RESEARCH
Systematic Review

# Effect of Dietary Acetic Acid Supplementation on Plasma Glucose, Lipid Profiles, and Body Mass Index in Human Adults: A Systematic Review and Meta-analysis

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**ABSTRACT**

**Background** Acetic acid is a short-chain fatty acid that has demonstrated biomedical potential as a dietary therapeutic agent for the management of chronic and metabolic illness comorbidities. In human beings, its consumption may improve glucose regulation and insulin sensitivity in individuals with cardiometabolic conditions and type 2 diabetes mellitus. Published clinical trial evidence evaluating its sustained supplementation effects on metabolic outcomes is inconsistent.

**Objective** This systematic review and meta-analysis summarized available evidence on potential therapeutic effects of dietary acetic acid supplementation via consumption of acetic acid–rich beverages and food sources on metabolic and anthropometric outcomes.

**Methods** A systematic search was conducted in Medline, Scopus, EMBASE, CINAHL Plus, and Web of Science from database inception until October 2020. Randomized controlled trials conducted in adults evaluating the effect of dietary acetic acid supplementation for a minimum of 1 week were included. Meta-analyses were performed using a random-effects model on fasting blood glucose (FBG), triacylglycerol (TAG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), body mass index (BMI), and body fat percentage. Statistical heterogeneity was assessed by calculation of Q and $I^2$ statistics, and publication bias was assessed by calculation of Egger's regression asymmetry and Begg's test.

**Results** Sixteen studies were included, involving 910 participants who consumed between 750 and 3600 mg acetic acid daily in interventions lasting an average of 8 weeks. Dietary acetic acid supplementation resulted in significant reductions in TAG concentrations in overweight and obese but otherwise healthy individuals (mean difference [MD] = −20.51 mg/dL [95% confidence intervals = −32.98, −8.04], $P = .001$) and people with type 2 diabetes (MD = −7.37 mg/dL [−10.15, −4.59], $P < .001$). Additionally, acetic acid supplementation significantly reduced FBG levels (MD = −35.73 mg/dL [−63.79, −7.67], $P = .01$) in subjects with type 2 diabetes compared with placebo and low-dose comparators. No other changes were seen for other metabolic or anthropometric outcomes assessed. Five of the 16 studies did not specify the dose of acetic acid delivered, and no studies measured blood acetate concentrations. Only one study controlled for background acetic acid-rich food consumption during intervention periods. Most studies had an unclear or high risk of bias.

**Conclusion** Supplementation with dietary acetic acid is well tolerated, has no adverse side effects, and has clinical potential to reduce plasma TAG and FBG concentrations in individuals with type 2 diabetes, and to reduce TAG levels in people who are overweight or obese. No significant effects of dietary acetic acid consumption were seen on HbA1c, HDL, or anthropometric markers. High-quality, longer-term studies in larger cohorts are required to confirm whether dietary acetic acid can act as an adjuvant therapeutic agent in metabolic comorbidities management.
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CHRONIC METABOLIC DISORDERS—OBESITY, CARdiovascular disease, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS)—are the primary causes of death worldwide, responsible for over 30 million (60%) annual deaths, a number expected to rise to 70% by the end of 2020.[1,2] Good evidence supports dietary interventions as first-line strategies for the management of chronic and metabolic diseases.[3-5] Nevertheless,

pharmacological agents, including weight-reduction medications, lipid-lowering drugs, and anti-diabetic agents, are widely used as adjunct long-term therapies to encourage weight loss and improve metabolic function in individuals with chronic cardiometabolic disease.[6,7] Although pharmacological agents consistently demonstrate significant improvements in circulating lipids, glucose tolerance, and body fat reduction in controlled trials, undesirable medication side effects such as fatigue, anxiety, headaches, gastrointestinal disturbances, muscle pain, hypertension, and upper respiratory disorders are frequently reported as a result of their sustained use.[7,8] Dietary interventions provide therapeutic benefits comparable to medications, while avoiding drug-associated side effects. The consumption of exogenous acetic acid through dietary sources has been proposed as a promising novel strategy for the prevention or management of chronic metabolic dysfunction.[9,10]

Acetic acid is a short-chain fatty acid produced in the colon as a byproduct of microbial fermentation of dietary fiber, that is, carbohydrates with a degree of polymerization greater than 2 that fail to be hydrolyzed in the small intestine.[11,12] In humans, acetic acid created by bacterial fermentation enters the bloodstream and reaches the liver via the portal vein, where it is converted to acetyl coenzyme A and used as an energy source and as substrate for the synthesis of long-chain fatty acids and cholesterol.[13] Between 50% and 70% of colonic-derived acetic acid reaches the liver, whereas the remaining 30% to 40% is released into circulation and becomes available for use by nonhepatic tissues.[14] Alternatively, acetic acid may be absorbed via the upper gastrointestinal tract after consumption of foods rich in natural acetic acid, particularly vinegars.[15,16] Vinegar is produced from the bacterial fermentation of carbohydrates found in grapes (wine vinegar), fruit (apple, cranberry vinegar), or other commonly consumed foods (rice wine vinegar).[17] An alternative rich source of acetic acid is kimchi—a traditional Korean condiment commonly made from fermented cabbage and radishes.[18,19] Once in the systemic circulation, acetic acid is detectable in the peripheral blood at micromolar concentrations and may be altered by consumption of alcohol or a high-fermentable fiber meal.[20,21]

Acetic acid has demonstrated therapeutic potential for the prevention or management of disorders of glucose and lipid metabolism in rodent models. Acute and sustained acetic acid ingestion can have several positive effects on mammalian metabolism. Acetic acid consumption has been reported to decrease hepatic glucose production while increasing hepatic lipid oxidation[22]; improve beta-cell function, resulting in increased insulin secretion[23]; increase hepatic and skeletal muscle glucose use and enhance tissue glycogen repletion[24]; encourage weight reduction; and improve circulating lipid profiles.[25,26] Vinegar consumption in adults with T2DM reduces fasting and postprandial circulating glucose and enhances insulin secretion.[27] The promising therapeutic effects gained from acetic acid consumption suggest it may represent a feasible adjunct therapy for the management of metabolic diseases.

This systematic review summarizes available evidence from randomized controlled clinical trials investigating the therapeutic effects of sustained dietary acetic acid supplementation on cardiometabolic and anthropometric outcomes in both healthy individuals and people with chronic metabolic conditions. The results of this review may assist in determining the potential utility of dietary acetic acid consumption as a nonpharmacological therapeutic agent for the improvement of biomarkers associated with chronic metabolic dysfunction.

### RESEARCH SNAPSHOT

**Research Question:** Can supplementation with dietary acetic acid act as an effective nonpharmacological therapeutic strategy for metabolic comorbidities management?

**Key Findings:** This systematic review identified 16 randomized controlled trials published up to October 2020, most of which had an unclear or high risk of bias. Studies evaluated dietary acetic acid supplementation for up to 12 weeks on important metabolic and anthropometric markers of 910 participants. Supplementation achieved clinically relevant reductions in fasting blood glucose (FBG) and triacylglycerol (TAG) levels in individuals with type 2 diabetes, and TAG reductions in people who were overweight or obese. Higher-quality studies in larger cohorts are warranted to definitively assess this research question.

## METHODS

The current review was registered in the International Prospective Register of Systematic Reviews in February 2018 (Registration No. CRD42018094178). It was designed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions recommendations[28] and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[29]

### Search Strategy

A literature search was performed in the electronic databases MEDLINE, Scopus, EMBASE, CINAHL Plus, and Web of Science from database inception to October 31, 2020, using a combination of free text terms, synonyms, and subject headings relevant to the objectives of this review in consultation with an experienced systematic review librarian (Figure 1). A multi-step search approach was taken to retrieve relevant studies through additional hand-searching of reference lists, searching conference abstracts, and review of the International Clinical Trials Register Search Portal and ClinicalTrials.gov to identify ongoing trials. There was no date restriction in the search strategy. The screening of articles was performed independently by two review authors (D. S. V. and D. S.), with disagreements resolved by consensus or a third reviewer (P. A. G.).

The Continuing Professional Education (CPE) quiz for this article is available for free to Academy members through the MyCDRGo app (available for iOS and Android devices) and through www.jandonline.org (click on "CPE" in the menu and then "Academy Journal CPE Articles"). Log in with your Academy of Nutrition and Dietetics or Commission on Dietetic Registration username and password, click "Journal Article Quiz" on the next page, then click the "Additional Journal CPE quizzes" button to view a list of available quizzes. Non-members may take CPE quizzes by sending a request to journal@eatright.org. There is a $45 fee per quiz (includes quiz and copy of article) for non-members. CPE quizzes are valid for 3 years after the issue date in which the articles are published.

**Ovid Medline: 1 January 1982 to 31 October 2020**

1. vinegar.tw.
2. Acetic Acid/
3. "acetic acid".tw.
4. "diet* acetate".tw.
5. AcOH.tw.
6. AcNA.tw.
7. Fermented.tw.
8. fermented foods/ or cultured milk products/ or kombucha tea/9. kombucha.tw.
10. "Apple cider vinegar".tw.
11. vinaigrette.tw.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. "postprandial glucose".tw.
14. "postprandial insulin".tw.
15. "postprandial response".tw.
16. "Postprandial level*".tw.
17. HbA1c.tw.
18. Glycated Hemoglobin A/19. Insulin Resistance/20. "insulin sensitivity".tw.
21. "insulin levels".tw.
22. "serum glucose".tw.
23. "circulating glucose".tw.
24. "blood glucose".tw.
25. "fast* glucose".tw.
26. "HOMA*".tw.
27. triglycerides/ or lipoproteins, hdl/ or lipoproteins, ldl/28. triacylglycerol.tw.
29. "plasma cholesterol".tw.
30. "serum cholesterol".tw.
31. homocysteine.tw.
32. Postprandial Period/33. CHOLESTEROL/34. 13 or 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
35. 27 or 28 or 29 or 30 or 31 or 32 or 33
36. 34 or 35
37. 12 and 36

**Figure 1.** Database search strategy used in this systematic review to explore the effect of dietary acetic acid consumption vs placebo/low-dose comparators on metabolic and anthropometric outcomes in adults.

## Study Selection

Search results were merged into the systematic review software package Covidence,[30] capable of automatic de-duplication. Remaining references were screened for eligibility using this software. Full-text articles of potentially relevant studies were sought and reviewed. Study authors were contacted by the primary author if additional data were required to assess study eligibility or to conduct the quantitative analysis.

Studies were included if they met all of the following criteria: 1) randomized controlled trial (RCT) design; 2) conducted in adults ($\geq$18 years of age) regardless of health status; 3) intervention provided acetic acid (or acetate) supplementation through a dietary source; 4) inclusion of either a placebo or low-dose control group; 5) intervention period lasting a minimum of 1 week; 6) measured at least one of the following outcomes both at baseline and at the end of the intervention period: fasting blood glucose (FBG) and triacylglycerol levels (TAGs), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glycated hemoglobin (HbA1c), body mass index (BMI) or body fat percentage; and 7) published in English. Outcomes were measured as the difference in end of intervention scores between the acetic acid supplementation and comparator groups. Studies providing pure acetic acid through nonfood sources via a pill or intravenous injection were excluded from this review. Additionally, studies solely investigating postprandial effects of acetic acid consumption were excluded, because two published systematic reviews have previously evaluated postprandial effects of vinegar consumption on human adult metabolic profiles.[27,31]

## Data Extraction and Risk of Bias Assessment

Data from included studies was extracted by one reviewer (D. S. V.) and verified by a second (D. S.). Data extracted included: country of publication, study design (duration, blinding, and "washout" periods where applicable), participant characteristics, and intervention details (dietary source of acetic acid–rich foods, comparator used, acetic acid quantity consumed per day, time of day acetic acid sources were consumed, and number of times these were ingested). Where studies used a crossover design, and were thus of a

within-subjects nature, data for the intervention and placebo periods were pooled if no carry-over effects were reported in the primary publication. Where studies involved multiple intervention groups of different acetic acid doses, the highest intervention dose was extracted.

The risk of bias of included studies was assessed independently by two authors (D. S. V. and N. K.), using the Cochrane Risk of Bias tool for assessment of RCTs.[32] Bias minimization items included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Studies were evaluated to have a "low risk," "high risk," or "unclear risk" based on the Cochrane recommendations. This review assessed "other bias" as financial or institutional conflicts of interest, failure to measure intervention compliance, incorporation of additional bioactive compounds as confounders in the evaluation of acetic acid effects, and nonassessment of dietary intake during lead-in, intervention, and washout periods.

### Statistical Analyses

The treatment effects of selected outcomes were calculated based on the differences in end of intervention values between the experimental and comparator groups. Variance was calculated from the published standard deviation or standard error values, with confidence intervals (CI) used where these values were not available.[33] Where end of intervention data was unable to be obtained, results were described in text only. Review outcomes were further separated into four subgroups specific to participant health status: 1) healthy, 2) overweight or obese but otherwise healthy, 3) metabolic conditions that included MetS, prediabetes, or hypercholesterolemia, and 4) T2DM.

Meta-analyses were performed where outcome subgroups were quantitatively reported in at least two studies using RevMan software.[34] The mean difference (MD) was used to calculate effect sizes, with study data converted to the same unit for each outcome where necessary[35]: data for FBG, TAGs, HDL-cholesterol, and LDL-cholesterol was converted to mg/dL units; and data for HbA1c and body fat was converted to percentages. Data from the final reporting time point were used for analysis; if data were not obtainable, then results were narratively described in text only.

A random effects model (Dersimonian-Laird with inverse variance weighting) was used to produce a pooled estimate of the MD. The $I^2$ statistic was used to quantify the inconsistencies between studies and subgroups, describing the percentage of variability in effect sizes. Heterogeneity was deemed significant if the $I^2$ statistic exceeded 50%.[36] Sensitivity analyses were conducted to explore sources of statistical heterogeneity, as well as for studies whose design or results appeared inconsistent with other analyzed studies, including large studies and studies with a high risk of bias. For outcomes with 10 or more studies, publication bias was assessed by calculation of Egger's regression asymmetry test and Begg's test,[37,38] with $P < .05$ considered evidence of small-study effects. Funnel plots were also constructed and visually assessed for funnel plot asymmetry.[39]

## RESULTS

### Characteristics of Included Studies

The flowchart of study identification and inclusion is detailed in the PRISMA diagram (Fig 2). The initial database search identified a total of 4246 studies. After duplicates were removed and nonrelevant studies (n = 2904) excluded, 76 studies were subjected to full text review. From these, 16 studies involving 910 participants comprehensively met inclusion criteria and were included.[40-55] From the 60 excluded studies, the most common reasons for exclusion were investigation of wrong intervention or route of administration (ie, delivery of pure acetic acid in the absence of a food/fluid matrix through intravenous injections or pill ingestion) (n = 23) and postprandial data being solely analyzed after the intervention (n = 15). All 16 included studies were eligible for quantitative assessment via meta-analysis.

Characteristics of included studies are detailed in Figure 3. Articles retrieved were published between the years of 2007 and 2019. Studies were mostly conducted in the Republic of Korea (n = 4), followed by the United States (n = 3), Iran (n = 3), and Pakistan (n = 3). Of the remaining studies, one trial was conducted in Japan, one in India, and another in Taiwan. A total of 910 participants aged 23 to 72 years and with BMIs ranging from 21.2 to 30.0 were investigated. Of the defined subgroups specific for participant health status, two studies investigated healthy individuals (n = 172),[43,44] four investigated overweight or obese participants who were otherwise healthy (n = 245),[48,49,51,53] three[41,42,46] investigated individuals with metabolic conditions such as prediabetes, MetS, or hypercholesterolemia (n = 111), and six recruited people with T2DM (n = 342).[40,45,47,50,54,55] The health status of participants was not reported in one study (n = 40)[52]; however, as reported, TAG and LDL baseline data were within the healthy adult range (mean, 94 mg/dL and 111.2 mg/dL, respectively); it was analyzed within the healthy individuals' subgroup. The duration of included studies ranged from 1 to 12 weeks, with most interventions conducted using a parallel design (n = 13).

Dietary sources of acetic acid were primarily vinegar-based beverages, including apple cider vinegar, honey vinegar syrup, white vinegar, pomegranate vinegar, cranberry vinegar, and red date vinegar. Fermented kimchi was the only solid food base source of dietary acetic acid reported. Daily acetic acid doses provided through dietary interventions ranged from 750 mg to 3600 mg; however, precise quantities of acetic acid delivered were not reported in 31% of included studies (n = 5).[42-44,48,52] Dietary acetic acid sources were predominantly delivered with meals (n = 12) once, twice, or three times per day. The habitual dietary intake of participants at baseline was assessed in 12 studies.[40-45,48,49,51,53-55] Intervention adherence measurements and collection of dietary intake data during the intervention periods were assessed in nine trials.[42-45,48,49,51,53,55] A run-in period was included in five studies, lasting either 1,[51] 2,[42,48,52] or 3 weeks.[49] All data obtained for quantitative analysis included end of intervention values, with the exception of one study[46] for which the final reported time point (6 weeks) was used. No studies reported adverse side effects after acetic acid consumption via any type of dietary source. The outcome of each meta-analysis performed is summarized in Table 1.

### Fasting Blood Glucose

Thirteen studies investigated the effect of dietary acetic acid intake on FBG (mg/dL) in participants who either were healthy,[43,44] were overweight or obese,[48,49,51,53] had a metabolic condition,[42,46] or had been diagnosed with T2DM,[40,45,50,54,55] all of which were included in the meta-

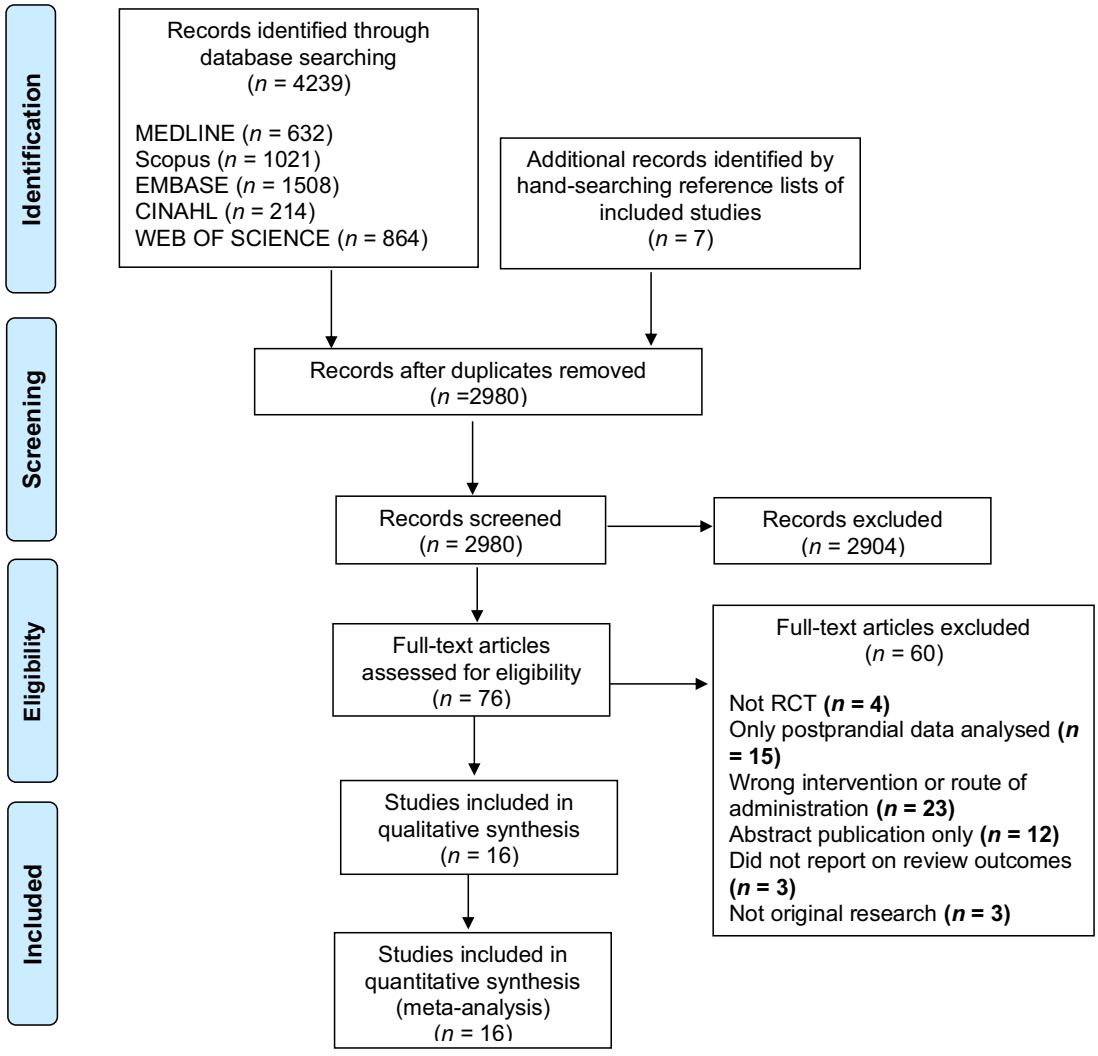



**Figure 2.** Flow diagram of the literature search and screening results for a systematic review of the effect of dietary acetic acid supplementation on fasting plasma glucose, lipid profiles, and body mass index in adults.

analysis (Fig 4). Dietary acetic acid supplementation did not significantly reduce FBG levels in the healthy, overweight or obese, or metabolic conditions subgroups. Four[40,45,50,55] of five studies conducted in people with T2DM reported significant decreases in FBG after acetic acid supplementation, resulting in a significant overall intervention effect (MD = −35.73 mg/dL, $P = .01$) and high within-group heterogeneity ($I^2 = 98\%$) (to convert mg/dL to mmol/L, multiply by 0.0555). Differences in FBG levels were less variable within the healthy (MD = −1.07 mg/dL, $P = .29$, $I^2 = 0\%$), overweight and obese (MD = −1.31 mg/dL, $P = .25$, $I^2 = 0\%$), and metabolic conditions (MD = −0.88 mg/dL, $P = .74$, $I^2 = 0\%$) subgroups. Sensitivity analysis (removal of one study at a time) did not significantly alter the result. Statistical heterogeneity ($I^2$) within the T2DM subgroup was reduced from 98% to 41% when the Nazni et al[55] data were removed, and was reduced from 98% to 0% when data from both Nazni et al[55] and Mahmoodi et al[50] were removed. Visual inspection of the funnel plot (Fig 5) indicated potential publication bias for studies involving participants with T2DM, but not for those involving healthy participants, individuals with overweight or obesity, or those with metabolic conditions. Egger's test was not significant for publication bias ($P = .902$). Begg's test was significant for publication bias ($P = .014$), but this significance disappeared when the Nazni et al[55] and Mahmoodi et al[50] studies (outliers on the funnel plot) were excluded from the calculation ($P = .062$).

## Triacylglycerol

Nine studies investigated the effects of daily dietary acetic acid intake on circulating TAG levels (mg/dL) in healthy,[44,52] overweight or obese individuals,[48,49,51] people with metabolic conditions,[41] and subjects with T2DM[40,50,54]; eight were included in the meta-analysis (Fig 6A). In overweight and obese participants (n = 222), dietary acetic acid supplementation resulted in a statistically significant reduction in TAG levels compared with placebo and low-dose comparators (MD = −20.5 mg/dL, $P = .001$) with minimal statistical heterogeneity ($I^2 = 4\%$) (to convert mg/dL to mmol/L, divide

| Author, year, country | Participants | | Interventions | | RCT[a] Design | |
|---|---|---|---|---|---|---|
| | Participants analyzed (N); mean age; % Males | Health status; mean BMI[b] (kg/m$^2$) | Acetate source and amount; acetic acid delivered; daily servings | Comparator; daily dose; acetate present (mg/d) | Design | Duration |
| Ali et al, 2018,[40] Pakistan | N = 55<br>Mean age: intervention 46.4 y, placebo 48.6 y<br>%Males: intervention 46.4%, placebo 48.1%. | T2DM[c];<br>Mean BMI: intervention 24.2, placebo 23.3. | Red date vinegar; 30 mL; 90 mg<br>One 30-mL serving in the morning or before bedtime without food | Honey diluted in water; 20 mL; none | Parallel, single-blind | 10 weeks |
| Ali et al, 2019,[41] Pakistan | N = 76<br>Mean age: intervention 49.8 y, placebo 50.4 y<br>%Males intervention 20.5%, placebo 18.9% | Mild hypercholesterolemia<br>Mean BMI: intervention 28.4, placebo 26.8 | Red date vinegar; 30 mL, 90 mg.<br>One 30-mL serving in the morning or before bedtime without food | Placebo drink, unspecified | Parallel, single-blind | 8 weeks |
| An et al, 2013,[42] Republic of Korea | N = 21<br>Mean age: 45.9 y<br>%Males: 33.3% | Prediabetes or MetS[d]<br>Mean BMI: 27.8 | Fermented kimchi; 300 g; unknown<br>Three 100-g servings with meals | Fresh kimchi; 300 g; unknown | Cross-over, not blinded | 8 weeks per leg. 4-week washout |
| Derakhshandeh-Rishehri et al, 2014,[44] Iran | N = 72<br>Mean age: intervention 28.3 y, control 31.6 y<br>%Males intervention 33.3%, control 28% | Healthy<br>Mean BMI: intervention 22.8, control 25.3 | Honey vinegar syrup; 21.7g; unknown<br>One 21.7g serving mixed in 250 mL water mid-morning or early evening | Water; 25 mL; none | Parallel, not blinded | 4 weeks |
| Gheflati et al, 2019,[45] Iran | N = 62<br>Mean age: intervention 49.5 y, control 52.1 y<br>%Males: intervention 31.3%, control 33.3% | T2DM and dyslipidemia<br>Mean BMI: intervention 29.0, control 28.9 | Apple cider vinegar; 2 0mL; 1000 mg.<br>Two 10-mL servings, before lunch and dinner | No intervention | Parallel, not blinded | 8 weeks |

*(continued on next page)*

**Figure 3.** Sample and study design characteristics of the 16 included randomized controlled trials investigating the effect of dietary acetic acid supplementation compared with placebo/low-dose comparators on metabolic and anthropometric outcomes in adults.

| Author, year, country | Participants | | Interventions | | RCT[a] Design | |
|---|---|---|---|---|---|---|
| | Participants analyzed (N); mean age; % Males | Health status; mean BMI[b] (kg/m$^2$) | Acetate source and amount; acetic acid delivered; daily servings | Comparator; daily dose; acetate present (mg/d) | Design | Duration |
| Jasbi et al, 2019,[53] USA[e] | N = 45<br>Mean age: intervention 29.6 y, comparator 30.1 y<br>%Males: intervention 95.2%, comparator 87.5% | Overweight<br>Mean BMI: intervention 27.8, comparator 28.5 | Red wine vinegar, 60 mL; 3600 mg. Two 30-mL servings diluted in water with meals | Apple cider vinegar pills, 45 mg. One pill (22.5 mg acetic acid) twice with meals | Parallel, not blinded | 8 weeks |
| Johnston et al, 2013,[46] USA | N = 14<br>Mean age: intervention 48.1 y comparator 43.9 y<br>%Males: total 7%, not provided per group | Prediabetes<br>Mean BMI: intervention 29.2, comparator 27.7 | Apple cider vinegar; 30 mL; 1500 mg. Two servings of commercially available vinegar drink with meals | Vinegar pill; 80 mg. One pill (40 mg acetic acid) twice with meals | Pilot, not blinded | 12 weeks. Follow-up data up to week 6 |
| Johnston et al, 2009,[47] USA | N = 15<br>Mean age: intervention 67.1 y comparator 62.9 y<br>%Males: intervention 20%, comparator 13% | T2DM<br>Mean BMI: Not reported | White vinegar; 30 mL; 1400 mg. Taken once with a meal<br>One 30-mL serving ingested with a meal | Vinegar pill; 15 mg/d. One pill taken with a meal | Parallel, not blinded | 12 weeks |
| Kausar et al, 2019,[54] Pakistan | N = 110<br>Mean age: intervention 51 y, placebo 50 y<br>%Males: intervention 38% placebo 47% | T2DM<br>Mean BMI: intervention 37.9 placebo reported as 20-30 | Apple cider vinegar, 15 mL, 700 mg<br>One 15-mL serving diluted in 200 mL water taken before bedtime | Artificial apple cider vinegar flavor, 15 mL, none<br>One 15-mL serve diluted in 200 mL water taken before bedtime | Parallel, single blind | 12 weeks |

*(continued on next page)*

**Figure 3.** *(continued)* Sample and study design characteristics of the 16 included randomized controlled trials investigating the effect of dietary acetic acid supplementation compared with placebo/low-dose comparators on metabolic and anthropometric outcomes in adults.

| Author, year, country | Participants | | Interventions | | RCT[a] Design | |
|---|---|---|---|---|---|---|
| | Participants analyzed (N); mean age; % Males | Health status; mean BMI[b] (kg/m$^2$) | Acetate source and amount; acetic acid delivered; daily servings | Comparator; daily dose; acetate present (mg/d) | Design | Duration |
| Kim et al, 2011,[48] Republic of Korea | N = 22<br>Mean age: 38.6 y,<br>%Males: 32% | Overweight and obese<br>Mean BMI: 27.7 | Fermented kimchi; 300 g; unknown<br>Three 100-g servings with meals | Fresh kimchi; 300g; unknown | Cross-over, not blinded | 4 weeks per leg 2-week washout |
| Kondo et al, 2009,[49] Japan | N =101<br>Mean age: intervention 43.4 y, placebo 44.1 y<br>%Males intervention 61%, placebo 64% | Obese<br>Mean BMI: intervention 27.0, placebo 26.9. | Vinegar drink; 500 mL; 1500 mg.<br>Test beverage consumed in two equal portions (250 mL) after breakfast and dinner | Placebo drink; 500 mL; none | Parallel, double blind | 12 weeks |
| Mahmoodi et al, 2013,[50] Iran | N = 60<br>Mean age: Reported as 30-60 y for both groups<br>%Males Not reported | T2DM<br>Mean BMI: Not reported | Vinegar (type not specified); 15 mL; 750 mg<br>One × 15-mL vinegar drink with lunch | No intervention | Parallel, double-blind | 4 weeks |
| Nazni et al, 2015,[55] India | N = 40<br>Mean age: intervention 42.3 y, control 50.1 y<br>% Males intervention 50%, control 60% | T2DM<br>Mean BMI: intervention 27.6, control 28.1 | Apple cider vinegar, 30 mL, unknown.<br>Two 15-mL servings before breakfast and dinner | No intervention | Parallel, not blinded | 12.8 weeks |
| Park et al, 2014,[51] Republic of Korea | N = 77<br>Mean age: intervention 41 y placebo 42 years<br>%Males: intervention 0%, placebo 0% | Overweight<br>Mean BMI: intervention 28.9, placebo 28.0 | Pomegranate vinegar; 200 mL; 1500 mg.<br>Two 100-mL test pouches with breakfast and dinner | Placebo drink; 200 mL; none | Parallel, double blind | 8 weeks |

*(continued on next page)*

**Figure 3.** *(continued)* Sample and study design characteristics of the 16 included randomized controlled trials investigating the effect of dietary acetic acid supplementation compared with placebo/low-dose comparators on metabolic and anthropometric outcomes in adults.

| Author, year, country | Participants | | Interventions | | RCT[a] Design | |
|---|---|---|---|---|---|---|
| | Participants analyzed (N); mean age; % Males | Health status; mean BMI[b] (kg/m$^2$) | Acetate source and amount; acetic acid delivered; daily servings | Comparator; daily dose; acetate present (mg/d) | Design | Duration |
| Wang et al, 2007,[52] Taiwan | N = 40<br>Mean age: Not reported<br>%Males: Not reported | Unknown<br>Mean BMI: Not reported | Cranberry vinegar; 400 mL; unknown. Two 200-mL servings, ingestion time not specified | Placebo drink; 400 mL; none | Parallel, not blinded | 10 weeks |

[a]RCT = randomized controlled trial.

[b]BMI = body mass index.

[c]T2DM = type 2 diabetes mellitus.

[d]MetS = metabolic syndrome.

[e]USA = United States of America.

**Figure 3.** *(continued)* Sample and study design characteristics of the 16 included randomized controlled trials investigating the effect of dietary acetic acid supplementation compared with placebo/low-dose comparators on metabolic and anthropometric outcomes in adults.

by 88.5). Of the three studies informing this result, only Kondo et al[49] found statistically significant reductions in TAG levels in obese individuals after 12 weeks of 1500 mg daily acetic acid supplementation. In contrast, Kim et al[48] and Park et al[51] found no significant reductions in TAG concentrations after acetic acid intake in their trials (which were of shorter duration), and it should be noted their study subjects were primarily overweight rather than obese. Studies involving individuals with T2DM (n = 225) showed a small but significant overall reduction in TAG levels (MD = −7.37 mg/dL, $P < .001$), with low heterogeneity between studies ($I^2 = 0\%$). Meta-analysis of studies involving healthy individuals (n = 101) indicated that dietary acetic acid supplementation had no effect on TAG levels compared with comparators (MD = 0.73 mg/dL, $P = .92$), with minimal statistical heterogeneity detected ($I^2 = 0\%$).

## BMI and Body Fat Percentage

Seven studies[42,43,48,49,51,53,55] investigated the effect of acetic acid consumption on BMI, four of which were studies conducted in overweight or obese participants (n = 267)[48,49,51,53] and were suitable for meta-analysis (Fig 6B). In these individuals, daily dietary acetic supplementation did not result in significant reductions in mean BMI compared with placebo or low-dose comparators (MD = −0.22, $P = .59$), with moderate statistical heterogeneity detected ($I^2 = 41\%$). No significant differences in BMI were reported in healthy individuals after daily dietary acetic acid intake ($P > 0.05$)[43]. An *et al*[42] also found no significant reduction in BMI in individuals with prediabetes after consumption of fermented kimchi ($P = .27$). In contrast, a single study[55] conducted in 40 subjects with T2DM reported a significant reduction in BMI after daily consumption of 30 mL apple cider vinegar for 3 months (MD = −2.40, $P < .001$).

The effect of dietary acetic acid supplementation on total body fat percentage was assessed in six of these studies,[42,43,48,49,51,53] with three trials conducted in overweight or obese individuals suitable for meta-analysis[48,49,53] ($n = 190$). Meta-analyses indicated no difference in body fat percentage after dietary acetic acid supplementation vs comparators (MD = 0.04 %, $P = .96$), with minimal heterogeneity detected ($I^2 = 0\%$) (Table 1). In agreement with no changes in BMI, there was no significant reduction in body fat percentage in healthy individuals after dietary acetic acid intervention (n = 100).[43] An et al[42] also reported no significant body fat percentage reduction ($P = .34$) after daily fermented kimchi consumption for 8 weeks in individuals with prediabetes.

## HDL-Cholesterol

Nine studies investigated the effect of daily dietary acetic acid supplementation on circulating HDL-cholesterol levels (mg/dL), with eight studies undergoing meta-analysis in participants who were either healthy,[43,44] overweight or obese,[48,49,51] or diagnosed with T2DM[40,50,54] (Fig 7A). Meta-analysis showed no significant increases in HDL-cholesterol levels in healthy subjects (MD = 0.24 mg/dL, $P = 0.94$, n = 161), people with overweight or obesity (MD = −0.31 mg/dL, $P = .84$, n = 222), or individuals with T2DM (MD = 1.75 mg/dL, $P = .47$, n = 225) (to convert mg/dL to mmol/L, divide by 38.6). High heterogeneity was observed in the healthy and T2DM subgroups ($I^2 = 70\%$ and 90%, respectively). Contrary to the results of others, Ali et al[41] found a small

**Table 1.** Statistical summary of metabolic and anthropometric outcomes reported in ≥2 trials per subgroup from the 16 included randomized controlled trials comparing dietary acetic acid consumption with placebo or low-dose comparators in adults. Data underwent meta-analysis using a random-effects model and are presented as mean difference (MD) and 95% confidence interval (95% CI). Statistical heterogeneity was assessed and quantified by the Q and $I^2$ statistics

| | | | | Results | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Subgroup | Studies included in meta-analysis | N | Mean difference (MD) [95% CI] | Overall effect (*P*) | $\chi^2$ test (Q) | *P* | $I^2$ [95% CI] |
| FBG[a] (mg/dL) | Healthy | 2[43,44] | 161 | −1.07 [−3.04, 0.90] | .29 | 0.58 | .45 | 0% [0,0] |
| | Overweight or obese | 4[48,49,51,53] | 267 | −1.31 [−3.54, 0.92] | .25 | 2.67 | .45 | 0% [0, 85] |
| | Metabolic conditions | 2[42,46] | 56 | −0.88 [−6.15, 4.40] | .74 | 0.02 | .88 | 0% [0,0] |
| | T2DM[b] | 5[40,45,50,54,55] | 327 | −35.75 [−63.79, −7.67] | <.001 | 198.8 | <.001 | 98% [97, 99] |
| TAG[c] (mg/dL) | Healthy | 2[44,52] | 101 | 0.73 [−14.45, 15.92] | .92 | 0.43 | .51 | 0% [0, 0] |
| | Overweight or obese | 3[48,49,51] | 222 | −20.51 [−32.98, −8.04] | .001 | 4.51 | .10 | 4% [0, 87] |
| | T2DM | 3[40,50,54] | 225 | −7.37 [−10.15. −4.59] | <.001 | 0.38 | .83 | 0% [0, 82] |
| HDL[d] (mg/dL) | Healthy | 2[43,44] | 161 | 0.24 [−6.13, 6.61] | .94 | 3.37 | .07 | 70% [0, 93] |
| | Overweight or obese | 3[48,49,51] | 222 | −0.31 [−3.31, 2.68] | .84 | 0.73 | .70 | 0% [0, 91] |
| | T2DM | 3[40,50,54] | 225 | 1.75 [−3.02, 6.52] | .47 | 20.06 | <.001 | 90% [50, 93] |
| LDL[e] (mg/dL) | Healthy | 3[43,44,52] | 201 | −0.63 [−7.45, 6.18] | .86 | 0.19 | .91 | 0% [0, 65] |
| | Overweight or obese | 3[48,49.51] | 222 | −2.40 [−10.26, 5.47] | .55 | 0.42 | .81 | 0% [0, 84] |
| | T2DM | 3[40,50,54] | 225 | −11.04 [−28.37, 6.30] | .21 | 16.63 | <.001 | 88% [69, 95] |
| HbA1c[f] (%) | T2DM | 5[40,47,50,54,55] | 280 | −1.40 [−2.95, 0.16] | .08 | 77.27 | <.001 | 95% [91, 97] |
| BMI[g] ($kg/m^2$) | Overweight or obese | 4[48,49,51,53] | 267 | −0.22 [−1.03, 0.58] | .59 | 5.12 | .16 | 41% [0, 80] |
| Body fat (%) | Overweight or obese | 3[48,49,53] | 190 | 0.04 [−1.67, 1.76] | .96 | 1.33 | .51 | 0% [0, 95] |

[a]FBG = fasting blood glucose (to convert mg/dL to mmol/L, multiply by 0.0555).
[b]T2DM = type 2 diabetes mellitus.
[c]TAG = triacylglycerol (to convert mg/dL to mmol/L, divide by 88.5).
[d]HDL = high-density lipoprotein (to convert mg/dL to mmol/L, divide by 38.6).
[e]LDL = low-density lipoprotein (to convert mg/dL to mmol/L, divide by 38.6).
[f]HbA1c = glycated hemoglobin.
[g]BMI = body mass index.

but significant increase in HDL-cholesterol after dietary acetic acid supplementation in people with hypercholesterolemia after 8 weeks (MD = 4.10 mg/dL, $P = .03$, n = 76).

## LDL-Cholesterol

Nine studies investigated the effects of dietary acetic acid supplementation on circulating LDL-cholesterol levels (mg/dL) in healthy,[43,44,52] overweight or obese participants,[48,49,51] individuals with metabolic conditions[41] and people with T2DM,[40,50,54] eight of which were suitable for meta-analysis (Fig 7B). Studies assessing LDL-cholesterol in healthy (MD = −0.63 mg/dL, $P = .86$, n = 201) and overweight or obese individuals (MD = −2.40 mg/dL, $P = 0.55$, n = 222) reported no effect of dietary acetic acid supplementation between intervention and comparator groups, with low heterogeneity within subgroups ($I^2 = 0\%$ for both) (to convert mg/dL to mmol/L, divide by 38.6). Additionally, meta-analyses indicated no significant change in LDL-cholesterol levels in participants with T2DM (MD = −11.04 mg/dL, $P = 0.21$, n = 225) and high heterogeneity within the subgroup ($I^2 = 88\%$). In contrast, a study conducted by Ali and colleagues[41] reported a significant reduction in LDL-cholesterol after acetic acid consumption in people with hypercholesterolemia after 8 weeks (MD = −45.20 ng/dL, $P < .001$, n = 76). Statistical heterogeneity ($I^2$) within the type 2 diabetes subgroup was reduced from 88% to 19% when the Ali et al[40] data were removed. Visual inspection of the funnel plot (Fig 5)

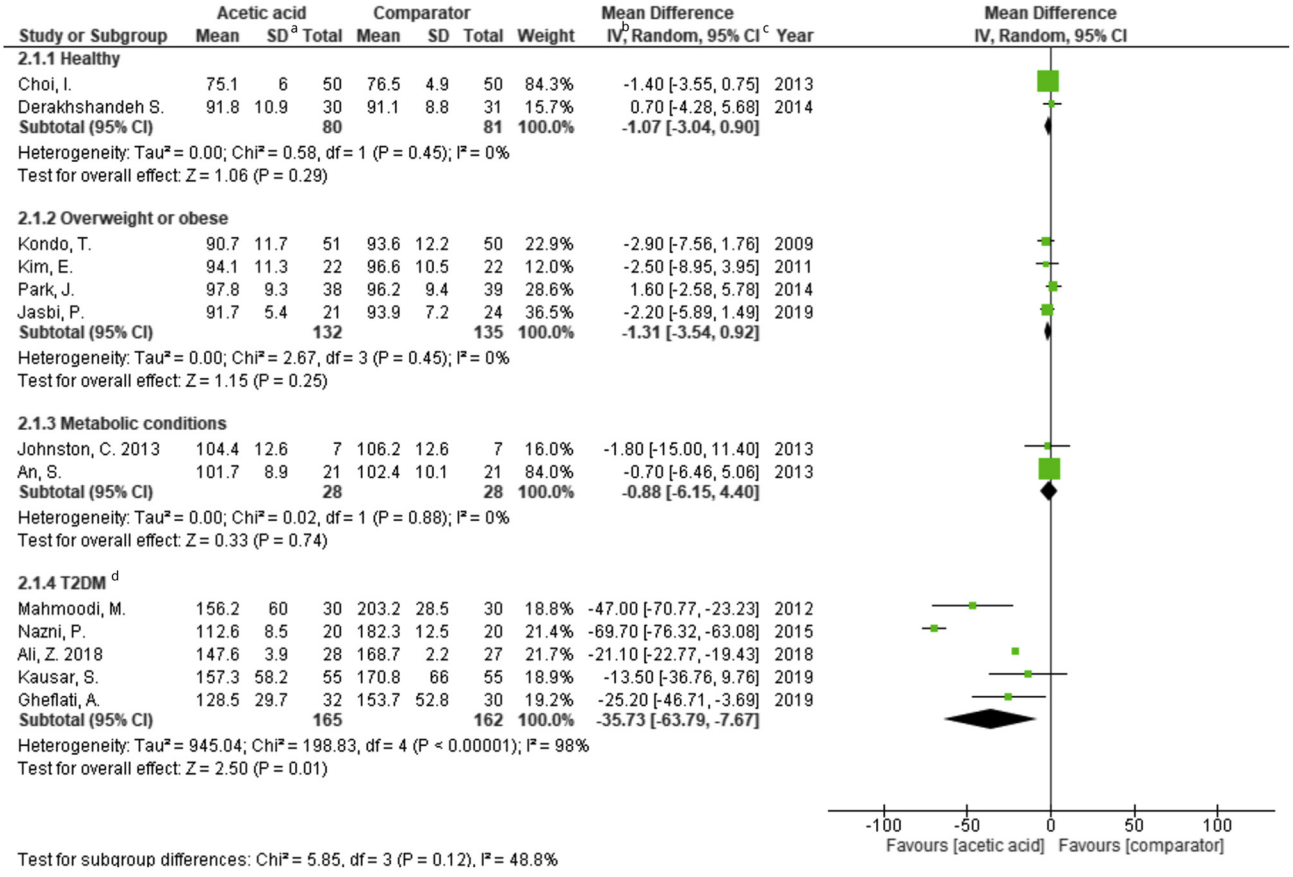



**Figure 4.** Effect of dietary acetic acid supplementation on fasting blood glucose levels (mg/dL) in healthy individuals, people who are overweight or obese, subjects with metabolic conditions, or those with type 2 diabetes compared with placebo or low-dose comparators. Significant effect estimate shown for the type 2 diabetes subgroup. Mean differences (MD) (95% confidence intervals) calculated via a random-effects model are shown.

indicated potential publication bias for the study involving participants with metabolic conditions, but not for those involving healthy participants, individuals with overweight or obesity, or those with T2DM. Begg's test was not significant for publication bias ($P = .93$), and Egger's regression asymmetry test was not significant ($P = .06$).

## HbA1c

The effect of acetic acid supplementation on HbA1c levels (%) was investigated in six studies involving individuals with metabolic conditions or T2DM,[40,41,47,49,50,54] five of which were suitable for meta-analysis (Table 1). Dietary acetic acid supplementation did not have a significant effect on glycated hemoglobin levels in participants with T2DM ($MD = -1.40\%$, $P = .08$, $n = 280$), with high interstudy heterogeneity detected ($I^2 = 95\%$). Sensitivity analysis did not significantly alter the result. Statistical heterogeneity ($I^2$) within the T2DM subgroup was reduced from 95% to 56% when the Nazni et al[55] data were removed.

## Risk of Bias of Included Studies

The risk of bias of included studies was evaluated by the Cochrane Risk-of-Bias tool[32] (Figure 8). Most of the included studies had either a high ($n = 10$) or unclear ($n = 4$) risk of bias. Only two studies[51,53] were assessed to have a low risk of bias. Six of the 16 studies reported the use of blinding of both participants and research personnel, nine assessed baseline dietary intake, and none evaluated circulating plasma levels of acetic acid. Additionally, only seven studies reported an intention-to-treat analysis,[40,41,44,45,51,53,54] and only one[53] evaluated the potential confounding effects of other bioactive compounds that were administered in parallel with foods or beverages rich in natural acetic acid.

Given the RCT study design of the included trials, the CONSORT Statement outlining clear reporting guidelines for RCTs was first published in 1996 and updated in 2010.[56,57] Because most studies in this review were published after 2010, inclusion of a comprehensive Methods section addressing the key criteria of the CONSORT statement would have been ideal.

# DISCUSSION

Preclinical studies in rodents have demonstrated that increasing dietary acetic acid delivery has potential to improve metabolic outcomes.[22,24,26,58-60] Acute supplementation in humans has been shown to reduce postprandial glucose and insulin responses[7,27,31,61]; however, little evidence supports the use of long-term acetic acid

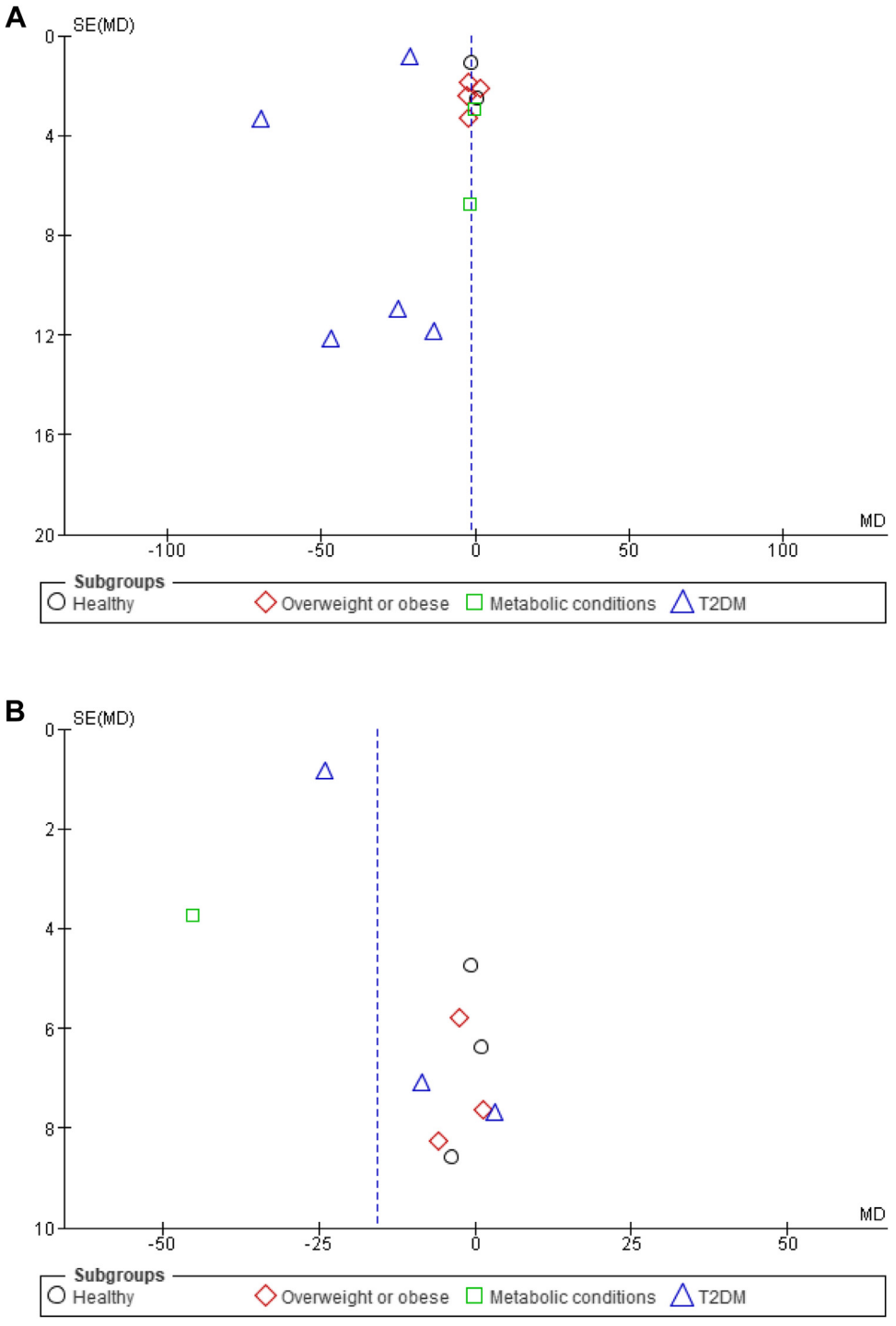



**Figure 5.** a) Funnel plot of individual studies indicating the effect of dietary acetic acid consumption vs placebo/low-dose comparators on fasting plasma glucose (mg/dL) in healthy subjects, people who are overweight or obese, individuals with metabolic conditions, or those with type 2 diabetes. Mean differences (MD) for individual studies are plotted against the standard error of the mean difference (SE[MD]) to estimate publication bias. b) Funnel plot of individual studies indicating the effect of dietary acetic acid consumption vs placebo/low-dose comparators on low-density lipoprotein (LDL)-cholesterol (mg/dL) in healthy subjects, people who are overweight or obese, individuals with metabolic conditions, or those with type 2 diabetes. Mean differences (MD) for individual studies are plotted against the standard error of the mean difference (SE[MD]) to estimate publication bias.

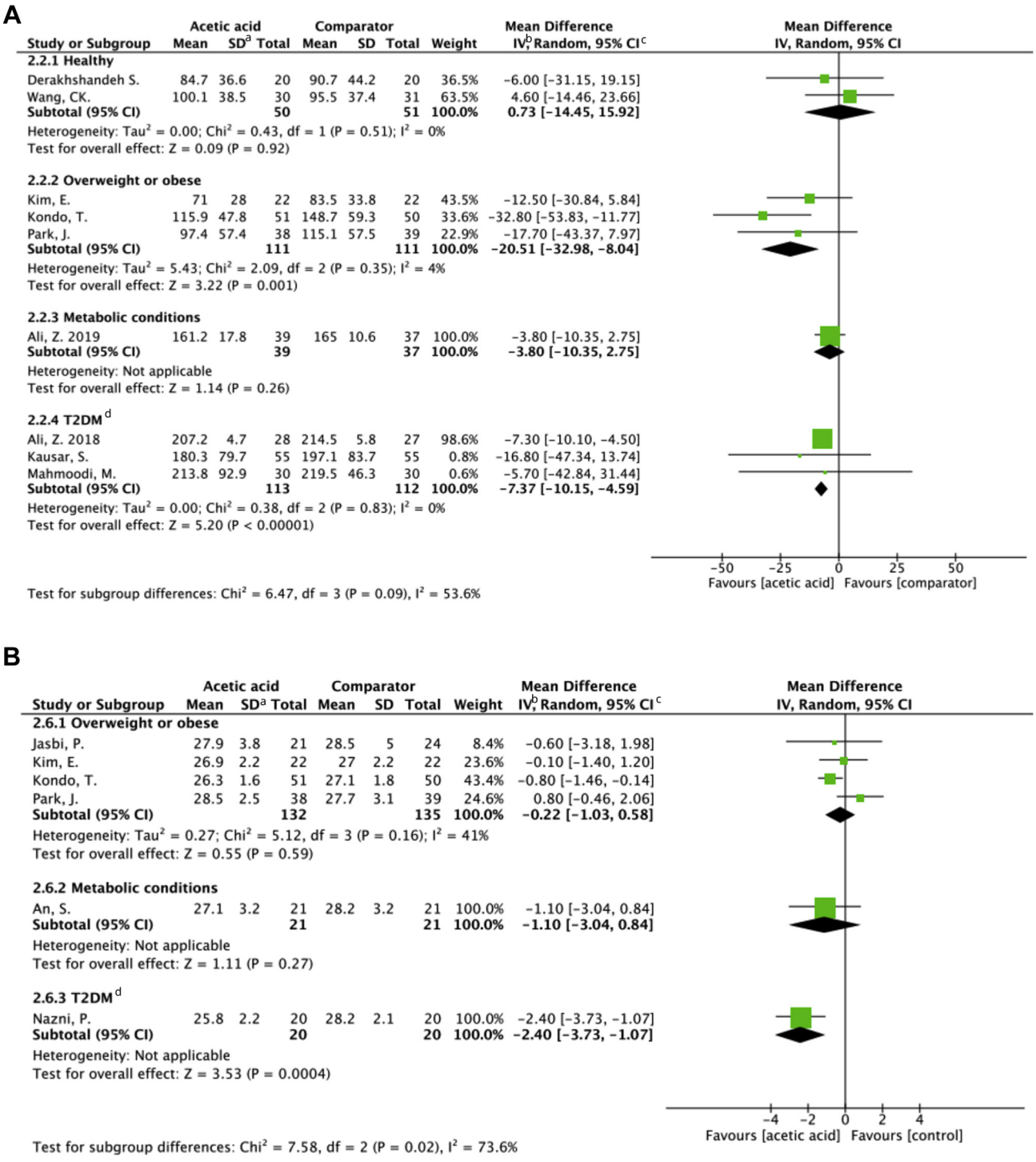
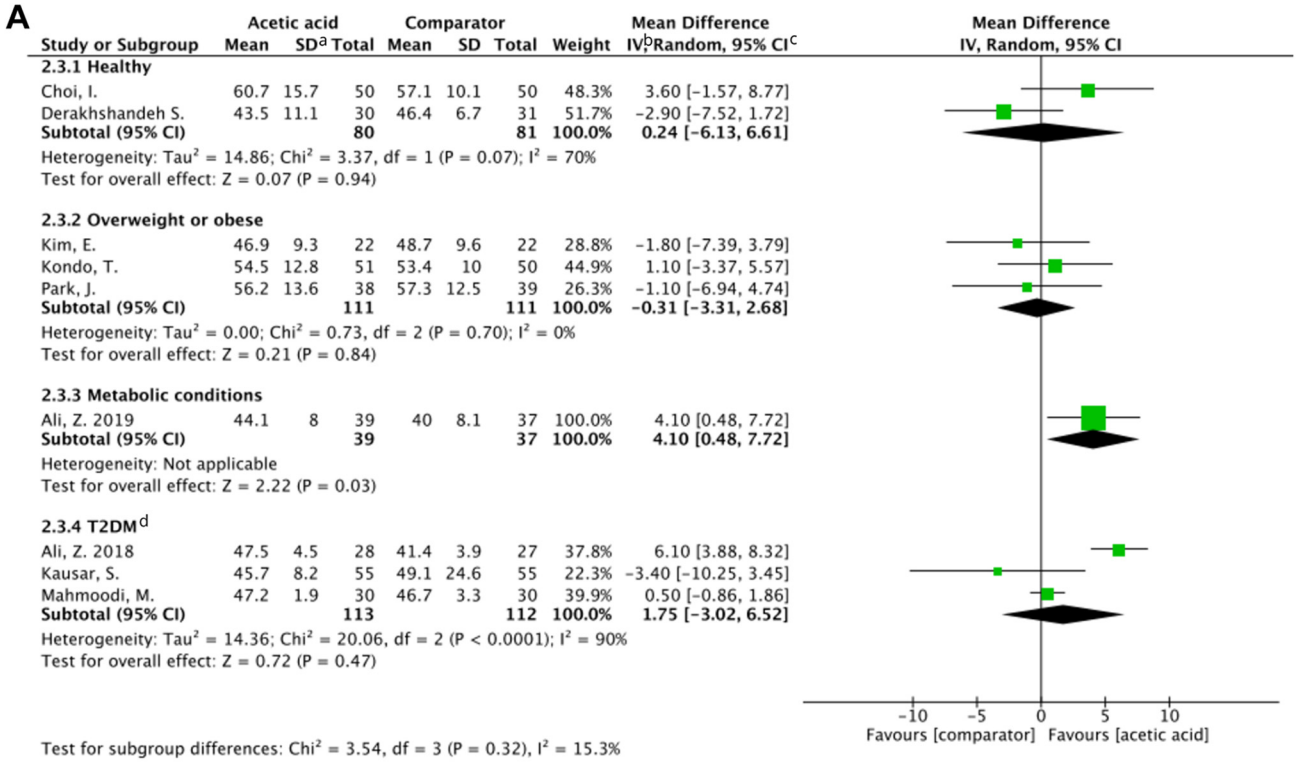



**Figure 6.** a) Effect of dietary acetic acid supplementation on triacylglycerol concentrations (mg/dL) in healthy individuals, people who are overweight or obese, subjects with metabolic conditions, or those with type 2 diabetes compared with placebo or low-dose comparators. Significant effect estimates shown for overweight or obese and type 2 diabetes subgroups. Mean differences (MD) (95% confidence intervals [CIs]) calculated via a random-effects model are shown. b) Effect of dietary acetic acid supplementation on body mass index (BMI) in individuals who are overweight or obese, subjects with metabolic conditions, or people with type 2 diabetes compared with placebo or low-dose comparators. Significant effect estimate shown for one trial conducted in people with type 2 diabetes. Mean differences (MD) (95% CIs) calculated via a random-effects model are shown.



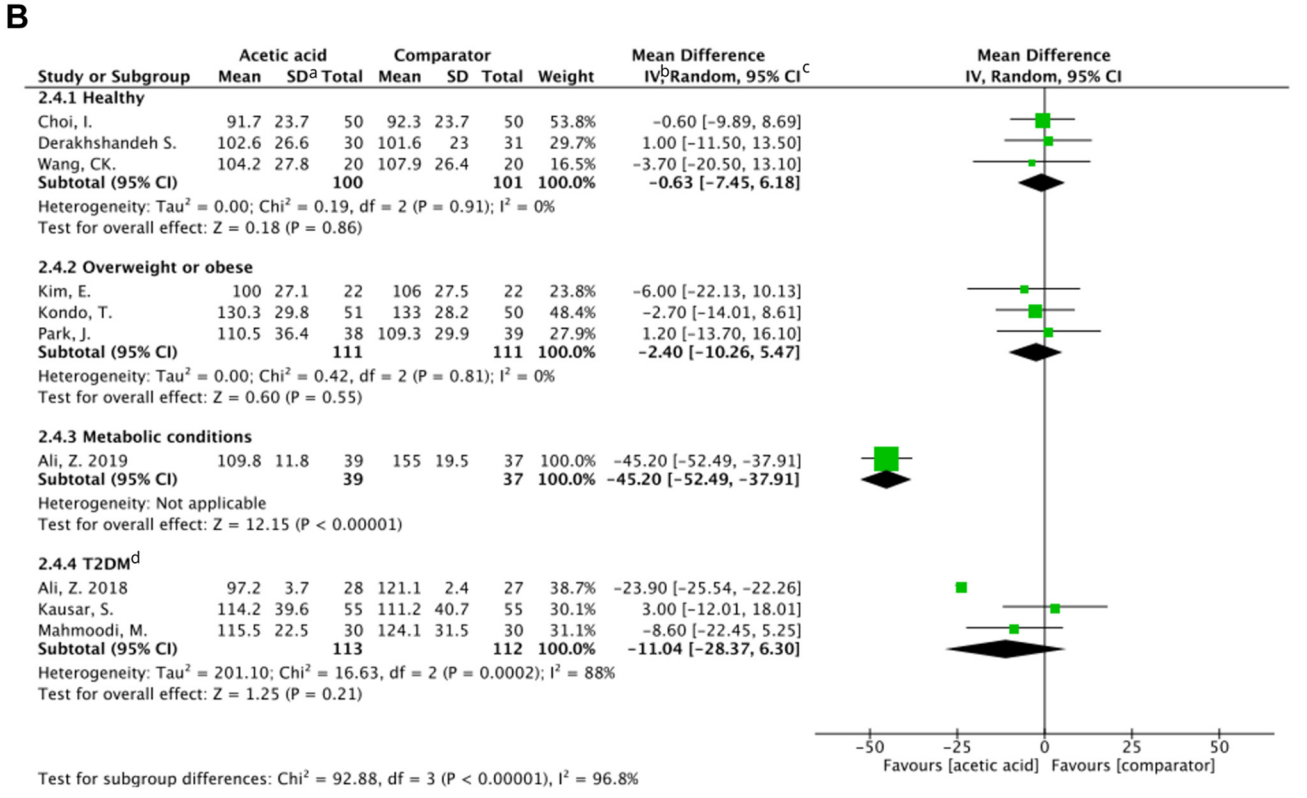




**Figure 7.** a) Effect of dietary acetic acid supplementation on HDL concentrations (mg/dL) in healthy individuals, subjects who are overweight or obese, people with metabolic conditions, or those with type 2 diabetes compared with placebo or low-dose comparators. Significant effect estimate shown for one trial conducted in people with metabolic conditions

supplementation to modify metabolic disease markers. This review summarized clinical trials exploring the potential of sustained dietary acetic acid supplementation as a therapeutic strategy for the improvement of metabolic and anthropometric markers in healthy individuals and those with chronic disease. Sixteen published randomized controlled trials[40-54] involving 910 participants were identified and included healthy individuals, people who were overweight or obese but otherwise healthy, individuals with metabolic conditions (including MetS, prediabetes, and hypercholesterolemia), and people with T2DM. Meta-analyses showed that supplementation of dietary acetic acid led to significant reductions in fasting blood glucose in people with T2DM, as well as reductions in TAG concentrations in people with T2DM and individuals who were overweight or obese. Acetic acid supplementation did not significantly impact glycated hemoglobin or body fat percentage in any of the populations evaluated.

Sustained dietary supplementation of acetic acid led to significantly lower fasting blood glucose in the T2DM group compared with placebo, without having a significant effect in healthy individuals, people with overweight or obesity, or those with metabolic conditions (Fig 4). Elevations in plasma acetic acid have been associated with normalization of blood glucose homeostasis,[61,62] optimization of hepatic and skeletal muscle glucose handling,[63] and increased insulin sensitivity.[64] Indeed, the effect of dietary acetic acid supplementation on FBG levels in individuals with T2DM is consistent with acute studies that report improved regulation of glucose and insulin levels in adults with metabolic dysfunction and T2DM after acute vinegar consumption.[27,65] The mean difference of −35.73 mg/dL seen in this meta-analysis also suggests that longer-term supplementation reduces FBG to a greater extent than that seen after acute supplementation.[66] A primary mechanism through which acetic acid is proposed to have therapeutic action is via binding of G protein−coupled receptor 43 (GPR43), which is expressed on human peripheral blood mononuclear cells, adipose cells, and in colonic cells, of which acetic acid is a strong activator at physiological concentrations of 50 to 200 $\mu$mol/L.[67-69] Ligation to GPR43 by acetic acid in the colonic epithelium results in increased secretion of glucagon-like peptide-1 (GLP-1), a hormone that promotes insulin action in muscle and adipose tissue and consequently enhances insulin sensitivity.[11,70] Moreover, the hormone GLP-1 is also responsible for indirectly regulating blood glucose levels by inhibiting excessive glucagon secretion and increasing glucose-dependent insulin secretion in the pancreas.[71] Similarly, increased GLP-1 production was observed in individuals with T2DM who achieved a significant reduction in FBG after 12 weeks of a high-fiber dietary intervention that increased acetic acid production.[72]

The studies analyzed in this review did not report plasma acetic acid concentrations after dietary supplementation. Consequently, ascertaining whether plasma acetic acid levels may have increased sufficiently to have a physiological effect and whether outcomes observed can be directly attributed to dietary acetic acid supplementation is difficult. Consumption of a 100-mL vinegar drink containing 750 mg acetic acid may increase plasma acetic acid concentrations from 140 to 349 $\mu$mol/L within 15 minutes.[73] However, levels return to baseline within 60 minutes, suggesting that regular consumption throughout the day may be needed to achieve metabolic effects. Indeed, most studies reported in this review instructed participants to consume vinegar 2 to 3 times per day alongside main meals, which is unlikely to keep plasma acetic acid levels elevated throughout the day. Because acetic acid levels within the body are tightly regulated, acetic acid metabolism by peripheral tissues may increase in response to increased delivery, as observed after hepatic metabolism of ethanol, which releases acetate into the peripheral circulation.[74] These metabolic changes in response to sustained delivery may result in rapid clearance of acetic acid from the peripheral blood but also could contribute to favorable changes in peripheral tissue metabolism.

Meta-analyses conducted in this review found that dietary acetic acid supplementation resulted in statistically significant reductions in TAG levels overweight and obese individuals who were otherwise healthy and people with TD2M, compared with controls (Fig 6a, Table 1). The greatest reduction in TAG levels observed was 32.80 mg/dL after 12 weeks of 1,500 mg/day acetic acid ingestion in an obese population,[49] with the average decrease among studies in overweight and obese individuals being 20.51 mg/dL. Increased exogenous acetic acid delivery may have exerted direct effects on circulating TAG levels by stimulating fat oxidation through engagement of GPR43 on the surface of white adipose tissue,[75,76] with subsequent reductions in insulin-mediated fatty acid uptake directly contributing to the suppression of fat accumulation.[64] Furthermore, obese individuals have been reported to have significantly decreased acetic acid turnover compared with healthy subjects, which may explain the variable effects of dietary acetic acid supplementation between populations.[77] Given that vinegar consumption has been reported to increase satiety and thus help in the regulation of body weight,[9] it is surprising that no significant reductions in anthropometric outcomes within the overweight and obese participant subgroup were observed in this review (Fig 6B, Table 1). However, analyzed studies did not control for altered background dietary intake, and most did not report dietary intake by subjects during the intervention periods, which may have confounded results.

The clinical relevance of the statistically significant changes to metabolic markers seen in the meta-analyses conducted in this review also must be considered. Reductions in circulating TAG concentrations by 88.5 mg/dL are associated with a 12% decrease in cardiovascular events and all-cause mortality in adults,[78] whereas the same 88.5 mg/dL increment in circulating TAG has been associated with cardiovascular risk

(hypercholesterolemia). Mean differences (MD) (95% confidence intervals [CIs]) calculated via a random-effects model are shown. b) Effect of dietary acetic acid supplementation on LDL concentrations (mg/dL) in healthy individuals, people who are overweight or obese, or subjects with metabolic conditions compared with placebo or low-dose comparators. Significant effect estimate shown for one trial conducted people with metabolic conditions (hypercholesterolemia). Mean differences (MD) (95% CIs) calculated via a random-effects model are shown.

| Study Author/year | Risk of bias | Bias Minimization Items[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1[b] | 2[c] | 3[d] | 4[e] | 5[f] | 6[g] | Other |
| Ali et al, 2018[40] | Unclear | + | ? | + | ? | + | ? | Funding and sponsorship free from bias |
| Ali et al, 2019[41] | High | + | ? | + | ? | + | − | Funding and sponsorship free from bias Significant differences between placebo and intervention groups at baseline not accounted for in statistical analyses. Authors reported within-group changes rather than between-group differences in outcomes. |
| An et al, 2013[42] | High | ? | ? | ? | ? | + | + | Unclear whether funding and sponsorship free from bias |
| Choi et al, 2013[43] | Unclear | ? | ? | + | ? | + | ? | Unclear whether funding and sponsorship free from bias |
| Derakhshandeh-Rishehri et al, 2014[44] | High | ? | ? | ? | ? | + | + | Funding and sponsorship free from bias Outcomes possibly related to honey rather than vinegar |
| Gheflati et al, 2019[45] | Unclear | + | ? | ? | ? | + | + | Funding and sponsorship free from bias |
| Jasbi et al, 2019[53] | Low | + | + | ? | + | + | + | Funding and sponsorship free from bias |
| Johnston et al, 2013[46] | High | ? | ? | + | ? | − | ? | Funding and sponsorship free from bias |
| Johnston et al, 2009[47] | High | ? | ? | ? | ? | ? | + | Funding and sponsorship free from bias Published as a brief report, with limited methodological information provided |
| Kausar et al, 2019[54] | High | + | ? | − | − | ? | − | Unclear whether funding and sponsorship free from bias Focus on within-groups analysis rather than between-groups analysis Clinical trial registered retrospectively |
| Kim et al, 2011[48] | High | − | − | ? | ? | − | ? | Funding and sponsorship free from bias. |
| Kondo et al, 2009[49] | Unclear | ? | ? | + | + | + | ? | Unclear whether funding and sponsorship free from bias |
| Mahmoodi et al, 2013[50] | High | ? | ? | ? | ? | − | ? | Unclear whether funding and sponsorship free from bias |
| Nazni et al, 2015[55] | High | + | ? | ? | ? | + | ? | Unclear whether funding and sponsorship free from bias |

*(continued on next page)*

**Figure 8.** Risk of bias summary for included studies investigating the effect of dietary acetic acid supplementation vs placebo/low-dose comparators on fasting glucose, lipid levels, and body composition in adults. Authors' judgments are shown for each risk of bias item for all included trials, according to the Cochrane Risk-of-Bias tool.[33]

increases of 14% in men and 37% in women.[79] Therefore, despite statistical significance, the reductions in TAG levels observed (−20.5 mg/dL in overweight and obese individuals and −7.4 mg/dL in people with T2DM) offer only modest clinical relevance, with possible clinical implications if stable reductions in TAG were able to be maintained through continued supplementation. Furthermore, statistically significant reductions in FBG (−35.73 mg/dL) observed in the T2DM subgroup did follow a similar trend of reduced HBA1c in this subgroup (−1.40%, $P = .08$), suggesting that continued supplementation beyond the intervention period may result in clinical improvement to disease. However, longer-term follow-up of HBA1c levels in people with T2DM over the course of several months (eg, 4-6 months) is needed to assess

| Study Author/year | Risk of bias | Bias Minimization Items[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1[b] | 2[c] | 3[d] | 4[e] | 5[f] | 6[g] | Other |
| Park et al, 2014[51] | Low | + | + | + | + | + | + | Funding and sponsorship free from bias Outcomes possibly related to pomegranate rather than vinegar |
| Wang et al, 2007[52] | High | ? | ? | ? | ? | + | ? | Unclear whether funding and sponsorship free from bias Outcomes possibly related to cranberry rather than vinegar |

[a]Bias minimization items: "+" = response of "yes" to use of the bias minimization item; "−" = response of "no" to use of the bias minimization item; "?" = response of "uncertain" to the use of the bias minimization item. Trials receiving a "+" response for most items are likely to have a low risk of bias.

[b]1. Random sequence generation (selection bias).

[c]2. Allocation concealment (selection bias).

[d]3. Blinding of participants and personnel (performance bias).

[e]4. Blinding of outcome assessment (detection bias).

[f]5. Complete outcome data (attrition bias).

[g]6. Nonselective reporting (reporting bias).

**Figure 8.** *(continued)* Risk of bias summary for included studies investigating the effect of dietary acetic acid supplementation vs placebo/low-dose comparators on fasting glucose, lipid levels, and body composition in adults. Authors' judgments are shown for each risk of bias item for all included trials, according to the Cochrane Risk-of-Bias tool.[33]

the clinical relevance of acetic acid supplementation.[80] Assessment of metabolic changes within each individual also may assist to identify patients who may receive clinical benefits from such intervention.

A high degree of heterogeneity was observed in a number of the study outcomes summarized in this review, and most of the included studies were judged to have a high risk of bias. Consequently, the results of some outcomes should be interpreted with caution, particularly the significant decrease in FBG reported in people with T2DM after acetic acid supplementation. The significant degree of heterogeneity observed ($I^2$ = 98%) could be attributed to several factors. First, a range of different dietary sources were used to deliver acetic acid. Dietary acetic acid was predominantly provided through vinegar drinks, including apple cider vinegar,[45,46] honey vinegar syrup,[44] white vinegar,[47] pomegranate vinegar,[51] cranberry vinegar,[52] date vinegar,[40,41] and unspecified vinegar drinks[49,50]; or through servings of fermented kimchi.[42,43,48] These dietary sources not only naturally contain differing levels of acetic acid, but they contain other bioactive compounds such as lactic, malic, and citric acid, as well as phenolic compounds, predominantly gallic acid, catechin, and chlorogenic acid, which may have confounded the effects observed.[18,81] Ideally, white vinegar should have been used to deliver acetic acid, because it is distilled and does not contain any other bioactive compounds.[82] Second, study participants were not instructed to avoid foods rich in natural acetic acid or fermentable fibers during run-in, intervention, or washout periods in any of the included studies. This is relevant because a standard serving of kimchi, kombucha, or fermented cucumber pickles may provide equivalent or greater amounts of acetic acid.[83,84] Finally, it is also possible that short-chain fatty acids produced through the colonic fermentation of dietary fibers could have elicited the physiological effects shown.[11,16] These study limitations have highlighted the necessity for future studies to account for potentially confounding bioactive molecules and how these affect blood acetic acid levels to reduce bias and more clearly attribute study outcomes to dietary acetic acid supplementation.

## CONCLUSION

The results from this review suggest that dietary acetic acid supplementation may offer the most benefit to those who are overweight or obese or have T2DM. However, the interpretation of findings for metabolic and anthropometric outcomes is challenging, given the high risk of bias of included studies, poor study design, heterogeneity of dietary sources, and limited study size. Nevertheless, dietary supplementation remains a desirable, less-invasive approach compared with intravenous or colonic acetic acid infusion. Results summarized in this review alongside a growing pool of preclinical evidence propose a role for acetic acid as a circulating glucose, lipid, and adipose tissue regulator, and may hold promise as a potential future therapy for the management of chronic and metabolic disease. Further investigation of the potential benefits of sustained dietary acetic acid consumption is required, using well-designed RCTs.

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### STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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### AUTHOR CONTRIBUTIONS

D. S. Valdes designed the review protocol, conducted the search, and drafted the manuscript. D. S. Valdes and D. So screened potentially eligible studies, and extracted and analyzed the data. D. S. Valdes and N. J. Kellow conducted risk of bias assessment. D. So, P. A. Gill, and N. J. Kellow drafted the manuscript, interpreted the data, and critically revised the manuscript for important intellectual content. All authors provided final approval of the manuscript to be submitted.