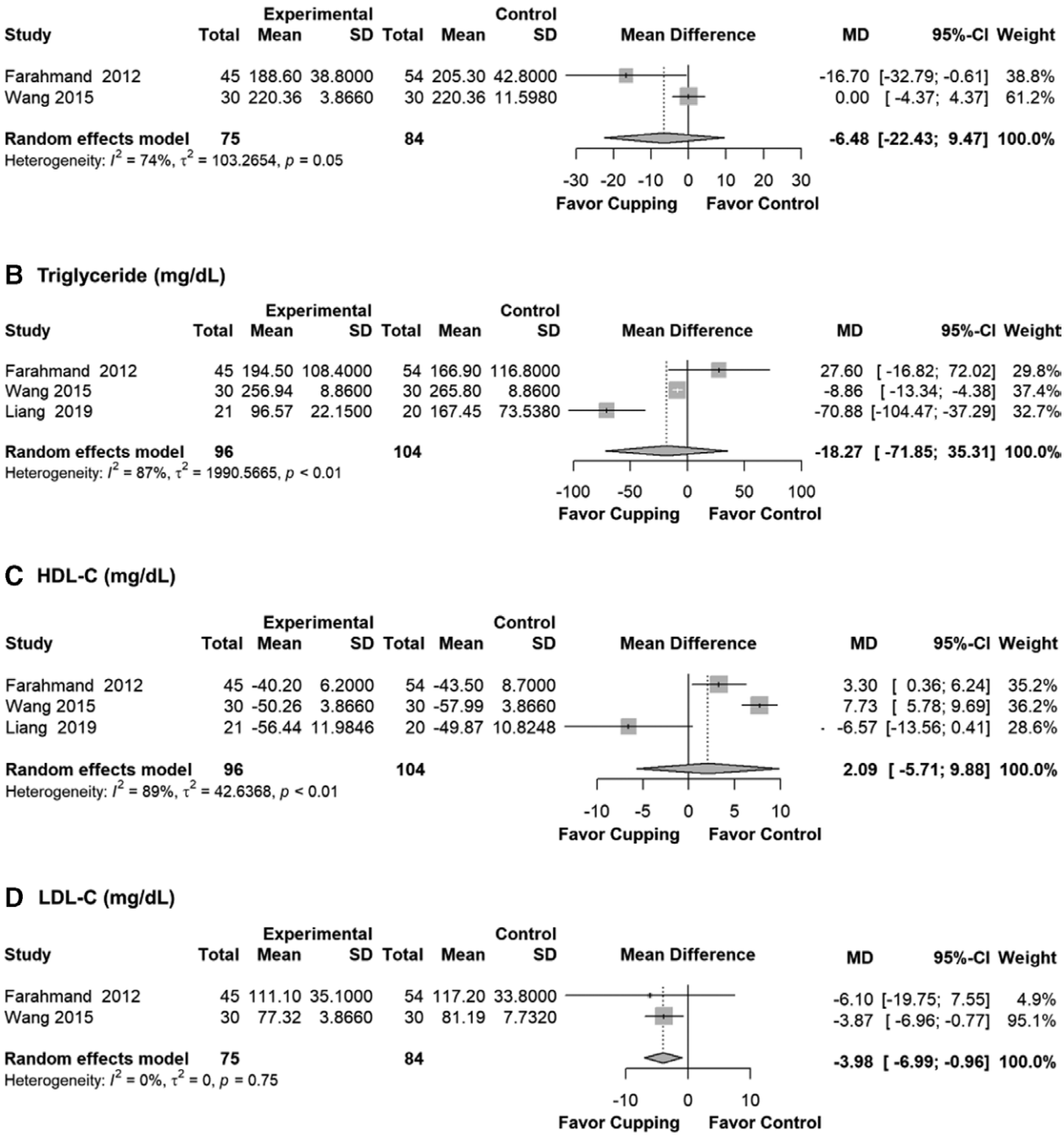

Figure 5. Lipid profile results after meta-analysis by mean difference. CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MD = mean difference.

the residual heterogeneity decreased to 0.0%. Low to moderate heterogeneity was observed in the results of weight, BMI, SBP, DBP, LDL-C, and hs-CRP levels. However, heterogeneity was still severe in the results for total fat percentage and TC, TG, HDL-C, and FBG levels. Heterogeneity between studies may have arisen from the clinical perspective or study design, such as differences in cupping methods, cupping point selection, treatment frequency, or treatment course.

4.4. Implications for clinical practice and future research

The results of this meta-analysis can be applied only to patients with MetS. Based on these results, no conclusive recommendations can be made regarding cupping therapy for the parameters of MetS. Despite some ROB and low to substantial heterogeneity of the included studies, cupping therapy can be considered a safe and effective complementary intervention for reducing waist circumference, body weight, BMI, and LDL-C in individuals with MetS. Cupping might be a complementary and alternative treatment for patients with AEs associated with weight loss drugs. By previous studies, acupuncture has been proven beneficial in the treatment of MetS and could serve as an alternative therapy for MetS-associated conditions.[36] However, fear of acupuncture needles limits the utilization of acupuncture. Thus, an increasing number of Traditional Chinese medicine

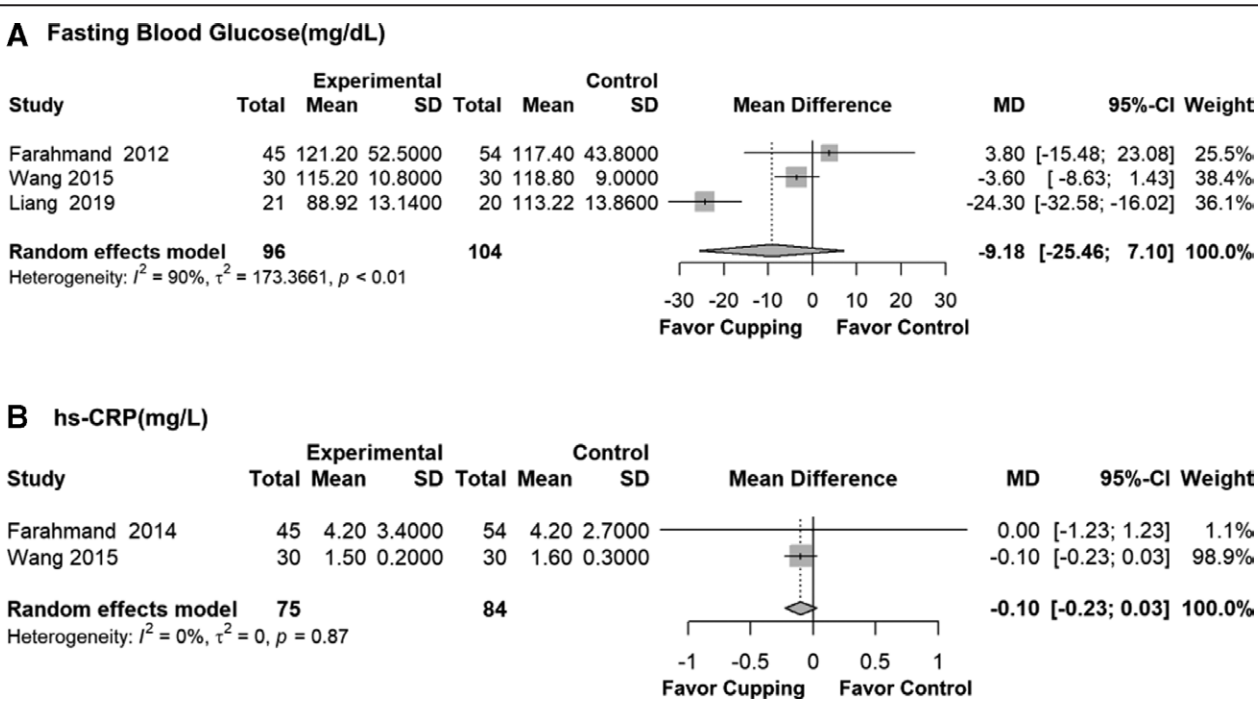

Figure 6. Biochemical marker results after meta-analysis by mean difference. CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, MD = mean difference.

Table 2

Details of the cupping method.

1st author year	Treatment period	Frequency of treatment	Total number of treatments	Cupping retention times	Number of cupping points	Cupping points selection
Farahmand (2012)[18]	12 wk	Once per 6 wk	2	NM	Several	Between 2 scapulae (T1–T3)
Farahmand (2014)[19]	12 wk	Once per 6 wk	2	NM	Several	Trapezius muscle near scapular spine
Wang (2015)[20]	60 d	Everyday	60	30 min	2	Zhongwan (Ren-12), Shuifen (Ren-9)
Liang (2019)[21]	8 wk	Twice per week	16	5 min	6–8	Zhongwan (Ren-12), Qihai (Ren-6) Tianshu (St-25, B), Daimai(GB-26, B), Liangmen (St-21, B), Shuidao (St-28, B)
Zhou (2021)[22]	30 d	Once every 2 d	15	5–10 min	Several	Abdomen around the umbilicus

B = bilateral, NM = not mentioned.

doctors are currently treating MetS by cupping. In the future, well-designed, high-quality, rigorous methodology, and long-term RCTs are required to assess the efficacy and safety of cupping therapy in patients with MetS. Future RCTs should ensure adequate randomization, allocation sequence concealment, intention-to-treat analysis, and blinding of the outcome assessors.

4.5. Limitations

This systematic review and meta-analysis had 3 main limitations. First, only 5 RCTs met the inclusion criteria were included. More RCTs evaluating the efficacy of cupping for MetS are required in the future. Second, the original heterogeneity of the MD on waist circumference after meta-analysis was high (I^2 = 61%). After subgroup analysis by variable "Location," the residual heterogeneity by *I*-square decreased to 0.0%. Third, there are various cupping methods, including dry cupping, wet cupping, bleeding cupping, fire cupping, flash cupping, herbal cupping, moving cupping, retained cupping, needling cupping, Hijama, and Al-Hijamah. Therefore, the efficacy and function of cupping should be discussed in more detail.

5. Conclusions

After meta-analysis, the pooled data of metabolic indices showed that cupping had a significant effect on waist circumference, body weight, BMI, and LDL-C, with moderate to high certainty of evidence. Cupping had no significant effect on total fat percentage, SBP, DBP, total cholesterol, triglyceride, HDL-C, fasting blood glucose, and hs-CRP in Mets patients. Despite some ROB and low to substantial heterogeneity of the included studies, cupping therapy can be considered a safe and effective complementary intervention for reducing waist circumference, body weight, BMI, and LDL-C in individuals with MetS. In the future, well-designed, high-quality, rigorous methodology, and long-term RCTs in this population are required to assess the efficacy and safety of cupping therapy.

Table 3

GRADE certainty of evidence of outcomes.

Outcomes	Number of participants (studies)	Illustrative comparative risks* (95% CI)		Absolute effect (95% CI)	Certainty of evidence (GRADE)
		Control	Cupping		
Waist circumference (cm)	302 (4 studies)	The mean WC loss in the control groups ranged from 3.9 lost to 0.33 lost	The mean WC loss in the intervention groups was 6.07 lower than control group	MD 6.07 lower (8.44–3.71 lower)	⊕⊕⊕⊖ moderate
Weight (kg)	261 (3 studies)	The mean Weight loss in the control groups ranged from 2.9 lost to 7.9 lost	The mean Weight loss in the intervention groups was 2.46 lower than control group	MD 2.46 lower (4.25–0.68 lower)	⊕⊕⊕⊕ high
BMI	261 (3 studies)	The mean BMI loss in the control groups ranged from 1.3 lost to 2.5 lost	The mean BMI loss in the intervention groups was 1.26 lower than control group	MD 1.26 lower (2.11–0.40 lower)	⊕⊕⊕⊕ high
Total fat (%)	159 (2 studies)	The mean total Fat loss in the control groups ranged from 0.2 lost to 1.29 lost	The mean total Fat loss in the intervention groups was 1.49 lower than control group	MD 1.49 lower (4.51 lower–1.54 higher)	⊕⊕⊖⊖ low
SBP (mm Hg)	200 (3 studies)	The mean SBP loss in the control groups ranged from 9.7 lost to 2.78 gain	The mean SBP loss in the intervention groups was 1.97 lower than control group	MD 1.97 lower (4.85 lower–0.92 higher)	⊕⊕⊕⊖ moderate
DBP (mm Hg)	200 (3 studies)	The mean DBP loss in the control groups ranged from 6 lost to 0.06 gain	The mean DBP loss in the intervention groups was 0.05 higher than control group	MD 0.05 higher (2.58 lower–2.68 higher)	⊕⊕⊕⊖ moderate
TC (mg/dL)	159 (2 studies)	The mean TC loss in the control groups ranged from 19.3 lost to 3.1 gain	The mean TC loss in the intervention groups was 6.48 lower than control group	MD 6.48 lower (22.43 lower–9.47 higher)	⊕⊕⊖⊖ low
TG (mg/dL)	200 (3 studies)	The mean TG loss in the control groups ranged from 71.9 lost to 18.6 lost	The mean TG loss in the intervention groups was 18.27 lower than control group	MD 18.27 lower (71.85 lower to 35.31 higher)	⊕⊖⊖⊖ very low
HDL-C (mg/dL)	200 (3 studies)	The mean HDL-C gain in the control groups ranged from 5.0 lost to 15.5 gain	The mean HDL-C gain in the intervention groups was 2.09 higher than control group	MD 2.09 higher (5.71 lower–9.88 higher)	⊕⊖⊖⊖ very low
LDL-C (mg/dL)	159 (2 studies)	The mean LDL-C loss in the control groups ranged from 15.4 lost to 0.9 lost	The mean LDL-C loss in the intervention groups was 3.98 lower than control group	MD 3.98 lower (6.99 lower–0.96 lower)	⊕⊕⊕⊕ high
FBG (mg/dL)	200 (3 studies)	The mean FBG loss in the control groups ranged from 21.6 lost to 8.3 gain	The mean FBG loss in the intervention groups was 9.18 lower than control group	MD 9.18 lower (25.46 lower–7.10 higher)	⊕⊖⊖⊖ very low
hs-CRP (mg/L)	159 (2 studies)	The mean hs-CRP loss in the control groups ranged from 0.6 lost to 0.2 lost	The mean hs-CRP loss in the intervention groups was 0.10 lower than control group	MD 0.10 lower (0.23 lower–0.03 higher)	⊕⊕⊕⊖ moderate

Population: patients with metabolic syndrome/Intervention: cupping therapy/Comparison: control group.

BMI = body mass index, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL-C = high density lipoprotein cholesterol, hs-CRP = high sensitivity C-Reactive Protein, LDL-C = low density lipoprotein cholesterol, MD = mean difference, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WC = waist circumference.

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