



Effects of pistachios on glycaemic control: a systematic review and meta-analysis of randomised controlled trials

Amir Hadi^{1†}, Omid Asbaghi^{2†}, Maryam Kazemi³, Hossein Khadem Haghghian⁴ and Ehsan Ghaedi^{5,6*}

¹Halal Research Center of IRI, Food and Drug Administration, Ministry of Health and Medical Education, Tebran, Iran

²Cancer Research Center, Shabid Beheshti University of Medical Sciences, Tebran, Iran

³Hilda and J. Lester Gabrilove Division of Endocrinology, Diabetes, and Bone Disease, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁴Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran

⁵Students' Scientific Research Center (SSRC), Tebran University of Medical Sciences (TUMS), Tebran, Iran

⁶Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tebran University of Medical Sciences, Tebran, Iran

(Submitted 14 October 2019 – Final revision received 14 June 2022 – Accepted 28 June 2022 – First published online 7 July 2022)

Abstract

To evaluate the effects of pistachio consumption on the glucoregulatory status in individuals with a high risk of CVD, a systematic review and meta-analysis of randomised controlled trials (RCT) were 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% CI. Eight RCTs were included in the analyses. Pistachio consumption, exchanged isocalorically for other foods, decreased FBS (WMD: -5.32 mg/dl, 95% CI $(-7.80, -2.64)$, $P < 0.001$) and insulin (WMD: -1.86 μ IU/ml, 95% CI $(-3.13, -0.59)$, $P < 0.01$) concentrations in individuals with a high risk of CVD. However, no changes were observed in the levels of HOMA-IR between the groups (WMD: -0.66 , 95% CI $(-1.89, 0.58)$, $P = 0.30$). 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.

Key words: Pistachio: Blood glucose: Insulin: Insulin resistance: Meta-analysis

Metabolic syndrome (MetS) is a complex of interrelated risk factors for CVD and type 2 diabetes (T2DM), including impaired glucose metabolism, dyslipidaemia, 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 hyperinsulinaemia characterised by an increased amount of circulating insulin are pivotal pathophysiological mechanisms in the development of MetS, which can be aggravated by obesity^(4–6). Identification

of a favourable diet that can mediate glucoregulatory status has become increasingly relevant due to the staggering health-care and economic burden of associated cardiometabolic comorbidities and the biological plausibility of the relationship between diet, as a modifiable risk factor and glycaemic control.

Pistachio (*Pistacia vera* L.) is a nutrient-dense nut with a cardioprotective dietary composition, including a favourable fatty acid profile rich in MUFA and PUFA, as well as vegetable proteins, dietary fibre, potassium, Mg and vitamin K⁽⁷⁾. These dietary factors have been shown to improve the glycaemic status, as evidenced by decreased IR and blood glucose concentrations^(8,9).

Abbreviations: FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; T2DM, type 2 diabetes.

* **Corresponding author:** Dr E. Ghaedi, email ehsanghaedi073@gmail.com

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

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 protection 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 Hb levels⁽¹⁵⁾. By contrast, others reported no changes in glycated Hb⁽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 four clinical trials representing 177 participants. The results indicated that pistachio consumptions significantly improved glycaemic 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 glycaemic markers. Whether new RCT 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 randomised controlled trials to synthesise and quantify the effects of pistachio consumption on the markers of glycaemic control in individuals who present with an increased risk of CVD including MetS, dyslipidaemia, dysglycaemia, obesity and T2DM.

Methods

Ethical considerations

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines 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 minimise any potential risk of publication bias.

Study selection

The reference manager software Endnote, version X8 (Thomson Reuters, NY, USA) was used to exclude duplicated publications and carry out the screening processes. The screening processes is summarised 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 RCT, 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 glycaemic control; (2) the study population were adults (aged 18–60 years) with an increased risk of CVD including MetS, dyslipidaemia, dysglycaemia, obesity and T2DM and (3) the duration of the intervention was a minimum of 4 weeks to ensure sufficient time to observe clinically meaningful changes in the biomarkers glycaemic markers post-intervention.

Data extraction

Two independent researchers (E.Gh and O.A.) extracted the following information for each included studies using a standardised 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, BMI and health history; (7) dosage of pistachio consumption in the intervention; (8) duration of the intervention and (9) the means and 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).

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 judgements were compared.

Statistical analyses

Statistical analyses were performed using STATA version 11.2 (Stata Corp.). 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 SD 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 between the groups who consumed pistachio and controls, with a 95% CI. If only SE were reported, SD 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/m²) or obese (≥ 30 kg/m²)); (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

Fig. 1 summarises 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 eighteen 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 randomisation⁽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 analysed 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 USA^(16,32,37), China⁽³³⁾, India^(34,36), Spain⁽³⁵⁾ and Iran⁽¹⁵⁾. The duration of the intervention varied between 4⁽¹⁶⁾ and 24⁽³⁴⁾ weeks across the included trials. The daily recommended dosage of pistachio consumption varied between 25 and 70 g 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 and mean baseline BMI varied from 26.1⁽³⁶⁾ to 32.0⁽¹⁵⁾ kg/m². Participants in the trials presented with cardiometabolic abnormalities including dysglycaemia⁽³⁵⁾, overweight⁽³⁷⁾, obesity⁽³²⁾, MetS^(33,34), dyslipidaemia⁽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 regard 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 fasting blood sugar 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 (weighted mean difference: -522 mg/dl, 95% CI: $(-7.80, -2.64)$, $P < 0.001$). There was a significant between-study heterogeneity ($I^2 = 68.5\%$, $P = 0.001$; Fig. 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



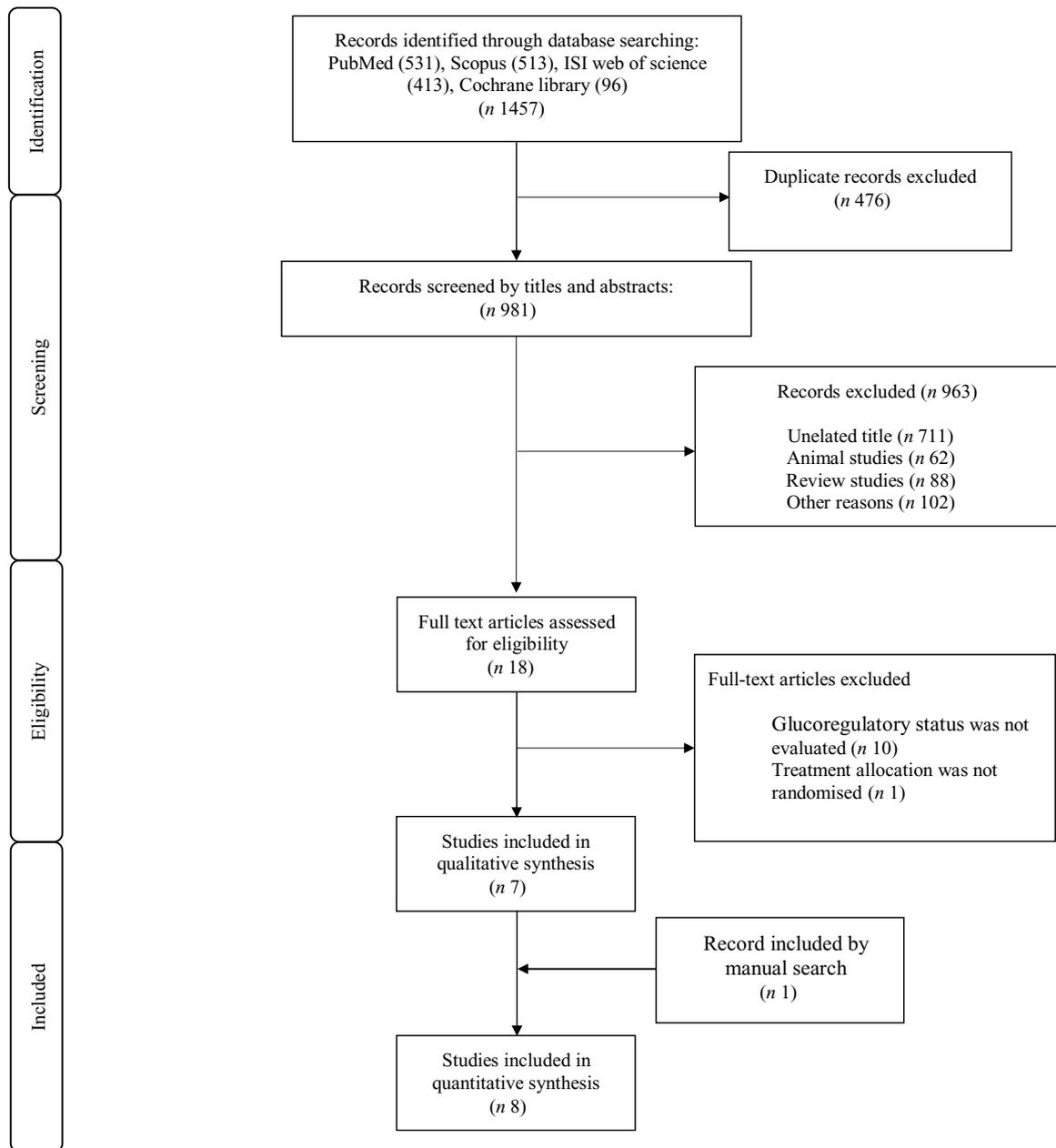


Fig. 1. PRISMA flow diagram of study selection process.

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 insulin concentrations (weighted mean difference: $-1.86 \mu\text{IU/ml}$, 95% CI: $(-3.13, -0.59)$, $P < 0.01$), despite a significant heterogeneity across the evaluated trials ($I^2 = 71.3\%$, $P < 0.01$; Fig. 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 ($-2.11 \mu\text{IU/ml}$, 95% CI: $(-4.39, 0.16)$). However, the omission of any of the studies could not reduce the heterogeneity.

Effects of pistachio consumption on homeostasis model assessment of insulin resistance R.

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 with controls (weighted mean difference: -0.66 , 95% CI $(-1.89, 0.58)$, $P = 0.30$). We also observed significant heterogeneity across

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

Pistachios dosage	Sample size (intervention/control)	Trial duration (weeks)	Mean BMI (kg/m ² , intervention/control)	Mean age (year, intervention/control)	Sex	Participants	Study design	Country	Year	Author
53 g	31/28	12	30.1/30.9	45.4/47.3	F/M	Subjects with obesity	R/CG/PA	USA	2009	Li
42 g	27/30	12	28.1/28.028.0/28.0	51.9/50.7	F/M	Subjects with metabolic syndrome	R/CG/PA	China	2012	Wang
70 g	29/30			51.8/50.7						
35.4 g	11/11	6	31.1/31.1	57.1/57.1	F/M	Overweight subjects	R/CG/PA	USA	2014	Wilson
57 g	54/54	16	28.9/28.9	55/55	F/M	Subjects with prediabetes	R/CG/CO	Spain	2014	Hernandez-Alonso
40 g	21/21	12	26.1/27.8	37.7/40.4	F/M	Patients with mild dyslipidaemia	R/CG/PA	India	2014	Kasliwal
25 g	30/30	12	32/30	53/55	F/M	Patients with type 2 diabetes	R/CG/CO	Iran	2014	Parham
20 % TEE	35/35	24	30.9/30.9	41.6/43.3	F/M	Subjects with metabolic syndrome	R/CG/PA	India	2014	Gulati
20 % TEE	30/30	4	31.2/31.2	56.1/56.1	F/M	Patients with type 2 diabetes	R/CG/CO	USA	2015	Sauder

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

Authors	Random sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Li <i>et al.</i>	L	L	H	U	U	U	L
Wang <i>et al.</i>	H	L	H	U	U	U	H
Gulati <i>et al.</i>	H	U	H	L	L	L	L
Hernandez-Alonso <i>et al.</i>	L	L	H	U	L	L	L
Wilson <i>et al.</i>	H	U	H	U	L	L	H
Kasliwal <i>et al.</i>	H	U	H	U	L	L	L
Parham <i>et al.</i>	L	L	H	L	L	U	L
Sauder <i>et al.</i>	H	L	H	L	L	L	L

L, low; H, high, U, unclear.

the evaluated trials ($I^2 = 85.4\%$, $P < 0.01$; Fig. 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 ($I^2 = 0.0\%$, $P = 0.89$).

Publication bias. Visual inspection of the funnel plots showed no evidence of asymmetry in the effects of pistachio consumption on the glycaemic 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 (< 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 glucoregulatory status in individuals at risk for CVD.

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 abnormalities compared with 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 glycaemic index pistachio nuts⁽³⁸⁾. Consumption of pistachio nuts with high carbohydrate foods with a high glycaemic index, including parboiled rice, pasta and mashed potatoes, has been shown to slow the intestinal absorption of carbohydrates and reduce total postprandial glycaemic response by 20–30%^(15,38). Consumption of pistachio nuts has been also associated with reduced rates of dietary fat digestion, slow energy release and increased digestibility of dietary fibre⁽³⁹⁾. The favourable nutritional composition

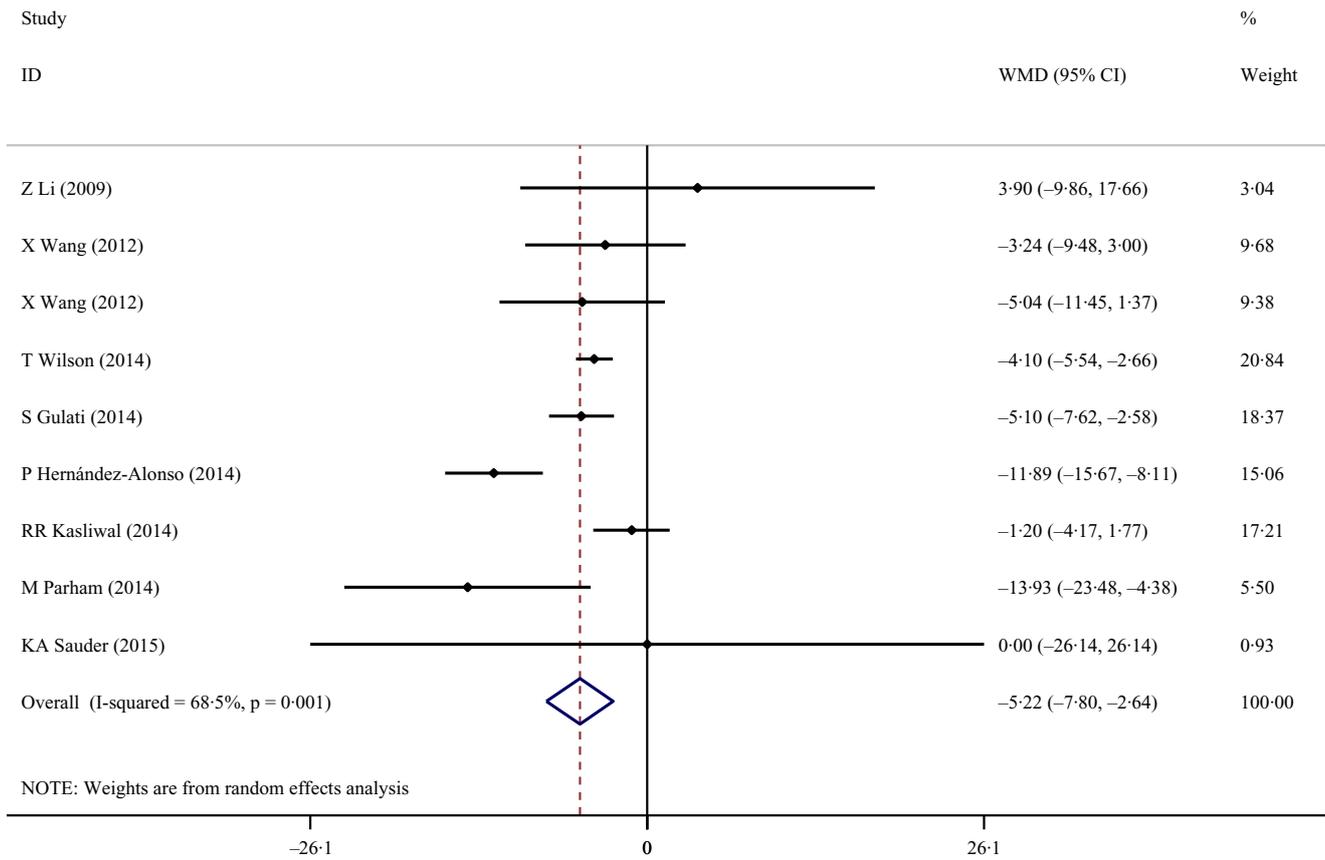


Fig. 2. Forest plot of the effects of pistachios on fasting blood sugar concentrations.

Table 3. Subgroup analyses of pistachios consumption on glycaemic profile (Coefficient values and 95 % confidence intervals)

Subsets	n	WMD	95 % CI	P within group	P heterogeneity	I ²
Overall (FBS)	9	-5.22	-7.80, -2.64	< 0.001	0.001	68.5
BMI status						
Obese	5	-4.72	-6.92, -2.52	< 0.001	0.215	31.0
Overweight	4	-5.40	-11.14, 0.34	0.065	< 0.001	84.5
Trial duration						
≥ 12 weeks	7	-5.61	-9.31, -1.90	0.003	< 0.001	75.3
< 12 weeks	2	-4.08	-5.52, -2.65	< 0.001	0.759	0.0
Type of disease						
T2DM	2	-12.29	-21.26, -3.31	0.007	0.327	0.0
MetS	3	-4.86	-7.05, -2.66	< 0.001	0.862	0.0
Other disease (overweight, obese, prediabetes, dyslipidaemia)	4	-4.73	-9.31, -0.15	0.043	< 0.001	85.8
Overall (insulin)	7	-1.86	-3.13, -0.59	0.004	0.002	71.3
BMI status						
Obese	4	-1.09	-2.29, 0.10	0.074	0.020	69.6
Overweight	3	-4.14	-5.82, -2.45	< 0.001	0.505	0.0
Trial duration						
≥ 12 weeks	5	-2.92	-5.06, -0.77	0.008	0.193	34.2
< 12 weeks	2	-1.05	-2.41, 0.30	0.128	0.005	87.6
Type of disease						
T2DM	1	-0.31	-1.16, 0.54	0.475	-	-
MetS	3	-0.91	-3.57, 1.74	0.501	0.554	0.0
Other disease (overweight, obese, prediabetes, dyslipidaemia)	3	-3.12	-5.50, -0.74	0.010	0.010	78.4

FBS, fasting blood sugar; T2DM, type 2 diabetes; MetS, metabolic syndrome; WMD, weighted mean differences.

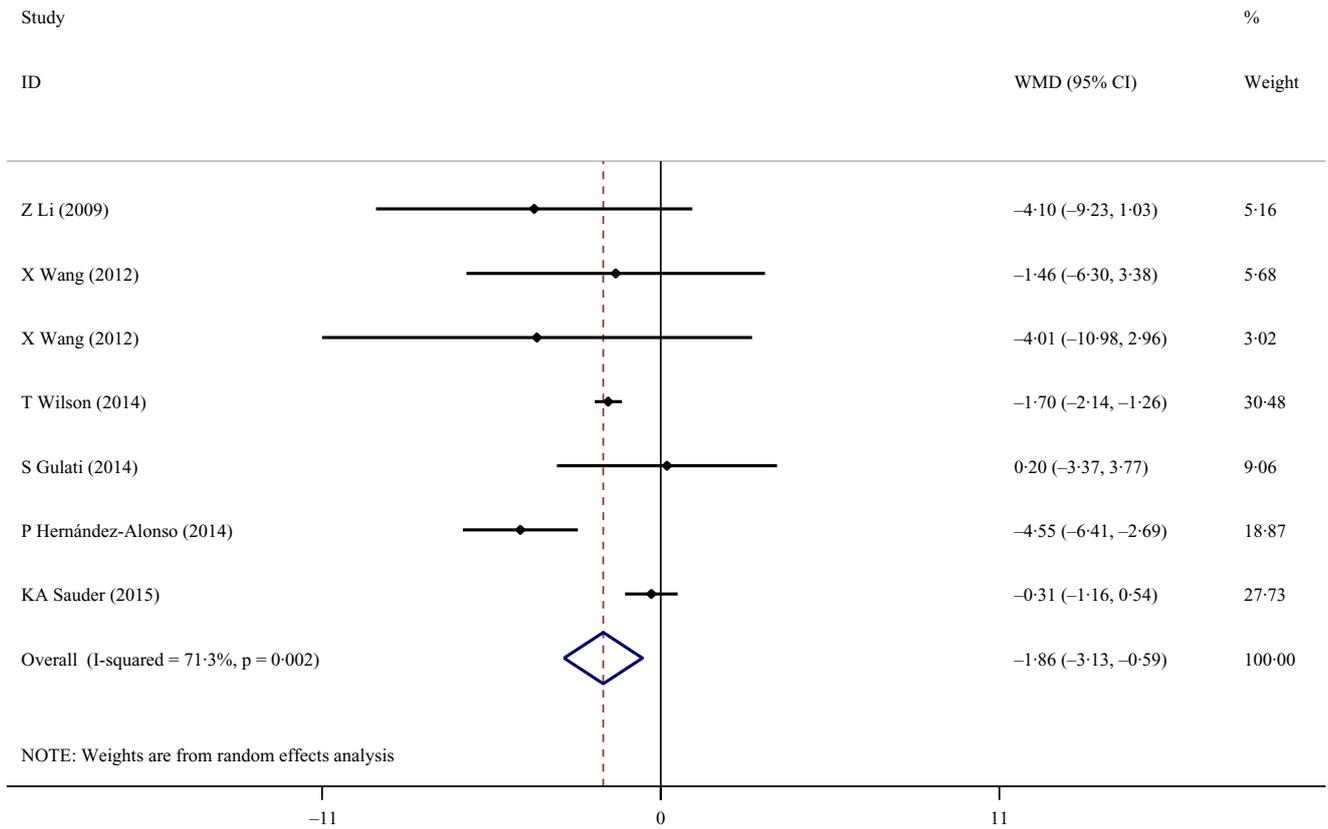


Fig. 3. Forest plot of the effects of pistachios on insulin concentrations.

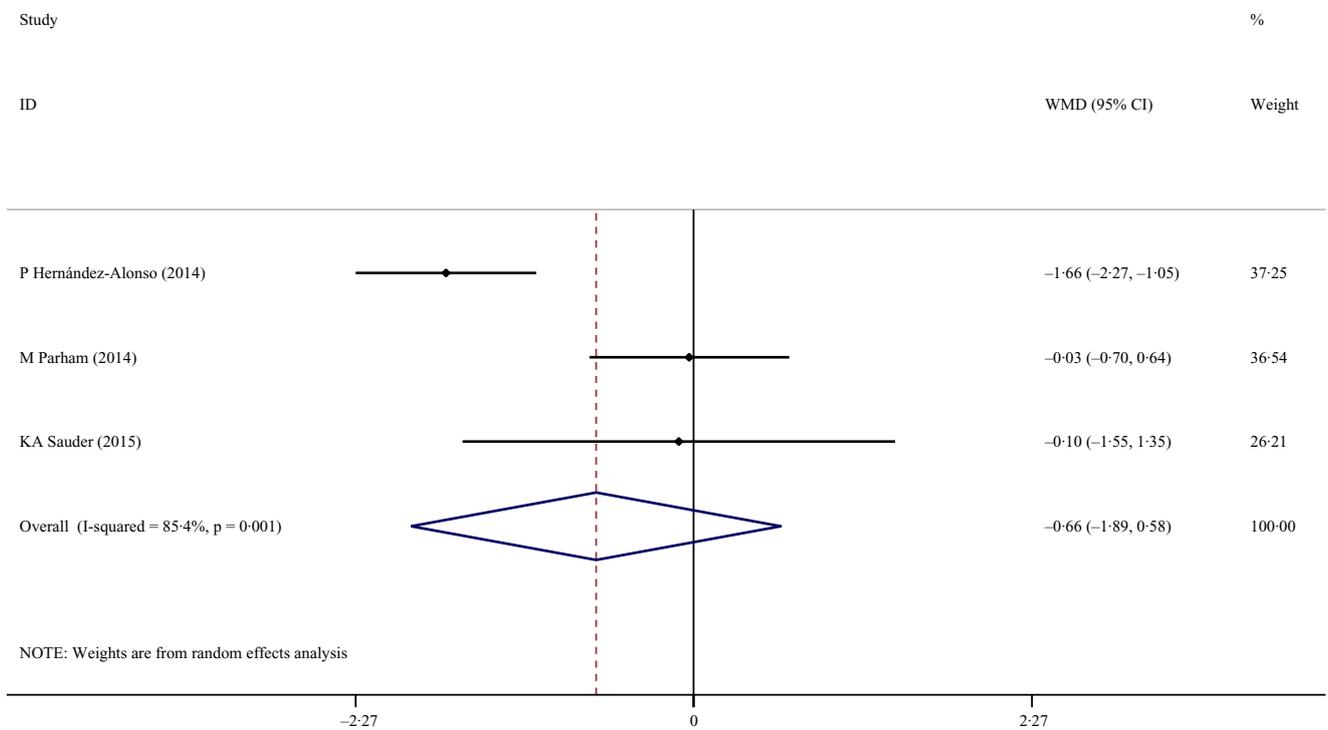


Fig. 4. Forest plot of the effects of pistachios on homeostasis model assessment of insulin resistance.

of pistachio nuts, including high MUFA and PUFA and low SFA content, may also contribute to these positive effects through mechanisms described⁽⁴⁰⁾. Replacement of SFA by MUFA and PUFA has been shown to improve glycaemic control and IR^(41,42,43). 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-glycaemic effects^(44,45,10) and were shown to reduce the risk of T2DM⁽⁴⁶⁾. Quercetin and catechin compounds have been reported to modulate the activity of intestinal α -glucosidase and pancreatic α -amylase and regulate intestinal glucose absorption^(47,48). Pistachio nuts have been shown to inhibit the oxidation of aldohexose⁽³³⁾. These mechanisms may explain the improved glycaemic response following the consumption of pistachio nuts. Pistachio nuts also have other favourable dietary factors, including a high Mg⁽⁴⁹⁾ and phosphorus content, with implications in the metabolism of B group vitamins, regulation of endocrine hormones and modulation of glucose response⁽¹¹⁾. Long-term consumption of pistachio nuts has been shown to induce glucagon-like peptide-1 release and insulin-sparing effects in individuals with prediabetes⁽¹⁴⁾. Similarly, the intake of pistachio nuts has been shown to upregulate the secretion of glucagon-like peptide-1 in individuals with MetS⁽⁵⁰⁾. The beneficial effects of pistachio nuts on insulin metabolism could be attributed, in part, to increased glucagon-like peptide-1 levels. Glucagon-like peptide-1 and gastric inhibitory polypeptide are gastric hormones which can stimulate pancreatic insulin secretion and suppress glucagon secretion in a glucose-dependent manner⁽⁵¹⁾. Other mechanisms have been also proposed to explain the positive effects of pistachio nuts intake on glycaemic control and insulin sensitivity, including the modulation of miRNA^(52,53) 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, diarrhoea, constipation, flatulence and abdominal pain, have been reported in some individuals attributed to the high fructan content of pistachio nuts⁽⁵⁴⁾. Further, the high energy content of pistachio nuts⁽⁷⁾ 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⁽³³⁾ – a finding that has been corroborated in other populations^(22,24). Current evidence does not support a relationship between nut consumption and weight gain, albeit nuts are energy-dense food⁽⁵⁵⁾. 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^(15,56), reduced rate of carbohydrate and fat digestion and absorption and inducing satiety, which decrease the consumption of unhealthy foods^(57,58).

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 Preferred Reporting Items for Systematic Reviews and Meta-analysis 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 -lkstudied 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 the glycaemic and insulinemic response to nuts⁽⁵⁹⁾. 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.

Acknowledgements

None.

The present work did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

O. A. and E. Gh. designed and conceived the study, searched databases, screened articles and extracted data. E. Gh. performed the statistical analyses. O. A. and E. Gh. interpreted the results and drafted the manuscript with contributions from A. H. and M. K. All authors reviewed and commented on subsequent drafts of the manuscript. O. A. and E. Gh. have the primary responsibility for the final content.

The authors declare that they have no competing interests.

References

1. Alberti KGMM, Eckel RH, Grundy SM, *et al.* (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **120**, 1640–1645.
2. Ranasinghe P, Mathangasinghe Y, Jayawardena R, *et al.* (2017) Prevalence and trends of metabolic syndrome among adults in the Asia-pacific region: a systematic review. *BMC Public Health* **17**, 101.
3. Al-Oubaidy SA, Awadh SA & Lafta MA (2022) Investigate the effects of the A16V MnSOD SNPs on insulin resistant index and metabolic profile levels in Iraqi metabolic syndrome patients. *J Pharm Negat Results* **13**, 95.





4. Avramoglu RK, Basciano H & Adeli K (2006) Lipid and lipoprotein dysregulation in insulin resistant states. *Clin Chim Acta* **368**, 1–19.
5. Scott CL (2003) Diagnosis, prevention, and intervention for the metabolic syndrome. *Am J Cardiol* **92**, 35–42.
6. Sowndarya K, Joseph JA, Shenoy A, *et al.* (2021) Evaluation of triglyceride/high-density lipoprotein ratio as a surrogate marker for insulin resistance in healthy young males. *J Nat Sci Biol Med* **12**, 213.
7. Dreher ML (2012) Pistachio nuts: composition and potential health benefits. *Nutr Rev* **70**, 234–240.
8. Risérus U (2008) Fatty acids and insulin sensitivity. *Curr Opin Clin Nutr Metab Care* **11**, 100–105.
9. Azemati B, Rajaram S, Jaceldo-Siegl K, *et al.* (2017) Animal-protein intake is associated with insulin resistance in Adventist health study 2 (AHS-2) calibration substudy participants: a cross-sectional analysis. *Curr Dev Nutr* **1**, e000299.
10. Tomaino A, Martorana M, Arcoraci T, *et al.* (2010) Antioxidant activity and phenolic profile of pistachio (*Pistacia vera* L., variety Bronte) seeds and skins. *Biochimie* **92**, 1115–1122.
11. Ghasemynasabparizi M, Ahmadi A & Mazloomi SM (2015) A review on pistachio: its composition and benefits regarding the prevention or treatment of diseases. *J Occup Health Epidemiol* **4**, 57–69.
12. Hadi A, Asbaghi O, Kazemi M, *et al.* (2021) Consumption of pistachio nuts positively affects lipid profiles: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*, 1–14.
13. Asbaghi O, Hadi A, Campbell MS, *et al.* (2021) Effects of pistachios on anthropometric indices, inflammatory markers, endothelial function and blood pressure in adults: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr* **126**, 1–12.
14. Hernández-Alonso P, Salas-Salvadó J, Baldrich-Mora M, *et al.* (2014) Beneficial effect of pistachio consumption on glucose metabolism, insulin resistance, inflammation, and related metabolic risk markers: a randomized clinical trial. *Diabetes Care* **37**, 3098–3105.
15. Parham M, Heidari S, Khorramirad A, *et al.* (2014) Effects of pistachio nut supplementation on blood glucose in patients with type 2 diabetes: a randomized crossover trial. *Rev Diabet Stud* **11**, 190.
16. Sauder KA, McCrea CE, Ullbrecht JS, *et al.* (2015) Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: a randomized trial. *Metabolism* **64**, 1521–1529.
17. Ribeiro PDM, Silva A, Almeida A, *et al.* (2019) Effect of chronic consumption of pistachios (*Pistacia vera* L.) on glucose metabolism in pre-diabetics and type 2 diabetics: a systematic review. *Crit Rev Food Sci Nutr* **59**, 1115–1123.
18. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* **151**, 264–269.
19. Higgins JP & Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons.
20. Higgins JP, Thomas J, Chandler J, *et al.* (2019) *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons.
21. Higgins JP, Thompson SG, Deeks JJ, *et al.* (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560.
22. Edwards K, Kwaw I, Matud J, *et al.* (1999) Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia. *J Am Coll Nutr* **18**, 229–232.
23. Kocyigit A, Koylu A & Keles H (2006) Effects of pistachio nuts consumption on plasma lipid profile and oxidative status in healthy volunteers. *Nutr Metab Cardiovasc Dis* **16**, 202–209.
24. Sheridan MJ, Cooper JN, Erario M, *et al.* (2007) Pistachio nut consumption and serum lipid levels. *J Am Coll Nutr* **26**, 141–148.
25. Gebauer SK, West SG, Kay CD, *et al.* (2008) Effects of pistachios on cardiovascular disease risk factors and potential mechanisms of action: a dose-response study. *Am J Clin Nutr* **88**, 651–659.
26. Kay CD, Gebauer SK, West SG, *et al.* (2010) Pistachios increase serum antioxidants and lower serum oxidized-LDL in hypercholesterolemic adults. *J Nutr* **140**, 1093–1098.
27. Aldemir M, Okulu E, Neşelioğlu S, *et al.* (2011) Pistachio diet improves erectile function parameters and serum lipid profiles in patients with erectile dysfunction. *Int J Impot Res* **23**, 32.
28. West SG, Gebauer SK, Kay CD, *et al.* (2012) Diets containing pistachios reduce systolic blood pressure and peripheral vascular responses to stress in adults with dyslipidemia. *Hypertension* **60**, 58–63.
29. Nieman DC, Scherr J, Luo B, *et al.* (2014) Influence of pistachios on performance and exercise-induced inflammation, oxidative stress, immune dysfunction, and metabolite shifts in cyclists: a randomized, crossover trial. *PLOS ONE* **9**, e113725.
30. Carughi A, Bellisle F, Dougkas A, *et al.* (2019) A randomized controlled pilot study to assess effects of a daily pistachio (*Pistacia vera*) afternoon snack on next-meal energy intake, satiety, and anthropometry in French women. *Nutrients* **11**, 767.
31. Sari I, Baltaci Y, Bagri C, *et al.* (2010) Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: a prospective study. *Nutrition* **26**, 399–404.
32. Li Z, Song R, Nguyen C, *et al.* (2010) Pistachio nuts reduce triglycerides and body weight by comparison to refined carbohydrate snack in obese subjects on a 12-week weight loss program. *J Am Coll Nutr* **29**, 198–203.
33. Wang X, Li Z, Liu Y, *et al.* (2012) Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. *Nutr J* **11**, 20.
34. Gulati S, Misra A, Pandey RM, *et al.* (2014) Effects of pistachio nuts on body composition, metabolic, inflammatory and oxidative stress parameters in Asian Indians with metabolic syndrome: a 24-weeks, randomized control trial. *Nutrition* **30**, 192–197.
35. Hernández-Alonso P, Salas-Salvadó J, Baldrich-Mora M, *et al.* (2015) Effect of pistachio consumption on plasma lipoprotein subclasses in pre-diabetic subjects. *Nutr Metab Cardiovasc Dis* **25**, 396–402.
36. Kasliwal RR, Bansal M, Mehrotra R, *et al.* (2015) Effect of pistachio nut consumption on endothelial function and arterial stiffness. *Nutrition* **31**, 678–685.
37. Wilson T (2014) Effect of bedtime pistachio consumption for 6 weeks on weight, lipid profile and glycemic status in overweight persons. *J Food Nutr Sci* **1**, 1–4.
38. Kendall C, Josse A, Esfahani A, *et al.* (2011) The impact of pistachio intake alone or in combination with high-carbohydrate foods on post-prandial glycemia. *Eur J Clin Nutr* **65**, 696.
39. Baer DJ, Gebauer SK & Novotny JA (2012) Measured energy value of pistachios in the human diet. *Br J Nutr* **107**, 120–125.
40. Siri-Tarino PW, Sun Q, Hu FB, *et al.* (2010) Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. *Curr Atheroscler Rep* **12**, 384–390.
41. Paniagua JA, de la Sacristana AG, Sánchez E, *et al.* (2007) A MUFA-rich diet improves postprandial glucose, lipid and

- GLP-1 responses in insulin-resistant subjects. *J Am Coll Nutr* **26**, 434–444.
42. Gillingham LG, Harris-Janz S & Jones PJ (2011) Dietary mono-unsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. *Lipids* **46**, 209–228.
 43. Moon JH, Lee JY, Kang SB, *et al.* (2010) Dietary monounsaturated fatty acids but not saturated fatty acids preserve the insulin signaling pathway via IRS-1/PI3K in Rat skeletal muscle. *Lipids* **45**, 1109–1116.
 44. Liu Y, Blumberg JB & Chen C-YO (2014) Quantification and bioaccessibility of California pistachio bioactives. *J Agric Food Chem* **62**, 1550–1556.
 45. Bellomo M & Fallico B (2007) Anthocyanins, chlorophylls and xanthophylls in pistachio nuts (*Pistacia vera*) of different geographic origin. *J Food Compos Anal* **20**, 352–359.
 46. Montonen J, Knekt P, Järvinen R, *et al.* (2004) Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care* **27**, 362–366.
 47. Akkarachiyasit S, Charoenlertkul P, Yibchok-Anun S, *et al.* (2010) Inhibitory activities of cyanidin and its glycosides and synergistic effect with acarbose against intestinal α -glucosidase and pancreatic α -amylase. *Int J Mol Sci* **11**, 3387–3396.
 48. Wilson T, Luebke JL, Morcomb EF, *et al.* (2010) Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. *J Food Sci* **75**, H218–H223.
 49. Hata A, Doi Y, Ninomiya T, *et al.* (2013) Magnesium intake decreases type 2 diabetes risk through the improvement of insulin resistance and inflammation: the Hisayama study. *Diabet Med* **30**, 1487–1494.
 50. Kendall C, West SG, Augustin L, *et al.* (2014) Acute effects of pistachio consumption on glucose and insulin, satiety hormones and endothelial function in the metabolic syndrome. *Eur J Clin Nutr* **68**, 370.
 51. Yabe D & Seino Y (2011) Two incretin hormones GLP-1 and GIP: comparison of their actions in insulin secretion and β cell preservation. *Prog Biophys Mol Biol* **107**, 248–256.
 52. Ortega FJ, Mercader JM, Moreno-Navarrete JM, *et al.* (2014) Profiling of circulating microRNAs reveals common microRNAs linked to type 2 diabetes that change with insulin sensitization. *Diabetes Care* **37**, 1375–1383.
 53. Hernández-Alonso P, Giardina S, Salas-Salvadó J, *et al.* (2017) Chronic pistachio intake modulates circulating microRNAs related to glucose metabolism and insulin resistance in prediabetic subjects. *Eur J Nutr* **56**, 2181–2191.
 54. Fedewa A & Rao SS (2014) Dietary fructose intolerance, fructan intolerance and FODMAPs. *Curr Gastroenterol Rep* **16**, 370.
 55. Flores-Mateo G, Rojas-Rueda D, Basora J, *et al.* (2013) Nut intake and adiposity: meta-analysis of clinical trials. *Am J Clin Nutr* **97**, 1346–1355.
 56. Coates AM & Howe PR (2007) Edible nuts and metabolic health. *Curr Opin Lipidol* **18**, 25–30.
 57. Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, *et al.* (2009) Prospective study of nut consumption, long-term weight change, and obesity risk in women. *Am J Clin Nutr* **89**, 1913–1919.
 58. Freisling H, Noh H, Slimani N, *et al.* (2018) Nut intake and 5-year changes in body weight and obesity risk in adults: results from the EPIC-PANACEA study. *Eur J Nutr* **57**, 2399–2408.
 59. Cassady BA, Hollis JH, Fulford AD, *et al.* (2009) Mastication of almonds: effects of lipid bioaccessibility, appetite, and hormone response. *Am J Clin Nutr* **89**, 794–800.