Effects of pistachios on glycemic control: A systematic review and meta-analysis of randomized controlled trials

Amir Hadi ¹*, Omid Asbaghi ²*, Maryam Kazemi ³, Hossein Khadem ⁴, Ehsan Ghaedi ⁵, ⁶*

¹Halal Research Center of IRI, Food and Drug Administration, Ministry of Health and Medical Education, Tehran, Iran
²Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
³Division of Nutritional Sciences, Human Metabolic Research Unit, Cornell University, Ithaca, NY, USA.
⁴Department of Nutrition, School of Health, Qazvin University of Medical Sciences, Qazvin, Iran
⁵Students’ Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
⁶Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

These two authors (A.H. and O.A) contributed equally to present work

*Corresponding Authors: Amir Hadi, Halal Research Center of IRI, FDA, Tehran, Iran.
E-mail: amirhadi.vnt@gmail.com, Ehsan Ghaedi, School of Nutrition Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. E-mail: ehsanghaedi073@gmail.com
Abstract

To evaluate the effects of pistachio consumption on the glucoregulatory status in individuals with a high risk of cardiovascular disease (CVD), a systematic review and meta-analysis of randomized controlled trials (RCT) was conducted. Online databases including PubMed, Scopus, Web of Science, and Cochrane Library were searched from inception until June 2019. Human trials that reported data for fasting blood sugar (FBS), fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) were included. Data were pooled using the random effect models and expressed as weighted mean difference (WMD) with 95% confidence interval (CI). Eight RCT were included in the analyses. Pistachio consumption, exchanged isocalorically for other foods, decreased FBS (WMD: -5.32 mg/dL, 95% CI: -7.80 to -2.64, P < 0.001), and insulin (WMD: -1.86 µIU/mL, 95% CI: -3.13 to -0.59, P < 0.01) concentrations in individuals with a high risk of cardiovascular disease. However, no changes were observed in the levels of HOMA-IR between the groups (WMD: -0.66, 95% CI: -1.89 to 0.58, P = 0.30). Pistachio consumption may improve glucoregulatory status in individuals at risk for CVD, as evidenced by reduced FBS and insulin concentrations. However, due to the limited availability of studies with diabetic cases and relatively small sample sizes of available studies, well-designed trials with adequate sample sizes aimed at diabetic populations are recommended.

Keywords: Pistachio, Blood Glucose, Insulin, Insulin Resistance, Meta-analysis
Introduction

Metabolic syndrome (MetS) is a complex of interrelated risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2DM), including impaired glucose metabolism, dyslipidemia, hypertension, and abdominal adiposity (1). The prevalence of MetS varies from 20-40% worldwide depending upon the chosen MetS diagnostic criteria, as well as regional, lifestyle, and ethnic variations, has been rapidly increasing over the past decades, and is predicted to continue to increase (2; 3). Insulin resistance (IR) and compensatory hyperinsulinemia characterized by an increased amount of circulating insulin are pivotal pathophysiological mechanisms in the development of MetS, which can be aggravated by obesity (4; 5; 6). Identification of a favorable diet that can mediate glucoregulatory status has become increasingly relevant due to the staggering healthcare and economic burden of associated cardiometabolic comorbidities and the biological plausibility of the relationship between diet, as a modifiable risk factor, and glycemic control.

Pistachio (Pistacia vera L.) is a nutrient-dense nut with a cardioprotective dietary composition, including a favorable fatty-acid profile rich in monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids, as well as vegetable proteins, dietary fiber, potassium, magnesium, and vitamin K (7). These dietary factors have been shown to improve the glycemic status, as evidenced by decreased IR and blood glucose concentrations (8; 9). Pistachio nuts also contain high phenolic compounds, such as anthocyanins, chlorophylls, carotenoids, phytosterols, and γ-tocopherol (10) with strong antioxidant properties. These compounds have been shown to reduce oxidative stress and protect against the risk of chronic diseases (11). Beneficial effects of pistachio consumption on CVD risk factors such as lipid profile (12), and blood pressure (13) have been reported in previous studies.

Some studies reported the effects of pistachio consumption on reducing fasting blood sugar (FBS), insulin concentrations, homeostasis model of insulin resistance (HOMA-IR) (14), and glycated hemoglobin (HbA1c) levels (15). By contrast, others reported no changes in HbA1c (14), FBS, insulin and HOMA-IR (16) levels following pistachio consumption. Inconsistent results from trials might be explained by different study designs, dose and duration of intervention, variety of age groups and gender.

In 2019, Ribeiro et al. (17) published a systematic review on this topic that included only 4 clinical trials representing 177 participants. The results indicated that pistachio consumptions
significantly improve glycemic control by reducing the FBS and HOMA-IR in T2DM patients. However, this study has only been reported qualitatively. In addition, several new trials are available and used different doses and duration to find the pistachio effect on glycemic markers. Whether new RCTs changed the result of the previous meta-analysis is unknown.

To address this gap in research, we conducted a systematic review and meta-analysis of randomized controlled trials to synthesize and quantify the effects of pistachio consumption on the markers of glycemic control in individuals who present with an increased risk of cardiovascular disease including MetS, dyslipidemia, dysglycemia, obesity, and T2DM.

**Methods**

**Ethical considerations**

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (PRISMA) guidelines for designing, conducting, and reporting the present work (18). No ethical committee approval was required or obtained due to the nature of this study.

**Literature search strategy**

Online databases (PubMed, Scopus, ISI Web of Science, and Cochrane Library) were searched systematically from inception until June 2019 using the following keywords: ("pistachio" OR "pistachios" OR "pistacia") AND ("intervention" OR "intervention study" OR "intervention studies" OR "controlled trial" OR "randomized" OR "randomized" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "clinical trial" OR "assignment" OR "randomized controlled trial" OR "randomized clinical trial" OR "RCT" OR "blinded" OR "double blind" OR "double blinded" OR "trial" OR "clinical trial" OR "trials" OR "pragmatic clinical trial" OR "cross-over studies" OR "cross-over" OR "cross-over study" OR "parallel" OR "parallel study" OR "parallel trial"). No language restriction was considered while searching the mentioned databases. Also, a reference list of all included relevant original research articles and review publications were manually screened to ensure the screening of any additional studies that were not identified in our online search results and to minimize any potential risk of publication bias.
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Study selection

The reference manager software Endnote, version X8 (Thomson Reuters, NY, U.S.) was used to exclude duplicated publications and carry out the screening processes. The screening processes is summarized below.

First, two investigators (OA and EGh) independently scanned the titles and abstracts of the retrieved articles to exclude the ineligible studies. Any conference proceedings, protocols of RCTs, letters to editors, commentaries, studies with insufficient data, or duplicate publications of identical studies were excluded. The full-texts of the remaining articles were reviewed by the same two researchers to attest the suitability for inclusion in the present study. In case of contradiction, a consensus was made through discussion with a third author (AH). Studies were included in the present analysis if: (1) they had an RCT design irrespective of a parallel or cross-over design, and examined the effects of pistachio consumption (without attention to the pistachio varieties) on the biomarkers of glycemic control; (2) the study population were adults (aged 18-60 years) with an increased risk of cardiovascular disease including MetS, dyslipidemia, dysglycemia, obesity, and T2DM; and, (3) the duration of the intervention was a minimum of four weeks to ensure sufficient time to observe clinically meaningful changes in the biomarkers glycemic markers post-intervention.

Data extraction

Two independent researchers (E.Gh and O.A.) extracted the following information for each included studies using a standardized protocol as follows: (1) surname of the first author; (2) geographical location of the study; (3) publication year of the study; (4) study design; (5) study sample size, (6) basic characteristics of the study participants, including gender, age, body mass index (BMI), and health history; (7) dosage of pistachio consumption in the intervention; (8) duration of the intervention; (9) and, the means and standard deviations (SD) for FBS concentrations, fasting serum insulin concentrations, and HOMA-IR levels in each study group. We contacted the corresponding authors of the trials via email to obtain the required endpoints that were not reported in the full-text of their study. Any disagreement or indistinct issues were resolved by consensus or consultation with a third reviewer (AH).
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Quality assessments

Seven items were used to assess the methodological quality of the enrolled studies based on the Cochrane Risk of Bias Assessment tool \(^{19}\): (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and researchers; (4) blinding of the outcome evaluators; (5) incomplete outcome data; (6) selective reporting, and, (7) other sources of bias as described \(^{19}\). We then evaluated each trial to ascertain whether there was a low, unclear, or high risk of bias. Quality assessment was performed by two authors (OA and EGh) independently and their judgments were compared.

Statistical analyses

Statistical analyses were performed using STATA version 11.2 (Stata Corp., College Station, TX, U.S.). To calculate effect sizes, mean changes and SD of fasted insulin and glucose concentrations and HOMA-IR levels were calculated by subtracting the post-intervention from the baseline concentration values in each of the intervention groups. In the event of standard deviation of the mean difference was not stated, we imputed it based on Cochrane guidance\(^{20}\), using a correlation coefficient of 0.5. Effect sizes were expressed as the weighted mean difference (WMD) between the groups who consumed pistachio and controls, with a 95% confidence interval (CI). If only standard errors (SEs) were reported, SDs were calculated using the formula: \(SD = SE \times \text{square root} (n)\), where \(n\) was the number of subjects in each group. We used the \(I^2\) statistics to test statistical heterogeneity among studies. An \(I^2\) value > 50% indicates substantial heterogeneity \(^{21}\). If significant heterogeneity between studies was observed, a random effects model was applied for all analyses. Also, subgroup analyses were performed to account for the impacts of certain factors including (1) the BMI of study participants (dichotomous: overweight [25–29.9 kg/m\(^2\)] or obese [≥ 30 kg/m\(^2\)]); (2) the duration of the intervention (dichotomous: ≥ 12 or < 12 weeks), and, (3) the type of disease (polytomous: T2DM, MetS, or other diseases). To detect the influence of a single study on the overall estimate, we conducted a sensitivity analysis by removing one study each time and re-calculating the analysis. Publication bias was assessed using a funnel plot and statistical analysis of Begg's test. Results were considered significant at \(P < 0.05\).
Results

Study selection

Figure 1 summarizes the flow of literature during the search and study selection protocol. A total of 1457 publications were identified in our initial online search, of which 476 duplicate records were excluded. The titles and abstracts of the 981 remaining articles were assessed, and 963 items were eliminated due to non-human RCT designs. Eighteen remaining items were then evaluated using by the review of the full text. Of the 18 evaluated items, eleven records were excluded due to the lack of information about the glucoregulatory status (14; 22; 23; 24; 25; 26; 27; 28; 29; 30) and randomization (31). After all the exclusion criteria were applied, seven trials were remained (15; 16; 32; 33; 34; 35; 36) using the online search. Also, one trial (37) was included in the final analyses via a manual search. The final analyses of the present meta-analysis included eight trials (15; 16; 32; 33; 34; 35; 36; 37). All included trials (15; 16; 32; 33; 34; 35; 36; 37) reported the effects of pistachios on FBS concentrations, six (16; 32; 33; 34; 35; 37) on insulin concentrations, and three (15; 16; 35) on HOMA-IR levels.

Study characteristics

Characteristics of analyzed trials are shown in Table 1. The eight trials (15; 16; 32; 33; 34; 35; 36; 37) included an overall 535 participants, of which 282 participants were allocated to pistachios consumption groups and 253 to control groups. The sample size of the included trials ranged from 22 (37) to 108 (35) participants individually. Studies were published between 2009 and 2015 and were conducted in the United States (16; 32; 37), China (33), India (34; 36), Spain (35) and Iran (15). The duration of the intervention varied between four (16) to 24 (34) weeks across the included trials. The daily recommended dosage of pistachio consumption varied between 25 and 70 grams or 20% and 35% of the total energy expenditure of study participants. Five (32; 33; 34; 36; 37) and three (15; 16; 35) trials had parallel or cross-over designs, respectively. All trials were carried out on both females and males (15; 16; 32; 33; 34; 35; 36; 37). The mean age of the participants ranged from 37.7 (36) to 57.1 (37) years old and mean baseline BMI varied from 26.1 (36) to 32.0 (15) kg/m². Participants in the trials presented with cardiometabolic abnormalities including dysglycemia (35), overweight (37), obesity (32), MetS (33; 34), dyslipidemia (36) and T2DM (15; 16).
Quality assessments

The random allocation of participants was described in all included trials (15; 16; 32; 33; 34; 35; 36; 37). Methods of random sequence generation were described in three of the trials (15; 32; 35) which had a low risk of bias, whereas the other five (16; 33; 34; 36; 37) had a high risk of bias. Five trials (15; 16; 32; 33; 35) exhibited a low risk of bias, and three (34; 36; 37) had an unclear risk when considering allocation concealment. The risk of bias was high in all of the evaluated studies with regards to the blinding of participants and researchers (15; 16; 32; 33; 34; 35; 36; 37). Five trials (32; 33; 35; 36; 37) had an unclear risk of bias when considering blinding of outcome assessors and three (15; 16; 34) had a low risk. Two trials (32; 33) had an unclear risk of bias when considering completing the outcome data and the other six (15; 16; 33; 34; 35; 36) showed a low risk of bias. Concerning selective outcome reporting, five trials (16; 34; 35; 36; 37) had a low risk of bias (Table 2).

Meta-analysis

Effects of pistachio consumption on FBS concentrations

Eight eligible studies with nine effect sizes, including a total of 535 participants, examined the effect of pistachio consumption on FBS. Combined results from the random-effects model indicated that FBS concentration significantly reduced following pistachio consumption (WMD: -522 mg/dL, 95% CI: -7.80 to -2.64, P < 0.001). There was a significant between-study heterogeneity (I² = 68.5 %, P = 0.001; Figure 2). Results of subgroup analyses showed the benefits of pistachio consumption on decreasing FBS concentrations in all the evaluated subgroups independent of the duration of the trial and type of cardiometabolic abnormalities; however, we observed these benefits only in participants with obesity, unlike their counterparts who presented with comorbid overweight (Table 3). Findings from sensitivity analysis showed that none of the studies significantly influenced the overall effect. Also, between-study heterogeneity was not affected by the omission of any of the studies.

Effects of pistachio consumption on insulin concentrations

A total of six trials with seven treatment arms, including 405 participants, reported the effects of pistachio consumption on fasting serum insulin concentrations. Pooled findings from the random-effects model showed the significant effects of pistachio consumption on serum
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insulin concentrations (WMD: -1.86 µIU/ml, 95% CI: -3.13 to -0.59, P < 0.01), despite a significant heterogeneity across the evaluated trials (I² = 71.3%, P < 0.01; Figure 3). Results of subgroup analyses revealed the positive effects of pistachio consumption on reducing serum insulin concentrations only in overweight participants who did not present with T2DM and MetS following an intervention period of ≥ 12 weeks as shown in Table 3. By removing Wilson’s study (37), the overall estimated effect of pistachio consumption on insulin concentrations changed to a non-significant value (-2.11 µIU/mL 95% CI: -4.39, 0.16). However, the omission of any of the studies could not reduce the heterogeneity.

**Effects of pistachio consumption on HOMA-IR**

After pooling effect sizes from three studies with a total of 256 participants, we observed that pistachio consumption did not affect HOMA-IR levels in the group who consumed pistachio compared to controls (WMD: -0.66, 95% CI: -1.89 to 0.58, P = 0.30). We also observed significant heterogeneity across the evaluated trials (I² = 85.4%, P < 0.01; Figure 4). However, subgroup analysis was not conducted because of the limited number of studies. In addition, the overall meta-analysis of HOMA-IR was not sensitive to individual studies. However, between-study heterogeneity disappeared after excluding the Hernández-Alonso et al. (24) study from the analysis (I² = 0.0%, P =0.89).

**Publication bias**

Visual inspection of the funnel plots showed no evidence of asymmetry in the effects of pistachio consumption on the glycemic indices. We observed no publication bias for FBS (P = 0.83), insulin (P = 0.88), and HOMA-IR (P = 0.60) levels. It should be noted that, given the small number of studies included in the present analysis (less than 10 studies), the funnel plot and statistical analysis of Begg’s test should be interpreted with caution.

**Discussion**

The present study is the first systematic review and meta-analysis of RCT that evaluated the effects of pistachio consumption on gluoregulatory status in individuals at risk for cardiovascular disease.
Our results showed that pistachio consumption can effectively reduce FBS and insulin concentrations compared with control. However, the results of this study should be interpreted with caution due to the high heterogeneity.

Results of subgroup analyses reiterated the benefits of pistachio consumption on decreasing FBS in cohorts with obesity independent of the duration of the trial and type of cardiometabolic abnormities compared to those with comorbid overweight. By contrast, pistachios consumption decreased serum insulin concentrations in overweight participants who did not present with T2DM and MetS and not in longer intervention periods (< 12 weeks).

The positive effects of pistachio consumption on glucoregulatory status could be attributed, in part, to the low glycemic index pistachio nuts. Consumption of pistachio nuts with high carbohydrate foods with a high glycemic index, including parboiled rice, pasta, and mashed potatoes, has been shown to slow the intestinal absorption of carbohydrates and reduce total postprandial glycemic response by 20–30%. Consumption of pistachio nuts has been also associated with reduced rates of dietary fat digestion, slow energy release, and increased digestibility of dietary fiber. The favorable nutritional composition of pistachio nuts, including high MUFA and PUFA and low saturated fatty acid (SFA) content may also contribute to these positive effects through mechanisms described. Replacement of SFA by MUFA and PUFA has been shown to improve glycemic control and IR. Pistachio nuts are rich in phenolic compounds and hypocholesterolemic agents including, anthocyanins, chlorophylls, catechins, carotenoids, phytosterols, and tocopherol with antioxidant properties. These biological compounds elicit anti-glycemic effects and were shown to reduce the risk of T2DM. Quercetin and catechin compounds have been reported to modulate the activity of intestinal α-glucosidase and pancreatic α-amylase and regulate intestinal glucose absorption. Pistachio nuts have been shown to inhibit the oxidation of aldohexose. These mechanisms may explain the improved glycemic response following the consumption of pistachio nuts. Pistachio nuts also have other favorable dietary factors, including a high magnesium and phosphorus content, with implications in the metabolism of B group vitamins, regulation of endocrine hormones, and modulation of glucose response. Long-term consumption of pistachio nuts has been shown to induce glucagon-like peptide-1 (GLP-1) release and insulin-sparing effects in individuals with prediabetes. Similarly, the intake of pistachio nuts have been shown to upregulate the secretion of GLP-1 in individuals with
MetS. The beneficial effects of pistachio nuts on insulin metabolism could be attributed, in part, to increased GLP-1 levels. GLP-1 and gastric inhibitory polypeptide (GIP) are gastric hormones which can stimulate pancreatic insulin secretion and suppress glucagon secretion in a glucose-dependent manner. Other mechanisms have been also proposed to explain the positive effects of pistachio nuts intake on glycemic control and insulin sensitivity, including the modulation of miRNA although the exact molecular mechanism remain to be elucidated.

Implications for practice and safety

Severe adverse effects were not reported following the consumption pistachio nuts. However, gastrointestinal symptoms, including bloating, diarrhea, constipation, flatulence, and abdominal pain have been reported in some individuals attributed to the high fructan content of pistachio nuts. Further, the high energy content of pistachio nuts could result in exceeding the daily total energy requirements and obesity; however, a previous trial showed that the daily consumption of either a high or recommended dose of pistachio nuts for 12 weeks, in individuals did not change BMI or waist-to-hip ratio in individuals with MetS compared with controls – a finding that has been corroborated in other populations. Current evidence does not support a relationship between nut consumption and weight gain, albeit nuts are energy-dense food. Indeed, the consumption of nuts has been associated with reduced risk of obesity, due to the inhibition of enzymatic activity of amylase and α-glucosidase, reduced rate of carbohydrate and fat digestion, and absorption, and inducing satiety, which decrease the consumption of unhealthy foods.

Strength and limitations

The strengths of the present study were the completion of the analyses based on mean changes between intervention and control groups that is more accurate than changes within groups and yielded greater effect sizes. In addition, the study complied with the PRISMA guidelines and comprehensive search. Our observations may be interpreted with cautioning due to some limitations, including the potential influence of confounding factors such as, racial and lifestyle factors across the studied cohorts and types of pistachio on the efficacy of pistachio consumption on outcomes which is not uncommon in studies of this type. Also, the pistachio varieties affect the clinical results. As, degree of mastication can also influence...
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the glycemic and insulinemic response to nuts (62). Further, the evaluated trials had a small sample size with shorter intervention periods.

Conclusions
Pistachio consumption may improve glucoregulatory status in individuals at risk for CVD, as evidenced by decreasing fasting glucose and insulin concentrations. Future long-term large-scale trials are needed to confirm our observations.

Ethics approval and consent to participate
All analysis were based on previous studies and no ethical approval and patent consent are needed.

Competing interests
The authors declare that they have no competing interests.

Acknowledgments
None.

Author contributions
OA and EGh designed and conceived the study, searched databases, screened articles, and extracted data. EGh performed the statistical analyses. OA and EGh interpreted the results and drafted the manuscript with contributions from AH and MK. All authors reviewed and commented on subsequent drafts of the manuscript. OA and EGh have the primary responsibility for the final content.

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References


Table 1. Characteristics of the included studies in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Participants</th>
<th>Sex</th>
<th>Mean age (year, intervention/control)</th>
<th>Mean BMI (kg/m², intervention/control)</th>
<th>Trial duration (weeks)</th>
<th>Sample size (intervention/control)</th>
<th>Pistachios dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z Li</td>
<td>2009</td>
<td>USA</td>
<td>R/CG/PA</td>
<td>Subject with obesity</td>
<td>F/M</td>
<td>45.4/47.3</td>
<td>30.1/30.9</td>
<td>12</td>
<td>31/28</td>
<td>53 g</td>
</tr>
<tr>
<td>X Wang</td>
<td>2012</td>
<td>China</td>
<td>R/CG/PA</td>
<td>Subject with metabolic syndrome</td>
<td>F/M</td>
<td>51.9/50.7</td>
<td>28.1/28.028</td>
<td>12</td>
<td>27/30</td>
<td>42 g 70 g</td>
</tr>
<tr>
<td>T Wilson</td>
<td>2014</td>
<td>USA</td>
<td>R/CG/PA</td>
<td>Overweight subjects</td>
<td>F/M</td>
<td>57.1/57.1</td>
<td>31.1/31.1</td>
<td>6</td>
<td>11/11</td>
<td>35.4 g</td>
</tr>
<tr>
<td>P Hernandez-Alonso</td>
<td>2014</td>
<td>Spain</td>
<td>R/CG/CO</td>
<td>Subject with prediabetes</td>
<td>F/M</td>
<td>55/55</td>
<td>28.9/28.9</td>
<td>16</td>
<td>54/54</td>
<td>57 g</td>
</tr>
<tr>
<td>RR Kasliwal</td>
<td>2014</td>
<td>India</td>
<td>R/CG/PA</td>
<td>Patients with mild dyslipidemia</td>
<td>F/M</td>
<td>37.7/40.4</td>
<td>26.1/27.8</td>
<td>12</td>
<td>21/21</td>
<td>40 g</td>
</tr>
<tr>
<td>M Parham</td>
<td>2014</td>
<td>Iran</td>
<td>R/CG/CO</td>
<td>Patients with type 2 diabetes</td>
<td>F/M</td>
<td>53/55</td>
<td>32/30</td>
<td>12</td>
<td>30/30</td>
<td>25 g</td>
</tr>
<tr>
<td>S Gulati</td>
<td>2014</td>
<td>India</td>
<td>R/CG/PA</td>
<td>Subject with metabolic syndrome</td>
<td>F/M</td>
<td>41.6/43.3</td>
<td>30.9/30.9</td>
<td>24</td>
<td>35/35</td>
<td>20% TEE</td>
</tr>
<tr>
<td>KA Sauder</td>
<td>2015</td>
<td>USA</td>
<td>R/CG/CO</td>
<td>Patients with type 2 diabetes</td>
<td>F/M</td>
<td>56.1/56.1</td>
<td>31.2/31.2</td>
<td>4</td>
<td>30/30</td>
<td>20% TEE</td>
</tr>
</tbody>
</table>

Abbreviations: DB, double-blinded; CG, control-group; CO, cross-over; PA, parallel; NR, not reported; F, Female; M, Male; TEE, total energy expenditure.
Table 2. Quality assessment of included studies based on Cochrane guidelines

<table>
<thead>
<tr>
<th>Authors</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
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<tr>
<td>Z Li et al.</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>U</td>
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<td>U</td>
<td>L</td>
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<td>RR Kasliwal et al.</td>
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<tr>
<td>M parham et al.</td>
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<td>L</td>
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<tr>
<td>KA Sauder et al.</td>
<td>H</td>
<td>L</td>
<td>H</td>
<td>L</td>
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</table>

(L, low; H, high, U, unclear)
Table 3: Subgroup analyses of pistachios consumption on glycemic profile

<table>
<thead>
<tr>
<th>Subsets</th>
<th>No.</th>
<th>WMD (95% CI)</th>
<th>P within group</th>
<th>P heterogeneity</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (FBS)</td>
<td>9</td>
<td>-5.22 (-7.80, -2.64)</td>
<td>&lt; 0.001</td>
<td>0.01</td>
<td>68.5</td>
</tr>
<tr>
<td><strong>BMI status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Obese</td>
<td>5</td>
<td>-4.92 (-6.92, -2.52)</td>
<td>&lt; 0.001</td>
<td>0.215</td>
<td>31.0</td>
</tr>
<tr>
<td>Overweight</td>
<td>4</td>
<td>-5.40 (-11.14, 0.34)</td>
<td>0.065</td>
<td>&lt; 0.001</td>
<td>84.5</td>
</tr>
<tr>
<td><strong>Trial duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 12 weeks</td>
<td>7</td>
<td>-5.61 (-9.31, -1.90)</td>
<td>0.003</td>
<td>&lt; 0.001</td>
<td>75.3</td>
</tr>
<tr>
<td>&lt; 12 weeks</td>
<td>2</td>
<td>-4.08 (-5.52, -2.65)</td>
<td>&lt; 0.001</td>
<td>0.759</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Type of disease</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>2</td>
<td>-12.29 (-21.26, -3.31)</td>
<td>0.007</td>
<td>0.327</td>
<td>0.0</td>
</tr>
<tr>
<td>MetS</td>
<td>3</td>
<td>-4.86 (-7.05, -2.66)</td>
<td>&lt; 0.001</td>
<td>0.862</td>
<td>0.0</td>
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<tr>
<td>Other disease</td>
<td>4</td>
<td>-4.73 (-9.31, -0.15)</td>
<td>0.043</td>
<td>&lt; 0.001</td>
<td>85.8</td>
</tr>
<tr>
<td>(overweight, obese,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prediabetes, dyslipidemia)</td>
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<td></td>
</tr>
<tr>
<td>Overall (insulin)</td>
<td>7</td>
<td>-1.86 (-3.13, -0.59)</td>
<td>0.004</td>
<td>0.002</td>
<td>71.3</td>
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<tr>
<td><strong>BMI status</strong></td>
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</tr>
<tr>
<td>Obese</td>
<td>4</td>
<td>-1.09 (-2.29, 0.10)</td>
<td>0.074</td>
<td>0.020</td>
<td>69.6</td>
</tr>
<tr>
<td>Overweight</td>
<td>3</td>
<td>-4.14 (-5.82, -2.45)</td>
<td>&lt; 0.001</td>
<td>0.505</td>
<td>0.0</td>
</tr>
</tbody>
</table>
### Trial duration

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>WMD (CI)</th>
<th>p</th>
<th>CI</th>
<th>p</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 12 weeks</td>
<td>5</td>
<td>-2.92 (-5.06, -0.77)</td>
<td><strong>0.008</strong></td>
<td>0.193</td>
<td>34.2%</td>
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</tr>
<tr>
<td>&lt; 12 weeks</td>
<td>2</td>
<td>-1.05 (-2.41, 0.30)</td>
<td>0.128</td>
<td>0.005</td>
<td>87.6%</td>
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</tr>
</tbody>
</table>

### Type of disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>WMD (CI)</th>
<th>p</th>
<th>CI</th>
<th>p</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>1</td>
<td>-0.31 (-1.16, 0.54)</td>
<td>0.475</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MetS</td>
<td>3</td>
<td>-0.91 (-3.57, 1.74)</td>
<td>0.501</td>
<td>0.554</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Other disease (overweight, obese, prediabetes, dyslipidemia)</td>
<td>3</td>
<td>-3.12 (-5.50, -0.74)</td>
<td><strong>0.010</strong></td>
<td>0.010</td>
<td>78.4%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FBS, fasting blood Sugar; T2DM, type 2 diabetes; MetS, metabolic syndrome; WMD, weighted mean differences; CI, confidence interval.
Figure 1. PRISMA flow diagram of study selection process
**Figure 2.** Forest plot of the effects of pistachios on fasting blood sugar concentrations.
**Figure 3.** Forest plot of the effects of pistachios on insulin concentrations.
Figure 4. Forest plot of the effects of pistachios on homeostasis model assessment of insulin resistance.